A Guide to the Clinical Care of Women with HIV

2013 Edition

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Preface

Recommendations change rapidly in HIV care, so the care provider is cautioned that this edition is dated November 2013. For the most current and continually updated HIV/AIDS treatment guidelines, contact AIDSinfo at:

http://www.aidsinfo.nih.gov

This *Guide* contains information relating to general principles of medical care that should not be construed as specific instructions for individual patients. Some of the information may cite the use of a particular drug in a dosage, for an indication, or in a manner other than recommended by the FDA. Therefore, the manufacturer's package inserts should be consulted for complete prescribing information.

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Introduction

HIV/AIDS clinical care has improved dramatically over the past two decades as new and effective medications have become available. Over that same period, our understanding of how best to use antiretrovirals and deliver primary care to persons living with HIV/AIDS has deepened as well. Positive change on such a massive scale, however, brings with it new demands on clinicians.

Along with innovations in HIV drug therapies, HIV/AIDS care has become more complex than ever before due to increasing comorbidities that are attributable to HIV treatment and the aging of the HIV-infected population in the United States. Patient needs also have expanded across a broad spectrum of medical, psychological, behavioral, and social needs. Notably, significant numbers of infected individuals are identified and enter care late in the course of their HIV disease. Combined with the specific challenges faced by women with HIV infection, clinicians are confronted with complex care challenges.

A Guide to the Clinical Care of Women with HIV is a comprehensive clinical manual that addresses primary care needs unique to women living with HIV infection. The book's target audiences are clinicians who provide primary care to women and those seeking a more in-depth understanding of how to care for women with HIV/AIDS. The 2013 edition of the guide, which was first published in 2001, has been updated, and chapters have been added on quality management and psychosocial, mental health, and substance abuse issues.

A manual devoted specifically to the care of women with HIV is important. Because women are often challenged by social isolation, poverty, discrimination, and lack of access to quality health care, they tend to be diagnosed later and to have poorer health status than men. They must often contend with vulnerability related to reproductive and gender issues and domestic violence. Finally, women living with HIV are usually relied upon to meet the care needs of children and other family members, many of whom are also HIV infected.

By presenting best practices in the clinical management of women with HIV/AIDS disease, the *Guide* can help us continue the remarkable advances in HIV/AIDS care that have made the Ryan White HIV/AIDS Program a model for health care delivery for our nation and for the world.

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Abbreviations and Acronyms

3TC	Lamivudine
5FC	5-flucytosine
5-FU	5-fluorouracil
AACTG	Adult AIDS Clinical Trial Groups
AaDO$_2$	Alveolar-arterial oxygen tension difference
AAHIVM	American Academy of HIV Medicine
ABC	Abacavir
AC/HS	Differential agglutination test
ACE	Angiotensin-converting-enzyme
ACOG	American Congress of Obstetricians and Gynecologists
ACRN	AIDS certified registered nurse
ACT	Artemisinin-based combination therapy
ADC	AIDS dementia complex
ADR	Adverse drug reaction
AEGIS	AIDS Education Global Information System
AETC	AIDS Education and Training Centers
AFASS	Acceptable, feasible, affordable, sustainable, and safe
AFB	Acid-fast bacillus
AFI	Amniotic fluid index
AFP	Alpha-fetoprotein
AGC	Atypical glandular cells
AGC-NOS	Atypical glandular cells not otherwise specified
AGCUS	Atypical glandular cells of undetermined significance
AIDS	Acquired immune deficiency syndrome
AIS	Adenocarcinoma in situ

ALT	Alanine aminotransferase
ANAC	Association of Nurses in AIDS Care
ANC	Absolute neutrophil count
APV	Amprenavir
ARCHITECT®	HIV Ag/Ab Combo assay
ARB	Angiotensin II receptor blocker
ART	Antiretroviral therapy
ARV	Antiretroviral
ASC	Atypical squamous cells
ASCCP	American Society for Colposcopy and Cervical Pathology
ASC-H	Atypical squamous cells, cannot rule out a high grade lesion
ASCUS	Atypical squamous cells of undetermined significance
ASCUS-H	Atypical squamous cells of undetermined significance – high-grade squamous intraepithelial lesion
ASIL	Anal squamous intraepithelial lesions
AST	Aspartate transaminase
ATV	Atazanavir
ATV/r	Ritonavir-boosted atazanavir
AUC	Area under the plasma drug concentration-time curve
AZT	Zidovudine (also **ZDV**)
AZT/3TC	Zidovudine/lamivudine
AZT/3TC/ABC	Abacavir/lamivudine/zidovudine)
B12	Vitamin B-12
BBP	Bloodborne pathogen
BCA	Bichloracetic acid
BCG	Bacillus Calmette-Guérin

bDNA	Branched DNA
beta-hCG	Beta subunit of human chorionic gonadotropin (also HCG)
BF	Breastfeeding
bid	Twice per day
BMD	Bone mineral density
BMGF	Bill & Melinda Gates Foundation
BMI	Body mass index
BP	Blood pressure
BPI	Brief Pain Inventory
BRCA-1; BRCA-2	Breast cancer gene 1; breast cancer gene 2
BUN	Blood urea nitrogen
BV	Bacterial vaginosis
bx	Biopsy
CAPRISA	Center for the AIDS Programme of Research in South Africa
CATIE	Canadian AIDS Treatment Information Exchange
CBC	Complete blood count
CCR5	C-C chemokine receptor type 5
CDC	U.S. Centers for Disease Control and Prevention
CDC NPIN	CDC National Prevention Information Network
CHF	Congestive heart failure
CIN	Cervical intraepithelial neoplasia
CLIA	Clinical Laboratory Improvements Amendments
Cmax	Maximum concentration
Cmin	Minimum concentration
CMV	Cytomegalovirus
CNS	Central nervous system
CONRAD	Contraceptive Research and Development Program

COPD	Chronic obstructive pulmonary disease
CPCRA	Community Programs for Clinical Research on AIDS
CPK	Creatine phosphokinase
CQI	Continuous quality improvement
Cr	Serum creatinine
CrCl	Creatinine clearance
CS	Cesarean section
CSF	Cerebrospinal fluid
CST	Contraction stress test
CT	Computed tomography
CTL	Cytotoxic T lymphocyte
Cu-IUD	Copper intrauterine device
CV	Cardiovascular
CVD	Cardiovascular disease
CVA	Cerebrovascular accident
CXCR4	C-X-C chemokine receptor type 4
CXR	Chest x-ray
CYP	Cytochrome P450
d	Day
DBP	Diastolic blood pressure
d/c	Discontinue
d4T	Stavudine
ddC	zalcitabine
ddI	Didanosine
DEET	*N,N*-Diethyl-3-methylbenzamide
DES	Diethylstilbestrol
DHAP	CDC Division of HIV/AIDS Prevention
DHHS	U.S. Department of Health and Human Services (obsolete – see **HHS**)
DLV	Delavirdine
DM	Diabetes mellitus

DMPA	Depot-medroxyprogesterone acetate		**FSFI**	Female Sexual Function Index	
DNA	Deoxyribonucleic acid		**FSH**	Follicle-stimulating hormone	
DOT	Directly observed therapy		**FTA-ABS**	Fluorescent treponemal antibody absorption test	
DRV	Darunavir		**FTC**	Emtricitabine	
DRV/r	Ritonavir-boosted darunavir		**G6PD**	Glucose-6-phosphate dehydrogenase deficiency	
DS	Double strength				
DSM-IV-TR	*Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., Text Revision		**GABA**	Gamma-aminobutyric acid	
			GBS	Group B streptococcus	
DVT	Deep venous thrombosis		**GC**	Gonorrhea culture	
EBV	Epstein-Barr virus		**GCSF**	Granulocyte colony-stimulating factor	
EC	Emergency contraception (Ch. 7)		**GFR**	Glomerular filtration rate	
	Enteric coated (Ch. 8, Ch. 13)		**GI**	Gastrointestinal	
			GNI	Gross national income	
ECG	Electrocardiogram		**gp**	Glycoproteins	
ED	Erectile dysfunction		**GTT**	Glucose tolerance test	
EE	Ethinyl estradiol		**h**	Hour	
EFV	Efavirenz		H_1	Histamine 1	
EIA	Enzyme immunoassay		H_2	Histamine 2	
ELISA	Enzyme-linked immunosorbent assay		**HAART**	Highly active antiretroviral therapy	
EKG	Electrocardiogram		**HAB**	HIV/AIDS Bureau	
EMB	Ethambutol		**HAV**	Hepatitis A virus	
ENF	Enfuvirtide		**Hb**	Hemoglobin	
EOL	End-of-life		**HbeAg+**	Hepatitis B e antigen	
ETG	Etonogestrel		**HBIG**	Hepatitis B immune globulin	
ETR	Etravirine		**HBsAb**	Hepatitis B surface antibody	
EVG	Elvitegravir				
FDA	U.S. Food and Drug Administration		**HBsAg**	Hepatitis B surface antigen	
FHI	Family Health International		**HBV**	Hepatitis B virus	
			HC	Hormonal contraception	
FI	Fusion inhibitor		**HCC**	Hepatocellular carcinoma	
FPV	Fosamprenavir		**HCG**	Human chorionic gonadotropin (also **beta-hCG**)	
FPV/r	Ritonavir-boosted Fosamprenavir				

HCl	Hydrochloride
HCV	Hepatitis C virus
HD	Hemodialysis
HDL	High-density lipoprotein
HELLP	Hemolysis, elevated liver enzymes, and low platelet count syndrome
HERS	HIV Epidemiology Research Study
HHS	U.S. Department of Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HIV Ab	HIV antibody
HIVAN	HIV-associated nephropathy
HIVMA	HIV Medicine Association
HIV RNA	HIV ribonucleic acid
HIV RNA PCR	HIV ribonucleic acid polymerase chain reaction
HLA	Human leukocyte antigen
HLA-B5701	Human leukocyte antigen B*5701
HMG-CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A
HMO	Health maintenance organization
HPTN	HIV Prevention Trials Network
HPV	Human papillomavirus
HR	Hazard ratio
HRSA	U.S. Health Resources and Services Administration
HRT	Hormone replacement therapy
hs	At bedtime
hs-CRP	High-sensitivity C-reactive protein
HSIL	High-grade squamous intraepithelial lesion

HSR	Hypersensitivity reaction
HSV	Herpes simplex virus
HSV-2	Herpes simplex virus 2
HTLV	Human T-cell lymphotropic virus
HTN	Hypertension
HVTN	HIV Vaccine Trials Network
IAS	International AIDS Society
IC	Inhibitory concentration
ICC	Invasive cervical cancer
ICSI	Intracytoplasmic sperm injection
IDSA	Infectious Diseases Society of America
IDU	Injection drug use/user
IDV	Indinavir
IFA	Immunofluorescence assay
IFN	Interferon
IgA	Immunoglobulin A (E, G, M, etc.)
IM	Intramuscular
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Group
IND	Investigational new drug
INH	Isoniazid
INR	International normalized ratio
INSTI	Integrase strand transfer inhibitor
IP	Intrapartum
iPrEX	Pre-exposure prophylaxis initiative
IPV	Inactivated polio vaccine (Table 4-9)
	Interpersonal violence (Ch. 9)
IQ	Intelligence quotient
IRIS	Immune reconstitution inflammatory syndrome
ITP	Idiopathic thrombocytopenic purpura

IU	International unit
IUD	Intrauterine device
IUI	Intrauterine insemination
IV	Intravenous
IVF	In vitro fertilization
KOH	Potassium hydroxide
KS	Kaposi's sarcoma
LDL	Low-density lipoprotein
LEEP	Loop electrosurgical excision procedure
LFT	Liver function test
LGV	Lymphogranuloma venereum
LMIC	Low- and middle-income countries
LMP	Last menstrual period
LMWH	Low-molecular-weight heparin
LNG	Levonorgestrel
LNg-IUD	Levonorgestrel-releasing intrauterine device
LPV	Lopinavir
LPV/r	Ritonavir-boosted lopinavir
LSIL	Low-grade squamous intraepithelial lesion
MAC	Mycobacterium avium complex
MCV	Mean corpuscular volume
MCV4	Meningococcal conjugate vaccine
MDD	Major depressive disorder
MDMA	Methylenedioxymetham-phetamine ("ecstasy")
MDP	Microbicides Development Programme
MDR	Multi-drug resistant
MI	Myocardial infarction
MIC	Minimum inhibitory concentration
MMR	Measles, mumps, and rubella

mo	Month
MRI	Magnetic resonance imaging
MSAFP	Maternal serum alpha-fetoprotein
MSAS	Memorial Symptom Assessment Scale
MSM	Men who have sex with men
MTB	*Mycobacterium tuberculosis*
MTCT	Mother-to-child transmission
mtDNA	Mitochondrial DNA
MTN	Microbicide Trials Network
MVC	Maraviroc
MY	Measurement year
N-9	Nonoxynol-9
n/a	Not applicable
NAAT	Nucleic acid amplification test
NAPWA	National Association of People with AIDS
NASBA	Nucleic acid sequence-based amplification
NDVL	Nondetectable viral load
NFV	Nelfinavir
NGO	Non-governmental organization
NIAID	National Institute of Allergy and Infectious Diseases
NICHD	The Eunice Kennedy Shriver National Institute of Child Health and Human Development
NIH	National Institutes of Health
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NOS	Not otherwise specified
nPEP	Nonoccupational postexposure prophylaxis
NQC	National Quality Center

NQF	National Quality Forum		**PHQ**	Patient Health Questionnaire
NRTI	Nucleoside reverse transcriptase inhibitor		**PI**	Protease inhibitor
NSAID	Nonsteroidal anti-inflammatory drug		**PID**	Pelvic inflammatory disease
NST	Non-stress test		**PI/r**	Ritonavir-boosted protease inhibitor
NTD	Neural tube defect		**PK**	Pharmacokinetic
NtRTI	Nucleotide reverse transcriptase inhibitor		**PML**	Progressive multifocal leukoencephalopathy
N/V	Nausea/vomiting		**PMTCT**	Prevention of mother-to-child transmission
NVP	Nevirapine		**po**	By mouth
OB	Obstetric		**PPD**	Purified protein derivative
OB-GYN	Obstetrics and gynecology		**PPI**	Proton pump inhibitor
OC	Oral contraceptive		**PPSV-23**	Pneumococcal vaccine
OI	Opportunistic infection		**PrEP**	Pre-exposure prophylaxis
OPV	Oral polio vaccine		**PRN**	As needed
OR	Odds ratio		**PT**	Prothrombin time
OTC	Over-the-counter		**PTSD**	Post-traumatic stress disorder
PACTG	Pediatric AIDS Clinical Trials Group		**pt-y**	Patient years
PAIN	Perianal dysplasia or intraepithelial neoplasia		**PTU**	Propylthiouracil
			PZA	Pyrazinamide
PAPP-A	Pregnancy-associated plasma protein A		**q**	Every
			QA	Quality assurance
PATH	Program for Appropriate Technology in Health		**qd**	Once per day
PCN	Penicillin		**QI**	Quality improvement
			qm	Once per month
PCP	*Pneumocystis jirovecii* [formerly *carinii*] pneumonia		**qod**	Once every other day
			QTc	Q-T corrected
PCR	Polymerase chain reaction		**qw**	Once per week
PD	Peritoneal dialysis		**RTV (also /r)**	Ritonavir
PEC	Preeclampsia		**RAL**	Raltegravir
pegIFN	Pegylated interferon		**RBC**	Red blood cell
PEP	Postexposure prophylaxis		**RBT**	Rifabutin
PEPFAR	President's Emergency Plan for AIDS Relief		**RBV**	Ribavirin
PGL	Persistent generalized lymphadenopathy			

REACH	Reaching for Excellence in Adolescent Care and Health		**TDF/FTC/ EFV**	Tenofovir/emtricitabine/ efavirenz
RIBA	Recombinant immunoblot assay		**TDM**	Therapeutic drug monitoring
RIF	Rifampin		**TG**	Triglycerides
RNA	Ribonucleic acid		**tid**	Three times per day
RPR	Rapid plasma reagin		**tiw**	Three times per week
RPV	Rilpivirine		**TMP**	Trimethoprim
RR	Relative risk		**TMP-SMX or TMP-SMZ**	Trimethoprim-sulfamethoxazole
RT	Resistance testing		**TPV**	Tipranavir
SAMHSA	Substance Abuse and Mental Health Services Administration		**TPV/r**	Ritonavir-boosted tipranavir
SBP	Systolic blood pressure		**TQM**	Total quality management
SC	Subcutaneous		**TSH**	Thyroid-stimulating hormone
SD	Standard dose		**TSS**	Toxic shock syndrome
sdNVP (also SDNVP)	Single dose nevirapine		**TST**	Tuberculin skin test
SIL	Squamous intraepithelial lesion		**UCSF**	University of California, San Francisco
SL	Sublingual		**UFH**	Unfractionated heparin
SMX or SMZ	Sulfamethoxazole		**UGT1**	Uridine 5'-diphospho-glucuronosyltransferase 1
SQV	Saquinavir		**UNAIDS**	Joint United Nations Programme on HIV/AIDS
SQV/r	Ritonavir-boosted saquinavir		**UNICEF**	United Nations Children's Fund
SS	Single strength		**USAID**	U.S. Agency for International Development
SSRI	Selective serotonin reuptake inhibitor		**USPHS**	U.S. Public Health Service
STD	Sexually transmitted disease		**UTI**	Urinary tract infection
STI	Sexually transmitted infection		**VAIN**	Vaginal intraepithelial neoplasia (aka vaginal dysplasia)
T-20	Enfuvirtide		**Vd**	Volume of distribution
TB	Tuberculosis		**VDRL**	Venereal disease reaction level
TCA	Trichloroacetic acid (Ch. 6)		**VIA**	Visual inspection with acetic acid
	Tricyclic antidepressant (Ch. 13)		**VIN**	Vulvar intraepithelial neoplasia (aka vulvar dysplasia)
TdaP	Tetanus-diphtheria-pertussis vaccine		**VL**	Viral load
TE	Toxoplasmic encephalitis			
TDF	Tenofovir			

VOICE	Vaginal and Oral Interventions to Control the Epidemic
VTE	Venous thromboembolism
VVC	Vulvovaginal candidiasis
VZIG	Varicella-zoster immune globulin
VZV	Varicella zoster virus
WBC	White blood cell
WHO	World Health Organization
WIHS	Women's Interagency HIV Study
WITS	Women and Infant Transmission Study
WORLD	Women Organized to Respond to Life-threatening Disease
wt	Weight
y	Year
ZDV	Zidovudine

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Chapter 1:

Epidemiology and Natural History of HIV Infection in Women

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Chapter 1: Epidemiology and Natural History of HIV Infection in Women

Chapter 1 at a Glance

The Global Epidemic of HIV Among Women

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In 2008, the Joint United Nations Programme on HIV/AIDS estimated that 15.7 million women worldwide were living with HIV infection and that about half of all people living with HIV infection are women (Figure 1-1). Although HIV remains a major global health threat, the epidemic is highly regionalized in terms of overall prevalence, demographics, access to therapy, and modes of transmission. What follows is an overview of the epidemic, focusing on major trends, particularly trends among women.

Major Trends

Figure 1-1

Percentage of Women Aged ≥15 Years Living With HIV by Geographic Region, 1990–2007
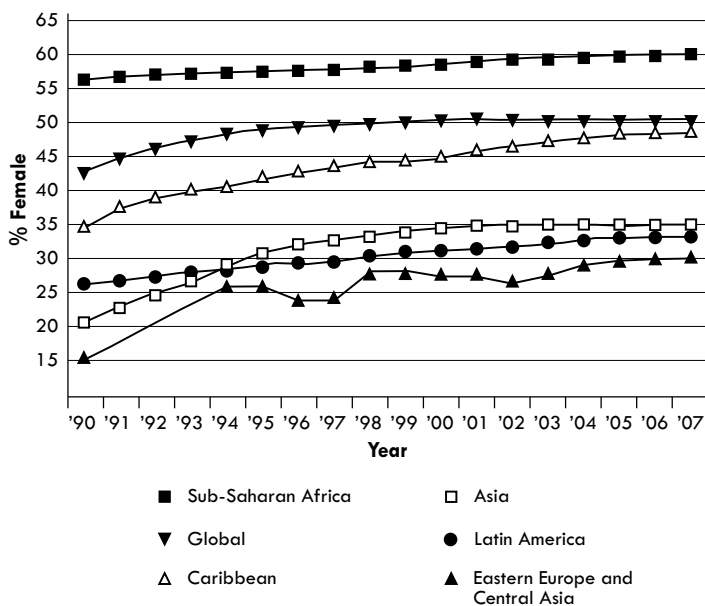
Source: UNAIDS/World Health Organization (WHO). *AIDS Epidemic Update*. 2009. Reprinted with permission.

Beyond the overall feminization of the HIV epidemic and the epidemic's continued impact on years of life lost among women, several other trends are now obvious as well.

Prevalence

The prevalence of HIV infection among women has increased in several regions, most notably sub-Saharan Africa, where almost 60% of cases occur in women and girls. However, at least seven African countries are meeting epidemic-control goals for the first time, with the prevalence of HIV infection among pregnant women aged 15–24 years now below 25%.

The worldwide HIV epidemic continues to afflict young women; at the same time, the number of women who acquired HIV infection at birth is slowly rising. In the United States, the largest number of new cases of HIV infection was in women and girls aged 13–29 years, but the highest prevalence of HIV infection was among women aged 30–39 years (*Diagnoses of HIV Infection and AIDS in the United States and Dependent Areas*, 2009. U.S. Centers for Disease Control and Prevention [CDC]; http://www.cdc.gov/hiv/surveillance/resources/reports/2009report/. Accessed 7/31/2012).

HIV infection in children peaked between 2000 and 2002 and has slowly decreased since 2003, most dramatically in areas where screening and treatment of pregnant women are common (*Diagnoses of HIV Infection and AIDS in the United States and Dependent Areas*, 2009. CDC).

Focused or "concentrated" epidemics: In several regions, focused epidemics among injection drug users are expanding to include heterosexual women, a pattern of evolution that introduces HIV into a huge population pool in which individual behaviors may not be overtly high risk. In Eastern Europe and Russia, a rapidly growing HIV epidemic is linked to injection drug use (IDU) and is currently extending into heterosexual young women who often lack the skills needed to assess risk and advocate for themselves (*J Urban Health* 2009;86 Suppl 1:121; *Eur J Public Health* 2011;21(5):613).

Declines in transmission: Recent declines in transmission to women have been clearly documented in three countries: the Dominican Republic, Tanzania, and Zambia (*AIDS Epidemic Update*. UNAIDS/World Health Organization (WHO). 2009). However, the prevalence of risk behaviors such as sex with a person who was not a spouse or a coresident has increased in some locations; thus, sustained control of the HIV epidemic among women in high-prevalence regions is far from assured.

Aging

Numbers increasing: The number and proportion of HIV cases in people aged ≥50 years has increased steadily since the introduction of potent antiretroviral therapy (ART) in high-resource areas. In the United States, before 2000, fewer than 10% of people living with HIV were aged ≥50 years; in 2007, however, 24% of those living with HIV infection were ≥50 and 16% of all HIV/AIDS diagnoses were made in that age group (calculations done on data in *Diagnoses of HIV Infection and AIDS in the United States and Dependent Areas*, 2009).

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The distribution of cases by race and location among older women is similar to that among women as a whole, although in the United States the prevalence of a history of IDU is lower among younger women living with HIV compared with older women. This pattern occurs in Europe as well; however, data documenting aging among HIV cases in resource-limited settings are sparse.

True incidence unknown: Although the number of infections identified in the ≥50 age group has increased, as has the total number of persons with HIV who are living to ages ≥50, the true *incidence* of HIV infections among people aged ≥50 years is not known. When compared with younger people, however, those aged ≥50 years are more likely to have clinical AIDS at the time of HIV diagnosis and they tend to have a shorter survival after diagnosis.

Current U.S. screening guidelines recommend routine opt-out screening of people aged 13–64 years. This is important because risk-based screening will miss many asymptomatic older women with HIV, who often do not have recognized risk factors.

Menopause: The emergence of HIV cases among women who are progressing through menopause raises new issues for clinicians, researchers, and patients. Conditions related to aging that may be promoted by HIV, such as cardiovascular disease, must be managed, as must metabolic perturbations (e.g., diabetes, bone demineralization) and neurocognitive deficits. In women, the effects on immune function of hormonal changes or hormonal replacement therapy must also be monitored and managed.

Sexual activity: Compared with younger women, older women are less sexually active and are less likely to use condoms and other risk-reduction strategies (*J Acquir Immune Defic Syndr* 2003;33 Suppl 2:S122; *Health Care Women Int* 1997;18(4):343). With the availability of drugs that support sexual function in men, however, rates of sexual activity among older women may increase. Thus, although older sexually active women are at risk for HIV infection, the precise extent of that risk is not known.

Demographics

Greater diversity among women: In resource-rich countries, the demographic characteristics of HIV and AIDS cases have been heavily influenced by the large proportion of infections among men who have sex with men, many of whom are educated and economically stable. However, patterns of cases among women demonstrate a much greater representation of ethnic minorities and people who are poor, less educated, mentally ill, and/or drug dependent, all of which are factors that may limit personal autonomy when it comes to making key decisions, including decisions related to sexual behavior. Among new HIV diagnoses in US women in 2011 63% were black/African-Americans, 17% Hispanic/Latino and 17% white; in the US population as a whole, 66% of women are white, 15% are Hispanic/Latino and 12% are black/African American (http://www.cdc.gov/hiv/library/slideSets/index.html) (accessed 05/14/2013).

In resource-limited countries, HIV cases among women can be linked with commercial sex work (often in an effort to support a family), social disruption, violent conflict, governmental policies, and/or local culture that tends to limit women's economic or sexual autonomy. For example, in some locations, married women do not have the right to refuse sex. In other areas, social and economic sanctions associated with widowhood, divorce, or HIV infection can promote denial of infection or avoidance of testing. Lack of autonomy over key personal decisions is a common theme among populations of women affected by HIV.

Key Trends in HIV Epidemiology Among Women

- The proportion of HIV cases among women is increasing globally, led by increases in sub-Saharan Africa and the Caribbean region.
- Some countries have demonstrated decreases in the incidence of new HIV cases among young women and children, which indicates that intensive public health interventions can be effective.
- In areas in which IDU has been the major means of HIV transmission, new trends show extension of the epidemic to young, heterosexually active women.
- The largest number of new cases and the highest HIV prevalence rates are among young women in their childbearing years.
- Increased survival related to potent ART has resulted in a substantial increase in cases among women aged ≥50 years; the incidence of new infections among women in this age group is largely undefined.

HIV Transmission to Women

Patterns of Transmission

Although sexual intercourse is a common occurrence in the general population, the estimated average HIV transmission rate per intercourse event is low. Tracking studies indicate that the likelihood of transmission is highly variable among individuals and that high rates of transmission occur in specific situations. Table 1-1 summarizes the risk of HIV transmission to women through heterosexual intercourse in various situations. Epidemiologic patterns of HIV transmission are summarized in Table 1-2.

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Table 1-1

Risk of HIV Transmission to Women Per Sexual Contact Event

Exposure	Transmission Probability Per Act
Any male to female vaginal intercourse	0.124 (0.078-0.199)
No commercial sex, male to female intercourse	0.143 (0.088-0.233)
Commercial sex, male to female intercourse	0.051 (0.020-0.131)
High-income countries, male to female intercourse	0.081 (0.060-0.109)
Low-income countries, male to female intercourse	0.193 (0.086 – 0.433)

Source: *Lancet Infect Dis* 2009; 9:118

Table 1-2

Epidemiologic Patterns of HIV Transmission

Pattern	Unique Characteristics	Related Factors	Regions
Epidemic* heterosexual	Risk often not recognized; often related to high-risk male partner	Poverty, lack of women's sexual and economic autonomy, sex work	Worldwide
Endemic† heterosexual	Seen in high-prevalence areas; affects general population of women	Poverty, lack of women's sexual and economic autonomy, sex work	High-prevalence epidemics in sub-Saharan Africa, Caribbean, Asia
Drug use predominant	IDU is major factor; often coincides with high rates of viral hepatitis; often overlaps with sexual risk	Poverty and sex work; bridging to non-IDU, especially among young women	Worldwide, notably in Eastern Europe and Russia; current rapid expansion of epidemic
Perinatal	Most common cause of HIV infection in children; some perinatally infected infants are now adults	Preventable with use of ART drugs; greatly diminished in high-resource countries and some lower-resource countries; failure to screen pregnant women is major risk factor for ongoing transmission	Worldwide; large epidemic in sub-Saharan Africa
Occupational	Usually preventable; PrEP is available	Rare; implementation of universal body fluid precautions can prevent most exposures	Worldwide

Table 1-2	*continued*		
Epidemiologic Patterns of HIV Transmission			
Pattern	**Unique Characteristics**	**Related Factors**	**Regions**
Iatrogenic	Related to poor medical practices (e.g., inadequate blood screening, unsafe injection practices)	Failure of adequate blood product handling, sterilization procedures; re-use of needles/syringes for injections; children often affected	Often seen in local epidemics, primarily in Eastern Europe and sub-Saharan Africa; cannot sustain epidemic as single mode of transmission

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

* Epidemic: Cases exceed the expected pattern in a population over a defined time period

† Endemic: The habitual presence of a disease within a geographic area

(*Epidemiology: An Introductory Text.* Philadelphia: W.B. Saunders Company; 1974)

Factors Influencing HIV Transmission in Women

Partner infectivity: Infectivity is increased when male partners have a higher plasma viral load (VL), which has been linked to higher rates of HIV shedding in semen. Infectivity is highest during acute or recent HIV infection, when VL and viral shedding are maximal and host immune response is incomplete (*AIDS* 2007;21:1723). Exposure during early infection is estimated to account for half of all transmission events in North America (*J Infect Dis* 2007;195(7):951). Use of ART decreases the risk of HIV transmission between heterosexual partners; however, limited study size and infrequent events make precise assessment of the extent of protection difficult (*AIDS* 2009;23:1397). Results from HPTN 052, a randomized clinical trial designed to evaluate the efficacy of ART for the prevention of sexual transmission among serodiscordant couples, found that earlier initiation of ART, at CD4+ cell counts of 350–550 cells/mm^3, reduced HIV transmission to the uninfected partner (*N Engl J Med* 2011;365(6):493).

Number of partners and commercial sex: It has been demonstrated in multiple settings that being paid for sex is associated with higher rates of HIV infection. In a systematic review of data from multiple sub-Saharan African countries, the odds ratio for HIV infection for women who reported being paid for sex was 2.29 compared with women who had never been paid for sex (*PloS One* 2007;2(10):e1001).

For women, having a larger number of male sexual partners is also consistently associated with an increased risk for HIV infection, with the effect size dependent on the number of partners, the region, and the population prevalence of HIV. Female sexual partners of women appear to present minimal risk of HIV transmission (*AIDS* 1998;12:450).

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Genital tract infections: Many genital tract infections have been reported to increase both infectivity and susceptibility to HIV, including gonorrhea, *Chlamydia trachomatis*, bacterial vaginosis, trichomonal vaginitis, and human papillomaviruses (*J Reprod Immunol* 2008;77:32; *PLoS One* 2010;5(4):e10094). The most consistent and significant association is seen with genital ulcer diseases such as syphilis, chancroid, and genital herpes. Because genital herpes simplex is the most prevalent cause of genital ulcers and is a chronic infection, it likely has the strongest and longest duration of influence on an individual's susceptibility to acquisition of HIV infection. Chen and colleagues, in a systematic review of published reports, found that having herpes simplex type 2 infection (usually genital) increased the odds of HIV infection 3.69-fold as compared with not having genital herpes (95% confidence interval, 2.78–4.89); the increase in the likelihood of infection was similar for both men and women (*PloS One* 2007; 2(10):e1001).

Region: Although significant regional differences exist in the predominant means and risk factors for HIV infection, all regions demonstrate multiple transmission modalities, which over time tend to extend into populations of young sexually active persons and often disproportionately afflict the poor.

Use of hormonal contraceptives or spermicides: Studies of the effects of hormonal contraceptives on susceptibility to sexually transmitted HIV infection have yielded mixed results (*AIDS* 2007;21:85; AIDS 2007;21:1771). A consensus is emerging, however, that oral estrogen-progestin contraceptives do increase susceptibility to HIV (*Endocr Rev* 2010;31(1):79). The evidence is even more consistent that depot medroxyprogesterone acetate (DMPA), an injectable progestin-only contraceptive, increases the risk of HIV acquisition. Studies of other progestin-only contraceptives and other delivery mechanisms are currently underway. Although further study is clearly warranted, hormonal contraception remains safe and highly effective for the prevention of unintended pregnancy and the promotion of reproductive autonomy, and the benefits are believed to strongly outweigh the risks. Use of the topical spermicide nonoxynol-9, which was evaluated as a candidate HIV microbicide, demonstrated a paradoxical increase in HIV susceptibility that was likely the result of increased genital tract inflammation (*J Acquir Immune Defic Syndr* 2005;40(1):1).

Pregnancy: Although the overwhelming volume of research and publications on pregnancy and HIV is focused on perinatal transmission, several studies indicate that pregnancy may be associated with increased rates of sexual HIV transmission to women (*Lancet* 2005;366:1182; *J Clin Virol* 2010; 48:180; *AIDS* 2009;23:1255), even when the analyses are controlled for sexual risk behaviors (*Lancet* 2005;366:1182). It is hypothesized that this heightened risk may be attributable to hormonal changes affecting the genital tract mucosa or immune responses. Condom use may also be less common during pregnancy, as many couples continue to view condoms primarily as a means of contraception. Healthcare providers must address appropriate preventive practices with at-risk pregnant women and be alert to signs and symptoms consistent with acute HIV infection during pregnancy. Surveillance for incident infections associated with pregnancy should extend to the postpartum period (*BMC Public Health* 2010;10:668) because women who are infected in late pregnancy may still be HIV seronegative at delivery.

Because of the possibility of increased susceptibility to HIV infection during pregnancy, and with the recent encouraging results with antiretroviral-based preexposure prophylaxis, it is important that pregnant women in HIV-discordant relationships be included in further testing of these interventions (see Chapter 7, *Preconception Care and Contraception*).

HIV Mortality in Women

Leading Cause of Death

Although the prevalence of HIV infection among women varies significantly by world region, AIDS remains a leading cause of death among women in many regions, including high-resource countries. Depending on age group, AIDS is among the top 10 causes of death for African-American and Hispanic women; among African-American women 25–54 years, HIV is the 4th leading cause of death (*Natl Vital Stat* Rep 2012;61(7):1).

AIDS deaths are a conservative indicator of the impact of HIV on women's survival because they are derived from statistics on deaths directly due to AIDS-defining conditions and do not include excess deaths due to non-AIDS conditions that are associated with HIV, such as cardiovascular disease, metabolic diseases, and malignancies. In addition, HIV is a prominent cause of years of life lost for women in the years of prime economic and childrearing activity.

Antiretroviral Therapy and Mortality

The prominence of AIDS as a cause of death among women has emerged during an era in which ART is generally available, which tends to refute the notion that the existence of effective treatment has diminished the major threat to women's health posed by HIV. Receipt of potent ART has been the strongest predictor of survival among women with HIV since those drugs were introduced in the 1990s. Even in populations with easy access to ART, however, excess deaths due to AIDS and non-AIDS conditions still occur among HIV infected patients, including women.

WIHS cohort: Sustained ART is associated with reduced AIDS and non-AIDS mortality. After the introduction of ART in the United States, the AIDS mortality rate within the WIHS, a large U.S. multisite observational cohort study of HIV in women, declined by almost 50%; however, HIV infection continued to be associated with AIDS deaths and with excess deaths due to heart disease and cancer (*J Acquir Immune Defic Syndr* 2009;51(4):399). Trauma/accidents/suicide and liver disease remain prominent causes of death among HIV infected and high-risk HIV uninfected WIHS participants. During the pre-ART era, HIV infected women demonstrated a lower incidence of breast cancer than did uninfected women; in the era of potent ART, however, breast cancer rates are equal in the two groups, perhaps owing to increased survival or other

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factors (*Clin Infect Dis* 2010; 51(8):957; *J Natl Cancer Inst* 2011;103(9):753; *Breast J* 2011;17(1):87). Use of alcohol and/or recreational drugs was also a predictor of mortality in WIHS participants (*Clin Infect Dis* 2007;44(2):287; *Addiction* 2005;100:990; *AIDS* 2008;22:1355).

Predictors of mortality: In the WIHS, CD4+ cell count below 200 cells/mm^3, VL of ≥1000 copies/mL, hepatitis B surface antigenemia, body mass index (BMI) <18.5, and a high depressive symptom score were each independently associated with mortality (*J Acquir Immune Defic Syndr* 2009;51(4):399). Hepatitis C infection was a predictor of mortality after the use of potent ART became commonplace, which is consistent with other observations that liver disease has become a prevalent cause of mortality among U.S. women whose survival with HIV infection is extended by ART. In resource-limited areas, low BMI and anemia are leading predictors of mortality after ART (*AIDS* 2006;20:2355; *S Afr Med J* 2007;97:587). In these settings, HIV infection continues to be associated with AIDS and non-AIDS mortality, with tuberculosis and CNS infections being the leading causes of death (*AIDS* 2006;20:1181).

Sex differences: In both the pre-ART and potent ART eras, there have been indications that HIV infected women have higher mortality rates than do their male counterparts. These findings, which result from studies conducted in both resource-rich and resource-poor countries, are sometimes attributed to sex differences in access to treatment, although in some studies the results were independent of treatment utilization (*J Infect Dis* 2009;199(7):991; *AIDS* 2005;19:357). Several reports have identified a difference in age at death between males and females, with peak deaths in females occurring 5–10 years earlier than in men (*S Afr Med J* 2007;97:587; *Lancet* 2008;371:1603); however, no clear independent sex difference in age at death has been seen in the setting of ART availability. Thus, although countered to some extent by studies that show no independent sex difference in survival among HIV infected adults in the ART era (*Clin Infect Dis* 2007;44(2):287; *AIDS* 2001;15:1115; *AIDS Patient Care STDS* 2007;21:321), the range of findings indicating higher mortality among women is cause for concern and warrants additional study.

Natural History of HIV Infection in Women

Staging of HIV Infection in Women

Case definitions for HIV infection—the criteria for diagnosis of HIV infection—are now based largely on serologic screening tests. The CDC issued its last case definition for AIDS in 1994. That definition incorporated the opportunistic infections, cancers, and wasting conditions that are closely linked with HIV infection and disease progression as evidenced by CD4+ lymphocyte cell depletion. The case definition also included invasive cervical cancer, a female-specific condition, as an AIDS-defining condition (in the presence of HIV infection) and chronic vaginal candidiasis and pelvic inflammatory disease as HIV-associated, but not AIDS-defining, conditions.

The CDC has recently revised the staging system and surveillance case definitions into a single case defintion sytem for HIV because of diagnostic and treatment improvements and to make the system simpler and easier to use (*MMWR* 2008;57(RR10):1–8). Clinical categories A and B have been eliminated, since many of the clinical conditions listed under these categories were not discrete diseases, were not necessarily indicators of immunosuppression, poorly matched current treatment guidelines and were not integrated into routine surveillance practices; furthermore, the role of CD4+ cell counts/percentages are central in the new system, as objective measures of immunosuppression and are routinely used in care. As with the older system, HIV disease progression is classified from less to more severe, and once cases are classified into a surveillance severity stage, they cannot be reclassified into a less severe stage. This system is intended for public health surveillance and not as guide for clinical diagnosis or care.

The CDC HIV/AIDS disease staging system (Table 1-3) assesses disease severity by CD4+ cell counts and by the presence of specific HIV-related conditions. By contrast, the WHO clinical staging and disease classification system (Table 1.4) is based on clinical findings that guide the diagnosis, evaluation, and management of HIV/AIDS. This staging system is particularly useful in resource-limited settings in which CD4+ testing or other laboratory-testing methods are not readily available and is used in many countries to assess eligibility for antiretroviral therapy.

Table 1-3

CDC Classification System for HIV-Infected Adults and Adolescents (2008)

Must meet laboratory criteria for HIV infection

Stage 1: no AIDS-defining condition and CD4+ cell count >/= 500 cells/microliter ot CD4+ % of total lymphocyte >/= 29%

Stage 2: no AIDS-defining condition and CD4+ cell count 200–499 cells/microliter or CD4+ % of total lymphocyte 14-28%

Stage 3 (AIDS): CD4+ cell count <200 cells/microliter or CD4+ % of total lymphocyte <14% or documentation of an AIDS-defining condition. Documentation of an AIDS-defining condition supersedes CD4+ cell count/%.

Stage Unknown: documented HIV infection but no information available on CD4+ counts/% or AIDS-defining conditions.

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Table 1-3	*continued*

CDC Classification System for HIV-Infected Adults and Adolescents (2008)

†Category C AIDS-Indicator Conditions

- Candidiasis of the bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical carcinoma, invasive, confirmed by biopsy
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 mo in duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Cytomegalovirus retinitis (with loss of vision) (may be diagnosed presumptively)
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcers (>1 mo in duration), or bronchitis, pneumonitis, or esophagitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 mo in duration)
- Kaposi sarcoma
- Lymphoma, Burkitt, immunoblastic, or primary central nervous system
- *Mycobacterium avium* complex or *Mycobacterium kansasii*, disseminated or extrapulmonary
- *Mycobacterium tuberculosis*, pulmonary or extrapulmonary
- *Mycobacterium*, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis jirovecii* (formerly *carinii*) pneumonia
- Pneumonia, recurrent
- Progressive multifocal leukoencephalopathy
- *Salmonella* septicemia, recurrent (non-typhoid)
- Toxoplasmosis of brain
- Wasting syndrome caused by HIV (involuntary weight loss >10% of baseline body weight) associated with either chronic diarrhea (≥2 loose stools per day for ≥1 mo) or chronic weakness and documented fever for ≥1 mo

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Source: *MMWR* 2008;57(RR10):1–8.

Table 1-4

World Health Organization HIV/AIDS Clinical Staging and Disease Classification System

Primary HIV Infection

- Asymptomatic
- Acute retroviral syndrome

Clinical Stage 1

- Asymptomatic
- PGL

Table 1-4   *continued*

World Health Organization HIV/AIDS Clinical Staging and Disease Classification System

Clinical Stage 2

- Moderate unexplained weight loss (<10% of presumed or measured body weight)
- Recurrent respiratory infections (sinusitis, tonsillitis, otitis media, and pharyngitis)
- Herpes zoster
- Angular cheilitis
- Recurrent oral ulceration
- Papular pruritic eruptions
- Seborrheic dermatitis
- Fungal nail infections

Clinical Stage 3

- Unexplained severe weight loss (>10% of presumed or measured body weight)
- Unexplained chronic diarrhea for >1 mo
- Unexplained persistent fever for >1 mo (>37.6°C, intermittent or constant)
- Persistent oral candidiasis (thrush)
- Oral hairy leukoplakia
- Pulmonary tuberculosis (current)
- Severe presumed bacterial infections (e.g., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia)
- Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis
- Unexplained anemia (hemoglobin <8 g/dL)
- Neutropenia (neutrophils <500 cells/mcgL)
- Chronic thrombocytopenia (platelets <50,000 cells/mcgL)

Clinical Stage 4

- HIV wasting syndrome, as defined by CDC (see Table 1-3)
- *Pneumocystis* pneumonia
- Recurrent severe bacterial pneumonia
- Chronic herpes simplex infection (orolabial, genital, or anorectal site for >1 mo or visceral herpes at any site)
- Esophageal candidiasis (or candidiasis of trachea, bronchi, or lungs)
- Extrapulmonary tuberculosis
- Kaposi sarcoma
- Cytomegalovirus infection (retinitis or infection of other organs)
- CNS toxoplasmosis
- HIV encephalopathy
- Cryptococcosis, extrapulmonary (including meningitis)
- Disseminated nontuberculosis mycobacteria infection
- Progressive multifocal leukoencephalopathy
- Candida of the trachea, bronchi, or lungs
- Chronic cryptosporidiosis (with diarrhea)
- Chronic isosporiasis
- Disseminated mycosis (e.g., histoplasmosis, coccidioidomycosis, penicilliosis)
- Recurrent nontyphoidal *Salmonella* bacteremia
- Lymphoma (cerebral or B-cell non-Hodgkin)
- Invasive cervical carcinoma
- Atypical disseminated leishmaniasis
- Symptomatic HIV-associated nephropathy
- Symptomatic HIV-associated cardiomyopathy
- Reactivation of American trypanosomiasis (meningoencephalitis or myocarditis)

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Source: AIDS Education & Training Centers National Resource Center. *HIV Classification: CDC and WHO Staging Systems.* 2012

Natural History of HIV Infection in the Absence of Antiretroviral Therapy

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Sex differences: Sex differences exist in CD4+ lymphocyte counts among HIV infected and uninfected individuals; when corrections can be made for differences in the extent of disease progression, females have CD4+ cell counts that are approximately 100 cells/mm3 higher than those of males early in HIV infection (*Clin Infect Dis* 2002;35(3):313). Assessing sex differences in rates of viral replication and plasma HIV RNA levels (VL) is more complex. Early in the course of HIV infection, females have lower HIV VLs than do males (*AIDS* 2007;21:835; *Clin Infect Dis* 2002;35(3):313). Because VL is a predictor of disease progression, a lower VL in females should be followed by slower progression as indicated by declines in CD4+ cell counts and clinical progression; however, no significant differences in rates of progression by sex have been identified (*Am J Epidemiol* 2008;168(5):532; *AIDS* 2003;17:353; *J Infect Dis* 1999;180:1018; *Lancet* 1998;352:1510). It appears, therefore, that females have better control of HIV replication than do males early in HIV infection, but lose this control later and progress more rapidly, thus catching up to their male counterparts. One clue to this loss of immunologic advantage was provided by Altfeld and colleagues, who reported that women have significantly more vigorous dendritic cell responses to HIV, which leads to greater CD8+ cell activation. CD8+ cell activation may result in the early control of HIV replication, but over time it could produce a chronic inflammatory state and increased lymphocyte loss (*Nat Med* 2009;15:955).

Host immune response: Variations in the pattern of HIV disease progression in the absence of ART are the focus of many studies that seek to characterize host immune responses to HIV. Much interest has been directed at *HIV controllers or elite controllers*, i.e., people whose CD4+ cells remain normal and stable and who have very low or undetectable VLs after HIV infection in the absence of ART. Because women tend to have higher CD4+ cell counts and lower HIV RNA levels than men, at least in the early stages after initial infection, one might expect sex differences in HIV control to exist. Such differences, however, have not been identified (*J Virol* 2009;83:329; *Immunity* 2007;27:406; *AIDS Res Ther* 2007;4:11), perhaps because natural HIV controllers are few in number and therefore studies of natural HIV control are small. Anecdotal reports indicate that sex differences exist in the prevalence of natural controllers, with a somewhat higher occurrence among women, but further study is needed.

Disease Progression in the Era of Antiretroviral Therapy

Sex differences in CD4+ cell counts persist after the initiation of ART; if these parameters form the basis for assessing ART outcome, women tend to fare better (*AIDS* 2007;21:835; *J Antimicrob Chemother* 2007;60(4):724; *AIDS Res Hum Retroviruses* 2010;;26:133). Most ART clinical trials, however, are not adequately powered to assess sex differences. The CASCADE Collaborative, which assessed sex differences in the survival of adult seroconverters in Europe, Canada, and Australia, concluded that ART increased the survival advantage of women, though sex differences existed in ART use and the results were not

adjusted for adherence (*Am J Epidemiol* 2008;168(5):532). In Europe, as in the United States, HIV risk factors and access to care appear to contribute to sex differences in HIV mortality during the ART era (*Int J Epidemio1* 2010;39:135; *J Epidemiol Community Health* 2004;58(11):944). In general, ART viral suppression does not differ by sex, and many reported sex differences in outcome disappear when the analysis is adjusted for treatment (*Clin Infect Dis* 2009;49:1570; *Lancet* 2003;362:1267; *J Womens Health (Larchmt)* 2007;16(7):1052). For both women and men, the use of ART is the strongest predictor of survival in HIV infection.

Influence of Pregnancy, Exogenous Steroids, and Aging

In both HIV infected and uninfected women, the absolute number of CD4+ lymphocytes temporarily declines during the third trimester of pregnancy as a result of hemodilution, but the CD4+ percentage remains relatively stable. No differences in overall HIV disease progression have been found to be related to pregnancy (*AIDS* 2005;19:357). Whether the use of hormonal contraception influences HIV disease acquisition or course is a controversial topic on which data conflict (see Chapter 7, **Preconception Care and Contraception**). Because sex steroids are important immune mediators, it is plausible that the changing hormone levels associated with menopause or hormone replacement therapy may influence the course of HIV infection. Data that might shed light on this issue are not currently available. Aging is associated with more rapid progression of untreated HIV disease, and sex differences in this phenomenon have not been reported (*Am J Med* 2008;121:1032; *J Am Geriatr Soc* 2009;57:2129).

Case Detection in Women

Unrecognized Risk

In resource-rich countries, most men with HIV report risk factors for infection such as sex with other men or parenteral drug use. For a woman, however, risk for HIV may be determined by the (often unknown) behavior of a male sexual partner or partners. In 2009, women accounted for 24% of new HIV infections in the United States, a figure that is likely to be artificially low because providers and patients underestimate the risk of HIV infection and may not test for it. For 2009, the CDC reported that heterosexual contact was the risk factor for 85% of women with HIV infection, IDU was associated with 15% of cases, and less than 1% of cases had no clear risk factor (*Diagnoses of HIV Infection and AIDS in the United States and Dependent Areas*, 2009. CDC; http://www.cdc.gov/hiv/surveillance/resources/reports/2009report/. Accessed 7/19/12.

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The process of risk assignment in this report differed significantly from past years in that cases reported with no known risk factor were assigned a likely risk factor, which for most women is heterosexual contact. The revised data, however, should not be seen as indicating that HIV infected women are now more likely to be aware that they are at risk for heterosexually acquired HIV infection. Prior to the adoption of the imputation approach, 30%–40% of HIV infected women had no recognized HIV risk factor.

It is likely that women frequently are unaware of their risk for HIV infection because that risk is related to the drug use or sexual behaviors of a male sexual partner or partners. Without awareness of their risk for HIV infection, women often do not express concerns about HIV or seek out screening. Routine HIV screening, in which HIV testing is included as part of routine healthcare, is an important means of increasing case recognition and access to early HIV treatment among women. In the absence of routine screening, HIV cases in women tend to be detected at the time of pregnancy or presentation of an AIDS-defining condition. Both scenarios represent lost opportunities for early treatment and prevention of transmission to others, because women may be less likely than men to delay entry into care once HIV infection has been detected (*AIDS Patient Care STDS* 2009;23:765).

Key Points on Natural History of HIV in Women

- Among HIV infected adults, women have higher CD4+ cell counts than men.
- During early infection, women have lower VLs than men, but this difference disappears as infection continues. Differences in CD8+ cell activation may explain some of the sex differences in VL.
- Overall, the rate of progression of HIV disease appears to be similar in women and men.
- Receipt of ART is the strongest predictor of survival with HIV among both women and men.
- Women and men respond to ART similarly; differences in outcomes are often related to drug use and access to treatment.

Summary

A Global Women's Health Problem

Even in resource-rich regions, HIV is a leading cause of death for women. Moreover, the number of HIV-related deaths among women is much higher when HIV-associated but non–AIDS-defining conditions are also considered. HIV kills women who are at the peak of their social and economic productivity. HIV, therefore, must be considered a major health concern for women.

Autonomy is Key

Reducing the incidence of HIV infection in women and improving access to treatment requires increased autonomy among vulnerable women. Autonomy can be viewed broadly as control over one's life and decision making, including decisions about sexuality and health, and depends on cultural factors, access to educational resources, and enlightened public policy. Women's autonomy, especially in matters of sexuality and health, also requires the availability of resources such as drug and mental health treatment that can assist women in avoiding drug use, violence, and coercive sex. Autonomy is also related to the acquisition of personal skills that support young women's ability to adhere to safe-sex practices and assess the risk of specific situations. Biological factors such as sexually transmitted infections and male-partner VL are important, but Dworkin and others have persuasively argued that the paradigm of risk for HIV infection in women should be extended to include social vulnerability (*Am J Public Health* 2010;100:435).

Routine HIV Screening Is Essential

Most women acquire HIV infection from a male sexual partner, and this trend is increasing. Furthermore, because many women are not aware that a male partner is HIV infected or at risk, risk-based screening is likely to miss cases of HIV among women. Making HIV screening a routine part of medical and reproductive healthcare for adolescents and adults is an important way to improve the ability to identify and provide care and treatment to women early in the course of HIV infection. Achievement of this goal is crucial for control of the HIV epidemic in women.

2

Chapter 2:

Approach to the Patient

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Chapter 2: Approach to the Patient

Chapter 2 at a Glance

The Woman With HIV Infection

2

She could be any woman: The woman with HIV infection is not distinguishable from most women seen in primary care today. She may be any age or color, live anywhere, have any cultural background, and have any level of education and income. She has all the health and lifestyle concerns that any other woman has. She is often asymptomatic, and she may not know she is infected. Often, she is a mother and a caretaker for other family members.

HIV is just one part of her life: The issues most important to the woman with HIV will be shaped by her personal circumstances. HIV is just one aspect of an infected woman's life; the perception of its role in her life will vary from woman to woman and from time to time. The healthcare provider–patient relationship begins with the particular circumstances and needs of each individual woman. To be most effective, that relationship must become a partnership based on mutual trust and respect.

This chapter reviews general guidelines for healthcare provider interactions with all patients, highlighting points that are particularly relevant to women with HIV infection. It also provides an overview of the initial and ongoing medical and psychosocial evaluation of women with HIV and discusses the changes in models of care as HIV has evolved into a chronic disease.

General Guidelines

Communication

Clear and nonjudgmental: The initial interaction of patient and provider should begin with introductions, and ensuing communications should be clear and nonjudgmental. The care provider's language and terminology should be sensitive, inoffensive, and easily understood by the patient. A patient's ability to understand what is being said to her will vary according to her age, cultural background, and level of education. Translation (of written materials) and/or interpretation (of speech) will be needed for women who are not able to understand or express themselves adequately in the language of the medical provider.

Whenever possible, questions should be asked in an open-ended manner, including questions about behavior and treatment adherence, and the patient should be given permission to be honest and to acknowledge failure with regard to relapse or nonadherence. She should be given adequate time and opportunity to ask questions and express concerns.

Written instructions: Patients should be given written instructions that detail how to make appointments and how to reach the care provider when there is a problem or when the patient has questions. Whenever possible, patients should be provided with written information about HIV and its treatment as well as with information about other health issues to supplement face-to-face discussions.

Communication for the gynecologic exam: Women undergoing gynecologic exams may feel especially anxious, vulnerable, or embarrassed, or they may fear discomfort or the discovery of pathology. This anxiety and vulnerability may be particularly pronounced in women with a history of sexual abuse, rates of which are greater in some populations of women living with HIV. If a woman needs additional time to develop trust and overcome anxiety, then the gynecologic exam may have to be postponed until a subsequent visit.

Adequate preparation for the exam is important. The care provider should explain what will be done and why, and he or she should explain the amount of discomfort the woman may experience. The process may be demystified by showing the patient charts, models, or equipment (such as specula). During the exam, before doing anything, the care provider should tell the patient what is going to happen next, and then describe what s/he sees or feels during the exam. The patient should be reassured when findings are normal.

Nonverbal communication: The importance of nonverbal communication should not be underestimated. Facial expression and body posture often convey far more than words. The most effective care providers are sensitive to these cues and use their own body language with care. Maintaining frequent eye contact encourages the patient's candor, builds rapport and trust, helps allay embarrassment and fear, and conveys a care provider's interest and attention.

Respect

Every patient deserves respect: Care providers should never be condescending, patronizing, or judgmental toward patients. Under no circumstances should a patient be treated as a sexual object. Although different circumstances may dictate different levels of formality, addressing a patient by her first name (without her express consent) or, especially, by terms of endearment (e.g., "honey" or "dear") is usually inappropriate and offensive.

Respect for the patient includes respect for her beliefs and values. The use of complementary therapies among HIV infected patients is common and should be respected, not ridiculed. This respect should be maintained even if a care provider must discourage potentially harmful remedies and emphasize the proven effectiveness of currently recommended regimens.

Sensitivity

Essential to effective care: Sensitivity is essential to a care provider's ability to gather and impart important information, foster trust, and ensure ongoing follow-up. It requires attention to how words are used, how questions are asked, and what body language and other unspoken aspects of communication convey. Responding to a patient's fear, anxiety, denial, or anger is an inevitable part of the health provider's role, and it requires consideration of the whole person and the entire context of her life, not just of her disease process. Any chronic and life-threatening disease carries with it an enormous burden of vulnerability and loss of control. Anything a care provider can do to give back some control to the woman will help ease that burden. The

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importance of adherence to antiretroviral therapy (ART) regimens for optimal effectiveness and for reduced potential for drug resistance has been well established. Taking into account a patient's values and lifestyle (e.g., work schedule, child care obligations) when choosing a treatment regimen may enhance adherence. In addition, understanding a woman's cultural background will enhance a care provider's sensitivity. For example, among Hispanic women, it is often important and reassuring when a patient's spouse or mother is involved during visits.

Confidentiality

Confidentiality is a cornerstone of the therapeutic relationship. It carries special meaning for HIV infected individuals, who may have experienced discrimination in the workplace and other settings, stigmatization, or even abandonment by friends or family. HIV infected women may be particularly vulnerable to the effects of stigma because of lower economic status, cultural traditions, general societal beliefs about the role of women, minority status, and child care or other caretaking responsibilities. Information about a patient's HIV status or details about her medical condition should be kept strictly confidential by providers and shared only with the express permission of the patient. At the same time, the patient should be encouraged and assisted in disclosing her status to others who need to know, such as sexual partners and healthcare providers.

Reporting: All States require reporting of AIDS cases, and in all 50 States, the District of Columbia, and six dependent areas, HIV cases are reported confidentially by name. The need to report and the safeguards of confidentiality that are in place should be discussed with each woman. The Health Insurance Portability and Accountability Act (HIPAA) of 1996 furthermore provides a federal mandate and standards for the protection of certain health information, addressing the use and disclosure of individuals' health information and standards for individuals' privacy rights to understand and control how their health information is used (See: http://www.hhs.gov/ocr/privacy/hipaa/understanding/summary/index.html).

Evaluation of the HIV Infected Woman

Team Approach

A complex disease: Because HIV disease is medically and socially complex, a team approach is essential to the care of women with HIV, and care should be coordinated and integrated with all members of the team. Moreover, as the time that primary care providers have available to spend with individual patients grows ever more limited, the role of other team members in educating and supporting women with HIV is becoming more important.

Multispecialty care: The expertise needed to provide care for women with HIV includes specialists in HIV medicine (including management of ART), gynecology, nursing, pharmacy, counseling, and social service assistance and case management. Primary medical management of HIV may be provided by physicians and, increasingly, by nurse practitioners or physician assistants with appropriate training and supervision. Throughout the course of HIV infection, multidisciplinary medical collaborations should be available for evaluation and management of the varied medical problems associated with HIV. As HIV has become a chronic disease, the inclusion of the patient and her family or other personal supporters as part of the team is ever more important. The involvement of peer counselors may be especially useful for helping women deal with the complexities of negotiating safer sexual practices, contraception and other reproductive concerns, medication adherence, and other issues where similar cultural background and personal experience with HIV may facilitate candid discussion and education.

HIV Experience

HIV expertise improves outcomes: Patients have better outcomes when their care, including ART, is managed by healthcare providers with expertise in treating HIV. Care provider experience is one of the few factors (specific to either providers or healthcare systems) that has been shown over time to increase the likelihood that a patient will receive effective ART and to prolong the life of people with HIV infection (*N Engl J Med* 1996; 334:701; *AIDS* 1998;12:417; *Arch Intern Med* 2005;165:1133). Care provider experience is increasing in importance as antiretroviral (ARV) management becomes steadily more complicated. Awareness of drug interactions and the ability to prevent and manage ARV-related adverse effects and drug resistance have significant effects on the short- and long-term health of HIV infected patients.

Role of primary care providers: As women with HIV infection live longer, the role of their primary care provider in treating other medical conditions is critical. When a woman must be referred to an HIV expert, it is important that her primary care provider assure the patient that she is not being abandoned. Primary care providers who have little or no experience treating patients with HIV, including providers in communities or geographic areas where there is a shortage of HIV expertise, should make referrals to and consult with HIV experts to ensure optimal patient care. Part C & D of the Ryan White HIV/AIDS Program funds clinics that can serve as resources for identifying experienced HIV providers and healthcare sites. The list of Ryan White–funded programs, including Part C & D programs, can be found at the website http://hab.hrsa.gov/.

HIV specialist care: Current U.S. Public Health Service (USPHS) treatment guidelines can be accessed at www.aidsinfo.nih.gov; many of these guidelines are living documents that are updated regularly online. The Health Resources and Services Administration also supports the AIDS Education and Training Centers warmline (800-933-3413), which is a resource for clinicians who need expert consultation. The HIV Medicine Association of the Infectious Diseases Society of America has outlined several qualifications that HIV physicians should meet to demonstrate appropriate experience, including direct care of at least

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25 HIV infected patients over 36 months and completion of at least 10 hours of Category 1 continuing medical education credits per year. The American Academy of HIV Medicine offers HIV specialist certification to MDs, DOs, nurse practitioners, and physician assistants who have at least 20 HIV patients, have acquired at least 30 HIV-related educational credits over the previous 24 months, and pass an examination every 2 years (www.aahivm.org).

Cultural Sensitivity

Cultural sensitivity is essential to a clinician's ability to provide optimal patient care and is addressed in more detail in Chapter 9, ***Psychosocial Issues, Mental Health, and Substance Abuse***. It is important that the provider recognize and understand the factors, including culture, that influence and guide a patient's behavior and decisions. A woman's traditions and beliefs affect her understanding of health and disease as well her acceptance of conventional medical treatment and reliance on alternative or complementary therapies. Her background shapes her view of herself as a woman, her role and responsibilities in society, and her beliefs and practices with regard to childbearing and contraception. Other factors may create barriers to care, as when a patient who has difficulty speaking, understanding, or reading English and receives care from a provider who can communicate only in English. Immigration status, as well as culturally based fears and mistrust of the U.S. healthcare system, also may impede care.

Special Circumstances

Many life circumstances may necessitate special approaches to care and unique sensitivity on the part of the care provider, as may be the case in treating women who are incarcerated, are victims of domestic or other violence, are addicted to alcohol or drugs, or have a psychiatric illness. Lesbians and transgender women also may require special sensitivity for treatment to be effective.

Some patient circumstances may arouse strong emotions in a care provider because of the provider's background or beliefs. It is essential that providers be willing and able to separate themselves from any personal connotations or associations they may assign to a patient's lifestyle or circumstances. They must provide care that is unbiased, sensitive, kind, and empathetic. If doing so is not possible, then the provider should refer the patient to a provider who can remain unbiased.

Spirituality

The spiritual dimension of a woman's life encompasses her beliefs and values and may give her life meaning and a sense of wholeness (*J Palliative Care* 2000;3:129). Spirituality is important throughout life, during periods of health and of illness, and a patient's beliefs and values can have a profound effect

on the way she views illness and its treatment. For instance, some women may view HIV as a punishment, and this belief may lessen their acceptance of treatment or put them at risk of nonadherence.

Major spiritual questions that often arise during illness may include the following:

- What gives my life meaning?

- Why is this happening to me?

- How will I survive this loss?

- What will happen to me when life ends?

It is important that the healthcare provider consider spirituality an essential component of a woman's physical, emotional, and mental health and that the provider learn about a patient's beliefs and what is important to her. A spiritual history should include specific questions about the patient's faith or beliefs, their importance and influence in her life, her involvement in a spiritual or religious community and its importance to her, and ways in which the healthcare provider may be able to help the patient integrate her beliefs and spiritual concerns into her care.

An ongoing concern: Spirituality may affect patient health outcomes directly or indirectly. Recent studies involving primary care and oncology patients found that spiritual well-being was positively associated with several outcomes relating to healthcare utilization and life satisfaction (*Ann Fam Med* 2008;6:412) and to quality of life (*Psychooncology* 2008;17:1121).

Spirituality should be addressed throughout a patient's care. Referrals to ministers, priests, rabbis, other spiritual guides, and community resources can be an important component of care. A care provider's personal spiritual beliefs may be a source of strength and may enhance the patient–provider relationship, but they should not be imposed on patients; the patient's beliefs should be recognized and respected.

Identifying Support Systems and Disclosure

During the initial evaluation, the HIV infected woman's social and emotional support system should be identified and reinforced; this information should be updated at each visit. The care provider also should ask about disclosure— to whom has the patient disclosed her HIV status, and what response(s) has she experienced? Many HIV infected women experience feelings of guilt and shame or fear violence or abandonment, and they are reluctant to trust anyone with knowledge of their infection or to share their feelings about it. Many communities still attach enormous stigma to HIV. A woman's fears about ostracism and abandonment should be addressed openly; a sense of isolation may harm a patient's physical and emotional well-being and lead to avoidance of clinic visits and nonadherence to drug therapy. Peer advocates and support groups may help many women with HIV cope with these fears and other issues on an ongoing basis.

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Disclosure to sexual partners, children, and other healthcare providers may require careful attention and assistance. A woman should be encouraged to disclose her status to partners and others who may be or have been at risk of HIV transmission; barriers to disclosure, such as fear of violence, should be identified and addressed. The care provider should offer assistance with disclosure when appropriate. A mother's decision to disclose or not disclose her HIV status to children, who may or may not be infected themselves, should be honored. The timing of a mother's disclosure to her perinatally infected child can be especially difficult and may reinforce a mother's feelings of guilt. The care provider should discuss the variety of considerations inherent in these decisions and offer the patient assistance if she needs it.

Education and Counseling

Despite dramatic advances in therapy, significant decreases in mortality and hospitalizations, and overall improvement in quality of life, HIV remains a life-threatening and often life-ending disease, and no cure is on the horizon. For women, life with HIV infection often is enveloped by poverty; isolation; personal, partner, or community drug use; and the competing priorities of children and family. Mental illness, substance abuse, or domestic violence may complicate a woman's clinical picture. Personal management of HIV disease now requires that a patient have a basic understanding of HIV infection and intense involvement in her own care.

Early and often: When encountering a woman newly diagnosed with HIV, care providers should be certain to educate the patient about the infection—natural history; clinical, immunologic, and virologic monitoring; and treatment—and about her medical condition in particular, including CD4+ cell count, clinical stage, and her need for treatment. The critical importance of adherence to care and to ART should be explained early and often. Barriers to care and to ART adherence, such as medication side effects and disclosure issues, should be assessed and addressed proactively.

Lifelong learning: Unlike patients with most other chronic medical conditions, those with HIV remain infectious for the rest of their lives and must learn about and become empowered to change behaviors that put themselves or others at risk (i.e., "prevention for positives"). Doing so successfully entails ongoing, lifelong learning and requires continual reinforcement. Perhaps the most important intervention for reducing sexual transmission to others is the use of effective ART. Observational studies and a meta-analysis have demonstrated decreased rates of HIV transmission among heterosexual serodiscordant couples on ART (particularly with fully suppressed HIV-RNA levels) as compared to those not on therapy (*AIDS* 2009;23:1397). Recent data from HPTN 052, a randomized clinical trial designed to evaluate ART as prevention of sexual transmission among serodiscordant couples, found that earlier initiation of ART (at CD4+ cell counts 350–550/mm^3) reduced HIV transmission to the uninfected partner by 96%. (*N Engl J Med* 2011; 365:493-505). Pre-exposure prophylaxis (PrEP) (see Chapter 3) is an additional option that can be considered to help protect HIV-uninfected partners.

Providers' ongoing patient education efforts should aim to correct misconceptions and uncover myths. Relapses in unsafe sexual or drug-using behaviors and at least episodic problems with adherence should be recognized as the norm rather than the exception. Patients also should be counseled about health-promoting practices in general (e.g., smoking cessation, exercise, nutrition) and about other personally relevant issues when appropriate (e.g., substance abuse, domestic violence). Education and counseling must be provided throughout the course of a patient's care, as knowledge and disease management change and the patient's life circumstances evolve. Peer advocates (HIV-affected women from similar cultural backgrounds) can be effective members of the clinical team to help educate patients, advocate for them, and provide counseling as needed.

Medical Evaluation

Several closely spaced visits: The initial medical evaluation of an HIV infected woman should include a comprehensive medical and psychosocial history and physical examination. It should also include gynecologic history—menstrual history, sexual practices (including genital, oral, and anal sex), contraception and condom use history, previous sexually transmitted and other genital tract infections, prior abnormal Pap smears, and other gynecologic illnesses or symptoms—as well as pelvic examination and recommended laboratory testing. This initial assessment should take place over several closely spaced visits. This approach will allow the woman and her clinical care team to become familiar with one another and to develop the trust and partnership that will form the foundation of the woman's ongoing care. It is particularly important for a woman newly diagnosed with HIV, who may be struggling with the shock, fear, denial, and despair that accompany the discovery of a life-threatening illness, to be given the opportunity to assimilate information about HIV and her own clinical status in small bites.

The intervals at which follow-up visits are scheduled should be based on the patient's HIV clinical, immunologic, and virologic status as well as other medical or comorbid conditions (e.g., substance abuse, mental illness) and her counseling or psychosocial support needs. At each visit, the patient should be questioned about new symptoms and side effects, her adherence with medications, and psychosocial issues and concerns. Her last menstrual period, current sexual activity, and use and consistency of use of condoms and contraception should be documented. Risk behaviors should be reassessed at regular intervals because sexual and drug-use patterns may change over time. Safe practices should be reinforced through positive prevention counseling (*MMWR* 2003;52 RR12:1). Pelvic examination should be repeated at least annually and should take place more frequently if gynecologic signs or symptoms develop or if the patient has a history of abnormal Pap smears, or current or recent unsafe sexual practices, or exposure to sexually transmitted infections. Medical and gynecologic evaluation of HIV infected women is described in more detail in Chapter 4, ***Primary Medical Care***, *and* Chapter 6, ***Gynecologic Problems***.

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Family-Centered Care

HIV is a disease of families. An infected woman's husband or partner and her children also may be living with HIV. Even when other family members are not infected, a woman is likely to be deeply affected by the presence of chronic and life-threatening illness within the family; she may be fearful of HIV transmission, and she may fear or face stigma. An HIV infected woman may neglect her own care while providing care to sick family members or to her children. The provider should encourage all HIV infected family members to receive appropriate care and should enlist family support for the infected woman by providing the family with information and education about HIV along with updates on the woman's condition (with her permission). The care provider also may help by identifying support systems for the entire family.

Access to Care

Two studies conducted at several multistate primary and specialty HIV care sites in different geographic regions highlighted persistent gender disparities in care by demonstrating that women were less likely to receive effective ART (*J Acquir Immune Defic Syndr* 2005;38:96) and had higher hospitalization rates (*Med Care* 2005;43 suppl 9:40). If women with HIV are to benefit equally from the advances in understanding and management of this disease, then attention must be paid at the individual, community, and societal levels to the many factors that continue to hinder equal access to care. Such factors include lack of empowerment; difficulty accessing child care, transportation, and insurance coverage; stigma and isolation; violence against women; and the competing concerns that many women face when they are responsible for providing food, housing, and care for other family members while caring for themselves. It is important to create appropriate linkages to services not available at the primary site of care, including substance abuse treatment, food and housing assistance, and additional medical expertise.

Limited-Resource Settings
(see also Chapter 16, *International Perspectives*)

In limited-resource settings, great progress has been made in scaling up access to HIV testing and counseling, ART, interventions to prevent mother-to-child transmission, and treatment of TB and other HIV-related infections, largely because of resources committed to the Global Fund to Fight AIDS, Tuberculosis, and Malaria; the U.S. President's Emergency Plan for AIDS Relief (PEPFAR); and other international organizations. Increasingly, HIV education and training is being integrated into medical, nursing, and midwifery school curricula to prepare new generations of healthcare providers for the ongoing pandemic. Moreover, task-shifting strategies have been implemented in many countries to expand the human resource pool rapidly and to use scarce human resources more efficiently. (*Task shifting* entails assigning specific tasks to less specialized healthcare workers, such as shifting responsibility for HIV testing and counseling to community workers or assigning nurses to prescribe and dispense ART.)

In settings with few resources, issues of cost, accessibility, stigma, and laboratory and healthcare infrastructure limit the use of ARVs; moreover, as new infections continue to occur, they threaten to overwhelm any fragile progress that has been made. Increasingly, attention is turning to the need for robust prevention programs and the use of biomedical prevention tools, such as male circumcision, in addition to—and integrated with—treatment resources. A new focus on integration and coordination of HIV prevention, care, and treatment with broader global health efforts, including linkage to women and children's health programs, has developed. Community involvement, laboratory infrastructure, and patient and provider education are interrelated and essential to all levels of HIV care. These components of the healthcare system must exist and must be strengthened if prevention, care, and treatment services are to succeed and ART is to reach those most in need.

The Chronic Care Model for HIV

With the advent of effective ART, life expectancy for HIV infected persons has been significantly extended and symptoms and disability related to HIV have decreased. This shift has required replacement of the acute and terminal illness model of care with a chronic care model. Analysis of a multinational cohort found that the average life expectancy for a 20-year-old with HIV who started ART between 2003 and 2005 is now extended to 49 years (*Lancet* 2008;372:293). However, a recent analysis based on HIV surveillance data from 25 States found that life expectancy improved less for women after a diagnosis of HIV from 1996 to 2005 than it did for men (*J Acquir Immune Defic Syndr* 2010;53:124). As people with HIV live longer, they are also subject to the same chronic illnesses as the general population. In some cases, they may be at increased risk for certain chronic diseases, such as cardiovascular and metabolic syndromes (see Chapter 4, ***Primary Medical Care***).

Chronic disease criteria: HIV meets several chronic disease criteria. It has an uncertain course and a prescribed treatment regimen; it requires self-care and carries some degree of stigma; it brings about changes in identity, roles, and relationships; and it may cause psychological distress (*AIDS* 2002;16 suppl 4:s69). As more HIV infected persons around the world have access to ART and are living longer, chronic disease management programs have become a global priority (UNAIDS 2008).

Objectives of chronic disease care: The objectives of chronic disease care include management of physical symptoms, maintenance or improvement of independence, and increased quality of life (*Psychology and Psychiatry: Integrating Medical Practice*. Chichester, UK: John Wiley & Sons; 2001; *Public Health* 2002;119:1130). The Chronic Care Model (www.improvingchroniccare. org) illustrated in Figure 2-1 was developed and refined by experts in chronic illness management to encourage high-quality integrated chronic disease care. It can be applied to a number of chronic illnesses, including HIV/AIDS. The

model identifies key elements in a system of care that can help patients to be healthier, providers to be more satisfied, and cost reductions to be realized throughout the system.

Figure 2-1
The Chronic Care Model

Community
Resources and Policies

Health Systems
Organization of Health Care

Self-Management Support

Delivery System Design

Decision Support

Clinical Information Systems

Informed, Activated Patient

Productive Interactions

Prepared, Proactive Practice Team

Improved Outcomes
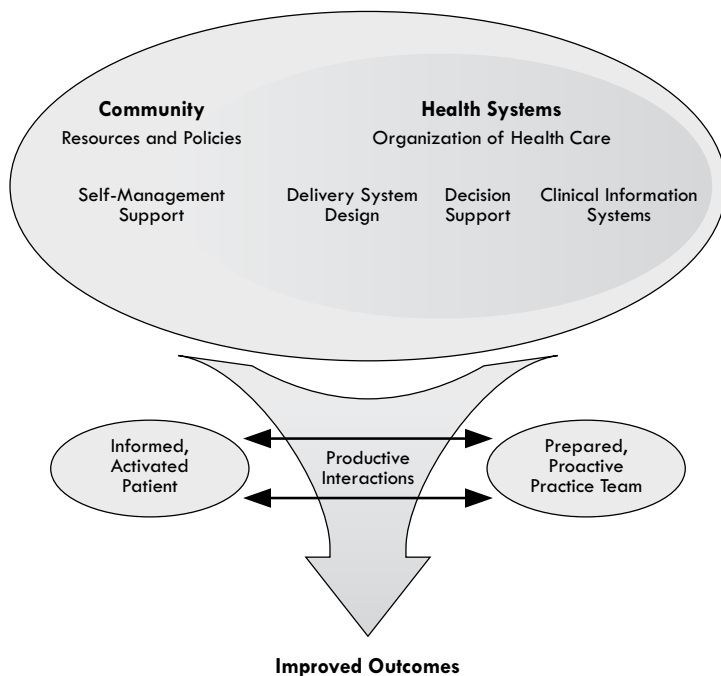
Source: *Eff Clin Pract* 1998;1:2. Copyright © 1998 by the American College of Physicians. Reprinted with permission.

Community Resources and Policies

Community programs can support and extend care for patients with HIV/AIDS. They can provide resources, fill gaps in needed services, promote better self-care, and play a broad role in advocating for patients and promoting health policies that can better sustain the lives of people living with HIV/AIDS.

Organization of the HIV Healthcare System

In delivering care for patients with HIV/AIDS, the healthcare system should be organized to promote safe and high-quality care. It should be flexible and nimble (i.e., able to change), offer appropriate resources

and support for providers and patients, and emphasize prevention and health maintenance rather than crisis-oriented care. The system also should encourage open and methodical handling of errors and quality problems and should promote effective improvement strategies aimed at comprehensive system change. Coordination of care within and across health system components, including coordination with primary and specialist clinical care, as needed, should be facilitated.

Decision Support

Because of the rapid advancements in knowledge about HIV and changes in clinical practice, HIV care providers need ongoing education and training to remain current. Treatment decisions should be founded on evidence-based guidelines. Primary care providers also should be kept informed and involved when patients are referred for specialist care. The USPHS has supported the development of evidence-based guidelines for HIV prevention and care (available at www.aidsinfo.gov).These and other high-quality online and consultative resources (e.g., warmlines, hotlines) are available to assist HIV providers in ensuring that care is based on the most current information and recommendations (see Chapter 15, *Resources*).

Healthcare Delivery System Design

The healthcare delivery system should be proactive and focused on keeping patients as healthy as possible. This approach requires determining what care is needed, delineating roles clearly among care team members, ensuring that team members have current information about patient status, and facilitating follow-up as a part of standard care. When necessary, care should be coordinated and integrated across different clinical settings, and access to community resources should be facilitated. Attention should be given to patient understanding of care, and care should be sensitive to a patient's cultural background and belief system. *Case management services*—defined as intensive, individually tailored, goal-oriented care—that are planned, coordinated, and managed by a single individual (case manager) or members of a team also should be provided.

Patient Self-Management Support

Successful HIV care depends on a well-informed and motivated patient. Although care providers are responsible for prescribing ARVs appropriately and can facilitate adherence, a woman with HIV is ultimately responsible for taking her medications properly and returning for regular care and follow-up. It is essential that patients be given tools to help them care for themselves, including information about how to take medications, recognize adverse effects, and minimize or prevent side effects. Patients often need help with developing problem solving, coping, and assertiveness skills. Finally, a woman should have a central role in making decisions about her care and in problem solving, both of which will help foster personal responsibility and a collaborative and trusting relationship with her care provider.

A patient's ability to engage in self-management of her HIV infection depends on specific knowledge and behaviors (*AIDS Care* 2009;21:1321), listed below and illustrated in Figure 2-2:

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- **Understanding illness and wellness in the context of HIV,** including understanding the need for ART to strengthen the immune system and the importance of adherence to reduce risk of resistance

- **Engaging in behaviors that promote personal health and prevent transmission to others,** such as safer sexual and drug injection practices and substance abuse treatment

- **Accessing appropriate treatment and other services,** such as regular HIV care and other needed clinical care

- **Attending to psychological health,** which may include developing an improved sense of control over one's life and actions, working to accept HIV as a part of life, and managing stress

- **Developing a healthy focus on social relationships,** which may include coping with stigma and decision making about disclosure, developing collaborative relationships with healthcare professionals, and seeking out supportive and affirming social networks.

Figure 2-2
Elements of Self-Management of HIV Infection
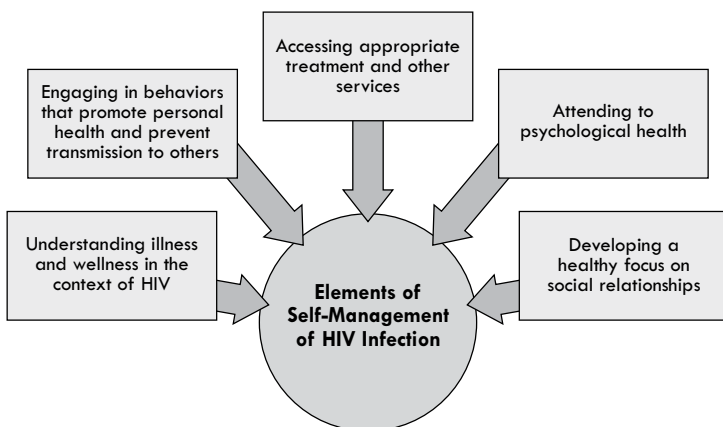
Source: *AIDS Care* 2009;21:1321

Clinical Information Systems

Information systems, such as electronic health records, are essential for tracking individuals and populations of patients with HIV/AIDS and can be used for both clinical and quality management purposes. They can facilitate efficient, coordinated, and effective care by supporting the sharing of patient information among care providers. Increasingly, telemedicine capabilities are being used to complement and extend standard care delivery by enabling greater exchange

of information among providers and with patients, virtual consultations, and telepharmacy for sending e-scripts, among other innovations (*Int J Med Inform* 2006;75:638). Clinical information technology can help prevent serious errors in care, such as medication errors (*JAMA* 1998;280:1311), and can provide timely reminders for providers and patients.

Quality Management

As the care of individuals with HIV has become increasingly complex and multifaceted, the importance of care monitoring to ensure quality and comprehensiveness has been highlighted. For instance, the American Medical Association recently led a collaborative initiative to explore opportunities to improve the quality of outpatient chronic care (*Jt Comm J Qual Patient Saf* 2009;35:248). That effort focused on incorporating validated and nationally endorsed performance measures and tools into clinical care. Performance measures specific to the care of patients with HIV have been developed as well (see Chapter 14, *Quality Management*) and can be used as both clinical aids by providers and quality measures in auditing comprehensiveness and effectiveness of care.

Effectiveness of the Chronic Care Model

To date, no studies have assessed the effects of implementing the chronic care model specifically in HIV care. However, a recent review of the model's use in the care of patients with other chronic illnesses found that multidisciplinary care, care coordination, patient self-management, and provider education had the greatest and most consistent effects on both clinical outcomes and process-of-care measures, such as increased provider adherence to treatment guidelines (*Intern Med J* 2008;38:427). In addition, patient self-management has been shown to reduce emergency and other outpatient visits, decrease health distress, and improve self-efficacy (*JAMA* 2002;288:2469). Some studies also indicate that decision support and feedback for healthcare providers, as well as case management and telemonitoring or telephone support for patients, confer clinical benefit (*Intern Med J* 2008;38:427).

From Research to Practice

Community-based participatory research is an emerging model that involves community members and patients to enhance ongoing clinical research. *A practice-based research network* is a group of care practices committed to patient care and to investigation of questions related to community-based practice and to improvement of outcomes and quality of care. These new research models are well positioned to examine such issues as healthcare disparities, prevention, chronic disease management, and mental health. The melding of the two research models has great potential for solving intractable problems, ensuring that studies match the needs of all stakeholders, and allowing rapid translation of results into clinical practice (*Exp Biol Med* 2010;235:290).

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Chapter 3:
Prevention of HIV Infection

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Chapter 3: Prevention of HIV Infection

Chapter 3 at a Glance

Introduction: A Global Public Health Priority

Women account for half of the 33 million adults living with HIV worldwide and more than half of new infections in global settings with the highest rates of HIV. Prevention of HIV infection in women is a global public health priority for the health of women, their sexual partners, and their children.

This chapter discusses HIV prevention with a focus on risk assessment, what does and does not work in prevention, and strategies in the research pipeline that may hold promise.

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Daunting Challenges

Nearly three decades into the HIV epidemic, scientists and clinicians working to prevent HIV continue to face daunting challenges. Measures that women can take to prevent HIV acquisition are well known—abstaining from intercourse, selecting low-risk partners, negotiating mutual monogamy, and using condoms. However, high rates of HIV among women in many parts of the world are a testament to the barriers that women may face in successfully implementing effective prevention strategies.

Multiple vulnerabilities: Women are often not aware of their partners' infection status or level of risk, and in many cases, they may not be able to negotiate sexual safety. Young women often face particularly high HIV risk because of emotional and physiological immaturity. In many areas of the world, risk is magnified by poverty and social vulnerability, leading to a greater likelihood of engaging in sexual relationships that lead to HIV exposure.

Risk magnified by disempowerment: Women in economically disadvantaged nations and in socially marginalized groups in the industrialized world may have less access to medical care for treatment of sexually transmitted infections (STIs) and contraception. They may not feel empowered to negotiate condom use, abstinence, or monogamy within their sexual relationships or to initiate HIV testing for themselves or their partners. An important issue is that fertility desires may overwhelm HIV prevention intentions, particularly condom use, even for women who perceive HIV risk.

Interventions for behavioral and biologic risk factors: Women who use injection drugs and some noninjection drugs (e.g., methamphetamine, cocaine) are at higher risk of HIV and need counseling that addresses both safe sexual practices and harm-reduction strategies related to drug use. Culturally sensitive interventions that target both behavioral and biologic risk factors for HIV are necessary to reduce transmission to women and girls. There remains, as well, a critical need to address the complex forces that fuel the HIV epidemic in women, including poverty, migration of populations, social and cultural disruption, gender discrimination, and stigma about STIs and HIV.

HIV Risk Assessment and Risk Reduction Counseling

Given that many patients will not voluntarily discuss their sexual activity or potential risk of HIV or STIs, it is incumbent on health care providers to ask a few open-ended questions in a comfortable, nonjudgmental manner. Otherwise, providers enable avoidance of discussion of sensitive sexual behavioral and HIV risks (e.g., "I won't ask; they won't tell"). Suggestions for risk assessment and patient-centered counseling are provided in the sections that follow.

Risk assessment for every patient: Just as most people would find celibacy an impractical means of reducing sexual risk, many individuals may find changing other specific sex behaviors difficult or unappealing. Although some sexual behaviors may be less mainstream than others, remember that participation in such behaviors reflects not a lack of morals or willpower but rather differing perceptions of what is enjoyable. Moreover, sexually active women may not realize that they are practicing behaviors that put them at risk for HIV infection. Guidelines for physicians and other healthcare providers recommend that HIV and STI risk assessment be conducted for every patient, ideally on a regular basis; however, most primary care physicians do not routinely incorporate questions about sexual behavior into routine patient care.

Managing provider discomfort: Clinician discomfort and fear of embarrassing or offending a patient when discussing sex may be impediments to effective risk assessment. In such circumstances, a clinician may find it more acceptable to frame the discussion by explaining the routine nature of such questions, thereby demonstrating that the patient is not being singled out because of mannerisms, appearance, or ethnicity. One effective approach may be to emphasize the importance of the discussion to the patient's care: "To be able to provide the best care for you today, we need to understand your risk for certain infections by talking about your sexual practices." Another may be to allude to the universality of many concerns: "Many women find it difficult to get their partners to wear condoms. Has this been a problem for you?" As with any type of medical history taking, open-ended questions probably serve as the most effective means of eliciting information when taking a sexual history. Language should be clear, easy to understand, and nonjudgmental.

Low threshold for recommending HIV testing: Some HIV risk factors for women can be derived from epidemiologic studies, such as history of gonorrhea or syphilis, crack cocaine use, and injection drug use (IDU). Increased risk with drug use is often mediated through both exposure to infected blood (especially with IDU) or through association with unsafe sexual practices. However, sometimes women are at risk through monogamous relationships with their HIV infected husbands. Factors that may increase risk in women, such as a history of unwanted pregnancy or an incarcerated sex partner, are not well recognized among healthcare providers. Therefore, identifying risk behaviors in women requires care and attention on the part of the provider. In many cases, a low threshold for recommending HIV testing is necessary. Important risk topic areas to cover are listed in Table 3-1 and can be ascertained through a written or computerized patient-administered questionnaire.

Table 3-1

Risk Assessment for STI/HIV for Women

Number of sex partners: ___ previous year ___ lifetime

Sex partners: ___ men ___ women ___ both

Sexual practices: ___ vaginal intercourse ___ anal intercourse
___ oral sex ___ sex toys ___ other (specify) _____

Consistent condom use: ___ yes ___ no

Use of: ___ injection drugs ___ crack cocaine ___ crystal methamphetamine

Patient perceives sex partner(s) to be at risk: ___ yes ___ no

Patient feels that sex partner(s) put her at risk: ___ yes ___ no

How does patient protect herself from HIV? _____
_____
_____

How does the patient protect herself from unplanned pregnancy? _____
_____
_____

History of abnormal PAP smear? ___ yes ___ no

History of STI? ___ yes ___ no

History of sex partner who was incarcerated? ___ yes ___ no

History of alcohol or drug abuse? ___ yes ___ no

History of: ___ injection drug use ___ sharing needles
___ crack cocaine use ___ crystal methamphetamine use

History of sexual, physical, or psychological abuse? ___ yes ___ no

Is there anything else that she feels she should mention to ensure good
medical care? _____
_____
_____

3

Practical Approaches to Risk Reduction Counseling

Individualize to the patient: Risk reduction counseling may seem overwhelming to a healthcare provider who has no special training in behavioral theory. However, the underlying principle is one that can be applied by any practitioner in any setting: Counseling should be individualized to the person receiving the counseling, and any attempt to individualize is superior to simply providing a didactic message.

Practical aspects of counseling:

- **Focus** the counseling session on risk reduction topics.

- **Listen** and react to the patient.

- **Do not** stick to a practiced script.

- **Avoid** overambitious risk reduction plans; focus on realistic goals.

- **Give** the patient written documentation of the risk reduction plan.

- **Use** culturally sensitive and ethnicity-specific language and terminology, when available and appropriate.

- **Consider** issues specifically relevant to women.

Focus the session: The cornerstone of the counseling session is to focus the session on a patient's recent sexual activities, her perception of their risk, and her motivation to reduce her risk of HIV/STI exposure. The provider should redirect the patient to this topic whenever necessary. Clinicians and counselors may become distracted by providing excessive information about scientific data and principles in response to patient questioning. Such information is probably more effectively dispensed in pamphlet form or by referral to other patient information sources. In addition, women at risk for STIs, including HIV, often come to clinic with multiple complicating issues, including poverty, domestic violence, substance abuse, and child care problems. A counselor may begin to feel responsible for addressing all of these issues and discouraged by what seems to be a host of insurmountable problems. Moreover, because the patient may be uncomfortable discussing her own risk, she may be emotionally invested in distracting the counselor from that subject. For these reasons, the counselor should remember that, during a limited period of interaction with a woman, the primary goal is to directly address and, ideally, have an impact on risky sexual behavior.

Appropriate objectives of risk reduction counseling
(Adapted from Kamb ML, 1998):

- **Enhance the patient's self-perception of risk:** Identify risk behavior; assess level of concern; identify ambivalent feelings about risk.

- **Explore specifics of the patient's most recent risk:** Identify specific risk details; address ability to communicate with partner(s).

- **Assess the patient's patterns of risk behavior:** Identify situations that make the patient vulnerable to risk and triggers of high-risk behavior.

- **Review previous risk reduction experience:** Identify successful attempts at risk reduction and obstacles to risk reduction; summarize, reflect, and synthesize patient risk patterns.

- **Address risk in the context of the patient's life:** Convey concerns and urgency regarding risk; support and encourage the patient to action.

Other longstanding issues may not be easily solvable and may be more appropriately referred to a social worker, substance abuse counselor, or mental health counselor.

Listen and react: While trying to convey prevention messages it is important to listen and react to the patient. It is a human quality that we enjoy talking and thinking about ourselves. The counseling technique of summarizing a patient's descriptions and viewpoints about her risk is an extremely effective communication tool. In an effort to be nonjudgmental, counselors may find themselves nodding supportively to just about any statement that the patient may make. Instead, direct and clear feedback from the counselor about self-destructive behavior may communicate more effectively the importance of reducing risk. For example, if a patient is describing an evening during which she had sex with multiple men while using crack cocaine, it may be more appropriate for the counselor to respond with emphasis that such behavior is dangerous. It would also be important to explore the emotional or physical needs leading to such risky sexual behavior and to identify potential alternatives to fulfilling such needs.

Avoid overambitious risk reduction plans: The most common error made by counselors is developing an overambitious risk reduction goal, particularly during sessions in which good rapport has been established. In many cases, a counselor may be convinced that a woman has acknowledged her risk to such a degree that she is now ready to eliminate any subsequent episodes of unprotected sex. Such goals are likely unrealistic. Behavioral specialists favor extremely concrete goals, such as "On Friday night I am going to ask my partner to wear a condom." Even modest goals, such as stopping at a drugstore and purchasing condoms on the way home from the session, may be suggested. Other possible goals are listed in Table 3-2.

Table 3-2	
Examples of Concrete Individualized Risk Reduction Plans	
Type of Plan	**Patient Actions**
Patient will talk about HIV/STI concern/risk to partner/friends.	• Disclose or communicate with partner, peers, and others
Patient plans to get herself tested or have partner(s) tested for HIV/STIs before having sex.	• Get tested again to ensure she is not infected • Have partner(s) tested for HIV/STI • Use condoms until partner(s) tested for HIV/STI • Abstain from sex until partner(s) is tested for HIV/STI
Patient plans to reduce, change, or eliminate at-risk partner(s).	• Break up with high-risk partner(s) • Eliminate a particular type of high-risk partner (e.g., prostitutes, anonymous partners) • Have fewer partners
Patient will change the type of partners she has.	• Get to know partners better before having sex • Remain monogamous with one partner for 3 mo • Abstain from sex for 3 mo
Patient plans to change use of alcohol and drugs.	• Decrease or eliminate alcohol and drug use when having sex • Generally decrease or eliminate a specific drug or alcohol • Will not share needles (she will exchange or obtain new) • Use clean needles or only share needles with partners known to be HIV uninfected • Seek medication-assisted therapy if addicted to heroin or other opiates
Patient plans to increase condom use or increase situations in which she uses condoms.	• Talk to partner(s) about using condoms • Buy condoms or have them more available • Have sex with condom use more often • Use condoms with all partners (vaginal and anal sex) • Use with all non main partners (vaginal and anal sex) • Use condoms with main partner (vaginal and anal sex)
Patient plans to change the kind of sex she will have.	• Have oral sex instead of vaginal or anal sex • Engage in mutual masturbation or petting (no penetrative sex)
Patient plans to make changes in the situations that are associated with risky behavior.	• Eliminate going to particularly risky place (e.g., bar, clubs) • Reduce frequency of going to a particularly risky place • Substitute behavior—go to gym, movies, etc., instead

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Adapted from *JAMA* 1998;280(13):1161 and from Beth Dillon, Project RESPECT training materials

Prevention Messages for HIV Infected Women

Important for women already infected with HIV: Although this chapter focuses on factors that may increase a woman's risk of acquiring HIV, prevention messages are equally important for women who are already HIV infected. Studies have shown that women with HIV are concerned about factors that may increase their infectiousness to their sexual partners and children. In general, the central messages for preventing sexual HIV transmission apply to HIV infected women as well as to those who are not infected but are at risk through their or their partners' behaviors. Important messages include the importance of knowing one's HIV status and that of one's sexual partner(s), the effectiveness of behavioral change in preventing transmission, and the potential role of consistent condom use in significantly reducing risk of HIV transmission.

3

What Works in HIV Prevention

Knowledge of Serostatus

Essential to prevention: Knowledge of one's HIV serostatus is the starting point for HIV prevention. An HIV-seropositive woman must know her status to prevent transmission to her infant and her partner(s) and so she can seek medical care for herself. For a seronegative woman, HIV testing is an opportunity for risk reduction counseling and strategizing on ways to remain uninfected. Unfortunately, most women at risk for HIV infection remain unaware of their HIV status, in part because they are often unaware of their partners' risks.

Routine provision of HIV testing recommended: Selective HIV screening — i.e., targeting patients at highest risk, such as intravenous drug users, men who have sex with men (MSM), and STI clinic attendees—has long been central as a strategy for HIV testing. The advantage of selective screening is cost savings, particularly in low-prevalence settings. However, selective screening has the potential to miss many people with HIV infection, particularly women, who may not possess traditional risk factors for HIV or who may not recognize their own HIV risk, and experts have increasingly favored recommendations for universal HIV screening. Estimates are that 1 in 5 HIV infected persons in the United States is unaware of his or her HIV serostatus. Universal screening offers several important advantages, including increased detection rates and, potentially, increased test acceptance, as universal screening reduces the stigma of HIV testing by eliminating testing based on sexual orientation, socioeconomic status, or race.

In the United States, the Centers for Disease Control and Prevention (CDC) recommends an opt-out approach to HIV screening, in which testing will be performed unless a patient declines. To increase routine HIV testing as a part of routine medical practice, the target populations for opt-out testing are broad: all pregnant women, everyone aged 13–64 years seeking health care (e.g., in primary care or emergency room settings, unless the prevalence

of undiagnosed HIV in that community has been documented to be <0.1%), everyone initiating TB treatment, and everyone seeking treatment for STIs (*MMWR* 2006;55:1). Making HIV testing routine and universal is cost effective (*N Engl J Med* 2005;352:586). The evidence is insufficient to determine optimum time intervals for HIV screening. One reasonable approach would be one-time screening of adolescent and adult patients to identify persons who are already HIV-positive, with repeated screening of those who are known to be at risk for HIV infection, those who are actively engaged in risky behaviors, and those who live or receive medical care in a high-prevalence setting.

Minimizing operational barriers to testing: Separate written consent for HIV testing should not be required unless mandated by local jurisdiction. Instead, general consent for medical care should be considered sufficient to encompass HIV testing. Rapid tests should be used to increase the likelihood that patients will receive their results. Unfortunately, routine HIV testing, particularly for hospitalized patients and those presenting to emergency care settings, has not yet been adopted widely, despite CDC guidelines. Some of the barriers to implementation of routine HIV testing include healthcare provider misconceptions about the amount of time testing requires, stigma associated with HIV/AIDS, and lack of reimbursement by some healthcare insurers.

In higher prevalence countries outside the United States, multilayered national programs have been initiated to increase universal knowledge of HIV serostatus, including widespread voluntary testing and counseling; opt-out testing in antenatal clinics; and door-to-door, home-based HIV counseling and testing, which rapidly increases knowledge of serostatus within a community and among families. Opt-out testing significantly increases HIV testing rates among pregnant women and is a key strategy in increasing uptake of antiretroviral (ARV) medications for prevention of mother-to-child HIV transmission.

Recommendations for counseling: In recognition that written consent and extensive pre- and posttest counseling reduced health care provider willingness to recommend and offer HIV testing, the 2006 CDC guidelines indicated that prevention counseling should not be required as part of HIV screening programs in healthcare settings. Prevention counseling is strongly encouraged for people at high risk for HIV, such as those seen in STI clinics.

Brief information about HIV tests should be provided with routine HIV testing, including the need for confirmatory tests if a rapid HIV test is positive. Patients at ongoing risk of HIV exposure should be counseled about risk reduction, and a concrete plan for reducing risk should be established by the patient. The need for annual HIV testing also should be communicated.

Table 3-3 describes appropriate goals for posttest counseling. For people who learn that they are HIV infected, disclosure to partners and the importance of linkage to care and antiretroviral therapy (ART) should be emphasized. Given that a substantial proportion of newly identified HIV infected persons do not follow up with care, it is important to obtain a CD4+ cell count, provide active referrals, and follow up with newly identified HIV positive persons within 2–4 weeks to determine whether they have had clinical follow-up with an HIV care program.

Table 3-3	
Goals of HIV Posttest Counseling	
Test Result	**Counseling Messages**
HIV seronegative	• Readdress and reinforce risk reduction plan. • Discuss need for repeat testing for people with recent (<3 mo) exposure or ongoing sexual and/or drug using risk behavior. • Discuss disclosure of results to sexual and drug-using partners.
Indeterminate HIV-1 Western blot	• Discuss prevalence of and risk factors for indeterminate test results. • For patients with p24 bands and those with high-risk behavior, discuss possibility of acute HIV infection. • Arrange for repeat testing in 1 mo and perform HIV DNA or RNA PCR to confirm infection status.
HIV seropositive	• Differentiate between being HIV infected and having AIDS. • Emphasize importance of early clinical intervention and make medical referral. • Discuss ways to avoid transmitting HIV to others. • Discuss disclosure of results to sexual and drug-use partners and offer assistance with disclosure, if needed. • Assess need for psychological support and provide referral if appropriate. • Assess possibility of domestic violence and provide referral if necessary. • Ensure patient has follow-up care.

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Rapid HIV testing: HIV testing is of value only if patients return for their test results; however, low return rates have been described in the United States and in many developing countries. Many U.S. testing programs use an ELISA with confirmation through Western blot. Rapid testing for HIV yields substantial cost savings and avoids high patient nonreturn rates for test results.

A number of rapid tests—defined as requiring less than 2 hours—are approved by the U.S. Food and Drug Administration (FDA) and available in the United States (Table 3-4). Some tests require as little as 5 minutes, use blood obtained from a fingerstick, and can be performed easily by clinical staff using only minimal laboratory facilities. Some have been approved by the FDA with a waiver from the Clinical Laboratory Improvements Amendments (CLIA) regulations; such waivers allow trained but nonprofessional staff to use the tests outside of traditional laboratory settings. Experience from CDC-led demonstration projects of rapid testing has been encouraging, and the assays have been found to have high sensitivity and specificity (*AIDS* 2006;20:1655). An increased rate of false positive results (<2%) with tests that use oral fluid rather than blood has been reported; positive results require confirmatory testing.

Patients who test negative can be given a definitive result without a return visit. Patients who test positive should be informed that their screening test was positive and that they should return to receive a confirmed test result.

In July 2012 the FDA approved the OraQuick In-Home HIV Test, a rapid home-use HIV test kit that provides a test result in 20–40 minutes and is approved for sale in stores and online to those 17 years and older. As with other rapid tests, positive tests must be confirmed by follow-up laboratory-based testing. (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm310542.htm)

Table 3-4

Rapid HIV Tests Approved by the FDA

Test	Manufacturer	Specimen Type	Sensitivity (%)	Specificity (%)	CLIA Waived
Clearview COMPLETE HIV 1/2	Inverness Medical Professional Diagnostics www.invernessmedicalpd.com	Whole blood*	99.7	99.9	Yes
		Serum/plasma	99.7	99.9	No
Clearview HIV 1/2 STAT-PAK	Inverness Medical Professional Diagnostics www.invernessmedicalpd.com	Whole blood*	99.7	99.9	Yes
		Serum/plasma	99.7	99.9	No
Multispot HIV-1/HIV-2 Rapid Test	BioRad Laboratories www.biorad.com	Serum	100	99.9	No
		Plasma	100	99.9	No
OraQuick ADVANCE Rapid HIV-1/2 Antibody Test	OraSure Technologies, Inc. www.orasure.com	Oral fluid	99.3	99.8	Yes
		Whole blood*	99.6	100	Yes
		Plasma	99.6	99.9	No
Reveal G-3 Rapid HIV-1 Antibody Test	MedMira, Inc. www.medmira.com	Serum	99.8	99.1	No
		Plasma	99.8	98.6	No
Uni-Gold Recombigen HIV	Trinity Biotech www.unigoldhiv.com	Whole blood*	100	99.7	Yes
		Plasma/serum	100	99.8	No
OraQuick In-Home HIV Test	Orasure Technologies, Inc., www.orasure.com	oral fluid	99.3	99.8	Yes

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

*e.g., fingerstick

Adapted from FDA-Approved Rapid HIV Antibody Screening Tests. February 4, 2008

Settings where rapid tests are valuable: Rapid testing is particularly valuable in areas of high prevalence where clinic return rates are low (e.g., STI clinics, emergency departments, nonmedical venues) or when an HIV diagnosis will influence immediate management decisions (e.g., postexposure prophylaxis, unknown HIV status in a pregnant woman presenting for labor and delivery). Rapid testing also has proven especially valuable in economically disadvantaged countries where HIV seroprevalence is high; laboratory resources are limited; and patient travel to and from clinic may be inconvenient, difficult, or too expensive.

Counseling remains the same: Some have expressed concern that rapid HIV testing may not offer patients sufficient time to digest counseling information and to decide whether they truly desire to know their HIV status. The principal components of HIV counseling remain the same for rapid testing as for traditional screening programs. Regardless of how HIV testing is performed, patients must be informed of the nature of the test and the risks and benefits of knowing their HIV status. They should consent voluntarily to the testing procedures, be informed that they can refuse testing, and have their confidentiality strictly preserved. Finally, they should be told that refusal of testing will not lead to denial of usual clinical services.

Does knowledge of HIV status change behavior? The literature in this area is difficult to synthesize, largely because of evolving counseling practices, varying lengths of follow-up, and few randomized trials with well-defined endpoints. A large study conducted in Kenya, Tanzania, and Trinidad randomly assigned individuals and couples to either voluntary HIV counseling and testing or basic health information (*Lancet* 2000;356:103). This trial found that counseling and testing resulted in a significant decline in unprotected intercourse with nonprimary partners by both male and female study participants. Newly identified HIV infected participants were more likely than HIV-uninfected participants to reduce episodes of unprotected intercourse. Among couples, unprotected intercourse was reduced more in those in which one or both members were diagnosed with HIV than in couples in which both members were HIV uninfected.

An ongoing randomized trial, Project Accept (HPTN 043), is evaluating whether community mobilization and mobile HIV testing reduce HIV incidence in South Africa, Tanzania, Thailand, and Zimbabwe. Studies have demonstrated the potential of HIV testing in couples with mutual disclosure of results. Among 963 HIV serodiscordant couples from Zambia, condom use increased from <3% to >80% after joint voluntary counseling and testing (*AIDS* 2003;17:733). Counseling and testing for couples should be a top HIV prevention priority, because it facilitates mutual disclosure of HIV serostatus between partners in the presence of a trained counselor.

Behavioral Interventions

Knowledge alone does not motivate change: Several well-designed randomized controlled trials have been conducted to assess the efficacy of various behavioral intervention strategies. Most of the studies conclude that such interventions result in decreased sexual risk taking (primarily unprotected

sex); some indicate decreased STI and HIV incidence. In contrast to didactic education sessions, behavioral interventions focus on recognizing risk and formulating effective risk reduction strategies. However, knowledge alone does not motivate change. To translate this concept into an issue many of us have experienced, consider the issue of weight reduction and diet modification. Despite widespread knowledge about the adverse health effects of eating fatty foods, adhering to a diet is notoriously difficult. Similarly, knowledge about STIs and HIV is not enough to implement change in sexual behavior, which involves changes in behavior for two people.

Brief counseling sessions may be effective: The 20-minute Project RESPECT counseling sessions may be most applicable to busy practitioners interested in conducting effective behavioral counseling (*JAMA* 1998; 280:1161). This study demonstrated that individual brief counseling, involving two sessions of 20 minutes each, was as effective in reducing STI incidence as four enhanced 60-minute sessions. Both intervention arms—the two 20-minute and four 60-minute counseling sessions—were superior to a didactic message.

The first of the two brief 20-minute sessions focused on recognizing HIV risk and barriers to risk reduction. After working with the client to agree on an achievable risk reduction plan, the counselors concluded the sessions by identifying a small risk reduction step that could be achieved before the second session. At the second session, counselors reviewed progress and barriers in achieving the behavioral goal and helped clients develop a long-term risk reduction plan.

Although the four 60-minute enhanced sessions also included recognizing risk and formulating risk reduction plans, more energy was focused on key theoretical behavioral elements, such as self-efficacy, attitudes, and social norms underlying risk behavior. The fact that the two brief 20-minute counseling sessions demonstrated efficacy equivalent to four 60-minute sessions is encouraging for healthcare providers who would like to integrate effective HIV counseling into busy clinical settings. Busy clinicians who cannot afford to offer even two 20-minute counseling sessions should determine whether referrals may be made to community-based organizations or to case managers who can provide brief client-centered counseling.

Use of Condoms

Effective for prevention: The National Institutes of Health (NIH) reviewed the scientific evidence and concluded that consistent use of latex condoms reduces a woman's risk of HIV by at least 85% (www.niaid.nih.gov/about/organization/dmid/documents/condomreport.pdf). Polyurethane condoms are thought to be as effective as latex condoms for preventing HIV. Natural skin condoms, however, are not effective in preventing transmission of HIV. Transmission of HIV that occurs with use of latex male condoms is likely due to technical failures or improper usage rather than to manufacturing defects. Studies reporting higher breakage rates tended to include populations from underdeveloped areas or those who participated in anal intercourse. Given the higher condom slippage and breakage rate with anal sex, use of water-based lubricants in conjunction with latex condoms is recommended for anal sex.

3

More control with female condoms: The female condom, made of polyurethane or nitrile, has been available for use in the United States since 1993; this device offers women more control over its use than does the male condom. The female condom is a sheath, closed at one end, with flexible rings at both ends. The FC2 device (shown in Figures 3-1 and 3-2) is inserted into the vagina by compressing the closed-end ring and pushing against the cervix; the outer ring covers the labia.

Results from a viral penetration study indicated that the physical-barrier properties of the FC2 Female Condom should provide adequate protection against viral particles *(FDA Summary of Safety and Effectiveness Data.* 2008; available at http://www.accessdata.fda.gov/cdrh_docs/pdf8/P080002b. pdf. Accessed 9/25/2012). New female condom prototypes have been developed; the development process included substantial evaluation of women's preferences and acceptability. The new devices are designed to address user complaints about the noise, appearance, and lubricant of the initial commercially available female condoms. When counseled about condom use, women should be advised to avoid simultaneous use of a female and a male condom, because doing so could increase the risk of slippage or breakage. Counseling messages about correct storage and use of condoms are important as well (see Table 3-5).

Figure 3-1
FC2 Female Condom

Source: © The Female Health Company. Chicago, IL. Reprinted with permission.

Figure 3-2
FC2 Female Condom Insertion and Positioning

Step 1

Inner ring is squeezed for insertion.
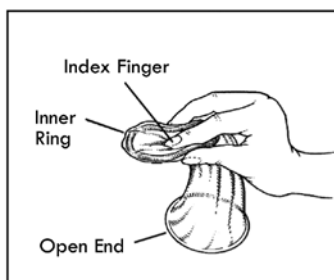
Step 2

Sheath is inserted, similarly to a tampon.
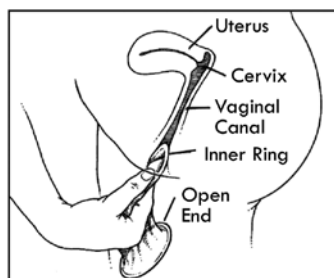
Step 3

Inner ring is pushed up as far as it can go with index finger, behind the pubic bone and over the cervix.
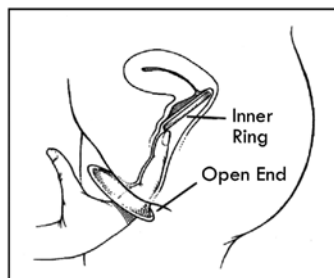
Step 4

Female condom is in place.
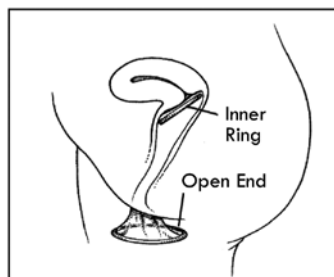
Source: © The Female Health Company. Chicago, IL. Adapted with permission.

Table 3-5

Proper Storage, Use, and Lubricants for Condoms

Condom Storage		• Store in cool, dry place, such as a bedroom drawer. • Avoid excessive humidity (e.g., don't store in a bathroom). • Avoid excessive heat (e.g., don't carry in wallet in trouser pocket). • Avoid exposure to direct sunlight.
Proper Use	**Lubricant**	• Use appropriate water-based lubricant that does not contain nonoxynol-9. • Avoid use of compounds that contain mineral oil, such as petroleum jelly, cooking oils, shortening, or lotions, because they can weaken latex.
	Male Condom	• Use at onset of male arousal, before penetration. • Hold tip of condom to create air-free reservoir for semen. • Make sure that condom is unrolled to extend completely to the penis base, leaving the reservoir. • Use enough lubrication to prevent excessive friction that might lead to breakage. • Hold condom at base during withdrawal to prevent slippage.
	Female Condom	• Inner ring must be placed completely onto cervix, or condom may twist. • Additional lubrication may be needed to prevent condom from twisting. • Care must be taken not to insert the penis between condom and vaginal wall. • The outer ring may need to be held in place to keep condom from slipping into vagina or anus. • Use of male and female condoms together is not recommended due to higher failure rate. • During anal intercourse, it may be advisable to remove inner ring to reduce likelihood of rectal bleeding.

3

Condom acceptability: Factors that influence condom use are complex and often differ between men and women. Surveys have shown that both men and women are influenced by perceived social norms and attitudes about condom use and by the recognition that condoms may prevent HIV and STIs. Ability to obtain condoms without excessive cost or embarrassment, ease of use, and preservation of pleasurable sexual sensation are clearly concerns for both men and women.

Acceptability of the male condom for both men and women is increased by normal appearance and feel, lack of odor, lack of slippage, the presence of a reservoir tip, and spermicidal lubrication. A man may be more likely to use the male condom if he feels that a woman may perceive him as being more sensitive and caring if he uses one. Conversely, women have complained that the interruption of foreplay has a negative effect on acceptability of both male and female condoms.

Both men and women have complained about the aesthetic appearance of the external ring of the female condom and the noise it creates during intercourse. Interestingly, in several surveys more women have said that they would be likely to use the female condom again than have said they liked using it, suggesting that women may be willing to sacrifice comfort and pleasure during sex for protection against HIV, STIs, and pregnancy. Many women have also expressed a strong preference for a female-controlled device to prevent STIs, even though the female condom cannot be used secretly.

Considerations for women who have sex with women: Discussion of recommended protective sexual practices should not be limited exclusively to heterosexual women. Sexual transmission of HIV between women has been described (*Clin Infect Dis* 2003; 36:e40). The use of barriers, such as cellophane or latex dental dams, should be recommended for oral–genital contact, particularly in HIV-discordant relationships. Sexual activity should be avoided during menstruation or when there are symptoms of genital tract infection. The sharing of sex toys contaminated with blood was implicated in at least one case of female-to-female sexual transmission of HIV.

Risk Reduction for Injection Drug Users

Drug abuse treatment is effective HIV prevention: Substance abuse treatment often removes HIV risk that accompanies sharing of contaminated syringes while reducing sexual transmission risks. For people who cannot or will not stop injecting drugs, provision of single-use sterile needles and syringes is a highly effective HIV prevention strategy. Syringes that have been cleaned with bleach or other disinfectants likely reduce HIV risk, but not nearly as well as sterile equipment. Other important strategies for reducing HIV risk in injection drug users include preventing initiation of drug injection, providing HIV prevention programs to drug users (including on the streets and in jails and prisons), and making risk reduction counseling and HIV testing available to drug users and their sex partners.

Male Circumcision

Benefits for men: In three landmark clinical trials, adult male circumcision was conclusively demonstrated to reduce men's susceptibility to HIV (*PLoS Med* 2005; 2:e298; *Lancet* 2007; 369:657; *Lancet* 2007; 369:643). Conducted in Kenya, South Africa, and Uganda, the studies together randomly assigned >11,000 uncircumcised HIV seronegative men to immediate versus delayed circumcision, then followed participants for HIV seroconversion for up to 2 years. Each study found a statistically clear 50%–60% reduction in HIV risk among men who were circumcised. In addition, the studies found direct benefits for the female partners of circumcised men in reduced rates of STIs, including genital ulcer disease, vaginitis, and HPV.

Adverse events associated with the circumcision procedure were rare. Sex should be deferred until complete healing of the glans is observed, because early resumption of sexual activity could increase risk of HIV acquisition if exposure occurs. Another significant finding is that concurrent research found no increase in risk-taking behaviors among men who underwent circumcision, suggesting that participants did not compensate for a perceived reduction in HIV risk by relaxing condom use and other behavioral prevention strategies.

More than 20 years of epidemiologic evidence, including more than a dozen prospective cohort studies, preceded the trial results. These epidemiologic studies generally compared HIV rates in men who were circumcised as infants or children with those who remained uncircumcised. Infant circumcision is technically easier than adult male circumcision and carries a lower risk of complications. Many countries are including infant circumcision promotion in their national rollout programs as part of an effort to decrease HIV transmission into the future. Biologic plausibility supports the association between a lack of circumcision and HIV risk—the foreskin contains large numbers of HIV target cells poorly protected by thin keratinized epithelium, and micro- and macroulceration of the foreskin may provide a portal of HIV entry.

Indirect benefits for women: Mathematical modeling studies suggest that widespread male circumcision will translate indirectly into substantial reductions in HIV among women in areas where male circumcision is uncommon. Acceptability surveys have found that a majority of women (69% across studies) favor circumcision of their male partners, and anecdotal reports suggest that women's positive opinions about circumcision have enhanced male uptake in areas in which rollout of the procedure has begun. In the United States, 79% of men are circumcised; prevalence of circumcision is lower in men of color.

Studies of circumcised HIV infected men have not shown conclusive evidence of protection from HIV transmission for women, and sex during wound healing after circumcision may increase the risk of a transmission from a man to his female partner. Nonetheless, circumcision substantially reduces HIV acquisition among men, thereby potentially decreasing the likelihood that a woman will encounter an HIV infected male partner. To the extent that this is true, make circumcision could translate into reduced risk for women, but it does not lead to a direct reduction in male-to-female HIV transmission. Finally, remember that circumcision is only partially protective against HIV for men; behavioral change, and particularly consistent condom use, should be emphasized for circumcised men to further reduce HIV risk for themselves and their partners.

3

What Has Not Worked in HIV Prevention

Nonspecific Vaginal Microbicides

Disappointing trial results: The concept of a topical microbicide—a vaginal or rectal gel, foam, or ring containing an active agent that protects against HIV infection—has been a topic of considerable interest. Microbicides hold great appeal because they can be female controlled, may be used without male partner knowledge, and would be active directly at the site of HIV exposure. To date, clinical trials have been completed for microbicide products that are designed to interfere with HIV through nonspecific mechanisms, such as by acting as a surfactant and disrupting the viral structure. Unfortunately, no product has shown encouraging protective results despite demonstrated high antiviral activity in laboratory studies and good safety profiles in early clinical studies (Table 3-6). Current attention in the microbicide field is being directed to ARV-containing products, which have the potential to target the virus specifically (discussed below). An important challenge in conducting microbicide research has been achieving high adherence to daily or coitally dependent products; future studies will explore novel ways to promote and accurately measure adherence. Community engagement has been particularly central to efforts to develop vaginal microbicides against HIV.

ARV-based microbicides: In July 2010, encouraging results from the first ARV-based topical microbicide, 1% tenofovir gel, were reported from the CAPRISA 004 trial (*Science* 2010; 329:1168). The risk of HIV acquisition was reduced by 39% among women randomized to use 1% tenofovir gel twice within 24 hours of having sex compared with women who used a placebo gel. Notably, there was higher efficacy among women who reported >80% adherence in use of the gel. In addition, a significant reduction in incidence of herpes simplex virus type 2 (HSV-2), the etiologic agent of genital herpes, occurred among women who used the tenofovir gel. The CAPRISA 004 results have invigorated the microbicide field, and multiple ARV-based compounds and delivery systems (e.g., vaginal rings) are in clinical development and undergoing evaluation. Disappointingly, in the VOICE study, a multi-country, multi-arm Phase IIb study of vaginal and oral PrEP in women at high risk of acquiring HIV, 1% TDF gel used daily was no better than placebo at reducing HIV transmission. (see Table 3-9).

Table 3-6

Completed Clinical Trials of Nonspecific Vaginal Microbicides

Product	Sponsor; Trial Location(s)	Outcome
Nonoxynol-9 sponge	University of Washington; Kenya	Trend for increased risk of HIV acquisition among women randomized to nonoxynol-9 compared with placebo (RR 1.7)
Nonoxynol-9 film	FHI; Cameroon	No effect on HIV acquisition
Nonoxynol-9 gel	UNAIDS; Benin, Côte d'Ivoire, South Africa, Thailand	Increased HIV incidence among nonoxynol-9 users compared with placebo users (HR 1.5); greater among women who used the product more than the mean of 3.5 times per day
Savvy (1% C31G) gel	FHI; Ghana, Nigeria	Two Phase III trials discontinued prematurely for futility because of lower than anticipated HIV incidence in the trial population. No evidence for protection against HIV or for harm
Carraguard gel	Population Council; South Africa	No statistically significant reduction in HIV incidence among women randomized to active product vs. placebo
Cellulose sulfate gel	CONRAD; Benin, India, Uganda, South Africa FHI; Nigeria	Two Phase III trials stopped when independent data and safety monitoring board of one study detected a trend toward increased HIV risk among women randomized to cellulose sulfate compared with placebo; no increased risk was observed at the time in the other study
PRO 2000 gel	NIH; Malawi, South Africa, United States, Zambia, Zimbabwe MDP; South Africa, Tanzania, Uganda, Zambia	Smaller Phase IIb study (NIH) suggested potentially 30% reduced HIV risk as a result of 1% PRO 2000 gel, but larger Phase III trial (MDP) subsequently found no reduction in risk
Buffergel	NIH; Malawi, South Africa, United States, Zambia, Zimbabwe	No statistically significant reduction in HIV incidence among women randomized to active product vs. placebo

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

HIV Vaccines

No efficacy yet: The search for a vaccine that protects against HIV acquisition has been challenging and has yielded surprising and sometimes perplexing results. Initial strategies focused on candidate vaccines that would elicit neutralizing antibodies, such as recombinant gp120, to envelope glycoproteins, a strategy that was tested through two parallel trials for subtype B and E infections in North America and Thailand, respectively (Table 3-7). No efficacy in reducing HIV acquisition was seen in either trial.

Table 3-7

Completed Efficacy Trials of Candidate HIV Vaccines (Through 2009)

Trial	Candidate Vaccine	Population	Outcome	Comments
AIDSVAX 003 and 004	Recombinant gp120 (subtypes B and E)	MSM in North America and IDUs in Thailand	No reduction in HIV-1 acquisition	
STEP	Adenovirus serotype 5 vector with HIV-1 gag/pol/ nef inserts	3,000 high-risk MSM and women in North and South America and Caribbean	1.2-fold increased risk of HIV acquisition in vaccine recipients Trial stopped at first interim analysis Increased risk of HIV associated with lack of circumcision; no significant association with adeno-5 seropositivity among MSM	75% of vaccine recipients developed a CTL response, as determined on the basis of gamma interferon response by ELISpot. Ongoing studies to assess mucosal immune response in uncircumcised men
RV144	Canarypox vector (vCP1251) with recombinant AIDSVAX subtype B/E gp120 boost	Low-risk population in southern Thailand	Vaccine efficacy 31% (95% CI 1–51%) in modified intent-to-treat analysis (nonsignificant trend of 26% efficacy in per protocol analyses)	First potential efficacy "signal" in HIV vaccine trial, although low efficacy No difference in viral set-point in breakthrough infections No humoral or cellular correlate in initial immune correlate assays; additional studies underway

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

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The vaccine field moved to candidate immunogens that would stimulate a cellular and humoral immune response, including an HIV-specific CD8 T-cell response that might lower viral load in early HIV infection and thus reduce HIV infectiousness and disease progression in people who became infected in spite of the vaccine. Merck developed a trivalent HIV candidate vaccine by inserting three HIV gene constructs (gag/pol/nef) from subtype B into an adenoviral serotype 5 vector (MRK Ad5). The vaccine was tested through the NIH's HIV Vaccine Trial Network (HVTN), in the STEP trial. The STEP trial was stopped after the first interim analysis, when a modest increased risk of HIV acquisition was observed in the vaccine arm in modified intent-to-treat analyses. This result was surprising and disappointing, given promising nonhuman primate studies and high immunogenicity in the human trials, in which 75% of vaccine recipients had a cytotoxic T-cell response to HIV immunogens (*Lancet* 2008;372:1881&1894). Among MSM vaccine recipients, uncircumcised men had a 2.5-fold increased risk, but this risk was not seen in placebo recipients.

Another study, called Phambili, of the trivalent MRK Ad5 vaccine in a heterosexual population in South Africa was stopped soon after the surprising STEP results. A study of the MRK Ad5 vaccine (HVTN 505) is being conducted among circumcised, Ad5 seronegative MSM to determine whether the MRK Ad5 vaccine is safe and immunogenic and reduces viral set point in patients with breakthrough HIV infections.

Some renewed optimism: The most recently completed HIV vaccine efficacy trial, RV144, was conducted in a low-HIV-prevalence setting in Thailand and utilized a prime-boost approach, with a viral vector (canarypox) to stimulate a T-cell response, followed by antibody boosting with recombinant gp-120. This is the first HIV-1 vaccine study to demonstrate efficacy, albeit modest, with just a 31% reduction in HIV-1 acquisition risk in the primary modified intent-to-treat analysis ($p = .04$) and 26% reduction in the per-protocol analysis (*N Engl J Med* 2009;361:2209). A surprising finding was the suggestion of increased efficacy among lower risk participants, although subgroup findings should be interpreted with caution given the relatively modest number of endpoints (51 and 74 endpoints in the vaccine and placebo arms, respectively), which limits the ability to evaluate the heterogeneity of vaccine protection. Initial analyses of potential immunologic correlates of protection have not identified a correlate.

The Thai RV144 trial has stimulated renewed optimism in the HIV vaccine field and identified multiple questions for research, including additional analyses of other potential immune correlates. Future priorities for the HIV vaccine field include evaluation of new HIV vaccine constructs, such as DNA, modified vaccinia vectors, and adenoviral mosaic vectors (e.g., Ad 25/35). Online updated lists of trials of HIV vaccines are maintained by the International AIDS Vaccine Initiative (www.iavi.org) and the HVTN (www.hvtn.org).

Treatment of Sexually Transmitted Infections

Increased susceptibility to HIV: STIs and other genital tract infections increase susceptibility to HIV. That STIs are important cofactors for HIV acquisition has been established by prospective studies from a variety of populations

examining risk factors for seroconversion. In such studies, women with genital ulcer disease, gonococcal or chlamydial cervicitis, or trichomoniasis were at twofold to fourfold increased risk for HIV infection. Several studies have demonstrated that disturbances in the normal microbial flora of the vagina— including bacterial vaginosis and vaginal candidiasis—may increase HIV risk, but randomized trials of vaginal infection treatment with an HIV endpoint have not been attempted to date. Even the best designed prospective studies have not been able to distinguish among STIs acquired at the same time as HIV infection and those already present that could have increased susceptibility.

STI interventions important to reduce risk, but treatment trials disappointing: Community trials of STI treatment have not found clear HIV reductions. Because of obvious ethical limitations, randomized trials that deny participants STI treatment cannot be conducted. As a result, community intervention trials of improved STI services or mass STI treatment have been conducted to determine the impact of STIs on population wide HIV transmission. Unfortunately, only one of six trials implementing STI treatment has shown a reduction in community HIV incidence. One principal reason is likely related to the stage of the epidemic: STIs play the greatest role in promoting HIV on a community level in early stages of an epidemic, when a core group of highest risk individuals, who are most likely to have concurrent STIs, contributes most to community HIV spread. Nevertheless, STIs clearly increase individual-level risk of HIV acquisition, and STI interventions should remain an important part of reducing HIV risk for individuals and populations, even where HIV is already well established.

Measures to reduce STIs:

- **Encourage** male and female condom use.

- **Encourage** early medical care for diagnosis and treatment of genital tract symptoms.

- **Provide** routine screening for genital tract infections among sexually active women.

- **Discourage** douching, which increases risk of bacterial vaginosis (BV) and pelvic inflammatory disease PID.

- **Teach** patients how to recognize genital herpes recurrences and prodromes; offer treatment to shorten/suppress recurrences.

For HIV infected persons, STI screening and treatment may reduce HIV infectiousness among those who are not taking ART and among those who are on therapy, because those infections may stimulate genital viral replication even in the context of good systemic HIV suppression.

Does suppression of HSV-2 reduce HIV transmission? Genital herpes may contribute substantially to HIV spread, but interventions to interrupt an effect of herpes on HIV risk have proved elusive. HSV-2 is common worldwide: Prevalence is approximately 20% among U.S. women and 50% or higher among populations in sub-Saharan Africa. A meta-analysis concluded that HSV-2 infection increased women's risk for HIV three-fold (*AIDS* 2006;20:73). Among HIV infected persons, symptomatic and asymptomatic HSV-2

reactivation increases HIV concentrations in the blood and genital tract, suggesting that HSV-2 activity enhances HIV infectiousness. Strong biologic plausibility exists for HSV-2 to enhance HIV susceptibility and infectiousness: HSV-2 causes genital ulcers that may serve as a portal for HIV entry or exit, and asymptomatic HSV-2 reactivation (occurring on average on 20% of days, without genital ulcers) may draw HIV target cells to the genital tract.

Acyclovir and the related compounds valacyclovir and famciclovir are routinely used as episodic treatment for symptomatic genital ulcer disease due to HSV-2 and as daily suppressive therapy to decrease the frequency of symptomatic HSV-2 reactivation and asymptomatic genital HSV-2 shedding. Unfortunately, two randomized trials of daily acyclovir HSV-2 suppressive therapy to reduce HIV acquisition and one trial of suppressive therapy to decrease HIV transmission from HIV infected persons to their sexual partners failed to demonstrate a protective effect of HSV-2 treatment. The results of these trials suggest that more potent and long-lasting HSV-2 suppressive therapies or, ultimately, a prophylactic HSV-2 vaccine might be needed to intervene in the relationship between HSV-2 and HIV.

While awaiting new HSV-2 prevention modalities, women with a history of genital herpes or with serologic evidence of HSV-2 infection should be taught how to recognize prodromes and recurrences. Suppressive herpes antiviral therapy should be considered in women with frequent recurrences, including those who report high-risk sexual behavior.

Antiretroviral-Based HIV Prevention Strategies

The role of ART in HIV prevention is a topic of significant public health interest. ART for HIV prevention comprises both treatment of HIV infected persons to decrease their infectiousness and post- or pre-exposure prophylaxis (PEP and PrEP, respectively) by HIV uninfected persons to prevent acquisition. Studies have now established potential efficacy for each of these approaches, although there is debate about how to implement preventive ART if it is proven to reduce HIV risk. Nonetheless, scientists and public health officials worldwide anticipate that ART-based prevention strategies may prove to be successful new ways to prevent HIV spread.

ART for Prevention

ART reduces HIV transmission risk: The amount of HIV in plasma is a primary determinant of the risk of sexual HIV transmission. In most people, ART reduces HIV plasma concentrations to undetectable levels within 6 months of initiation, and seminal and cervicovaginal HIV concentrations are also reduced to undetectable levels in most people as well. Use of ART during pregnancy, labor, and for the newborn has been responsible for the remarkable success in virtually eliminating mother-to-child HIV transmission in the United States.

Substantial reduction in the quantity of plasma and genital HIV in persons initiating ART translates into markedly reduced risk of HIV transmission to sexual partners. A meta-analysis of data from five prospective observational studies of HIV serodiscordant couples, some unpublished, found only five cases of HIV transmission to sexual partners in 1,098 person-years from HIV infected persons receiving ART; this finding is consistent with an infection rate of <1% per year (*AIDS* 2009:23:1397). Community-level data from Vancouver, British Columbia, has shown a significant decline in new HIV cases coincident with increased ART use (*Lancet* 2010;376:532).

Data from HPTN 052, a randomized clinical trial designed to evaluate ART for prevention of sexual transmission among serodiscordant couples, found that earlier initiation of ART (at CD4+ counts 350–550 cells/mm3) reduced HIV transmission to the uninfected partner by 96%. (*N Engl J Med* 2011;365(6):493–505). This study has major implications for the use of ART for prevention among serodiscordant couples, particularly those wishing to conceive or unable/unwilling to use safer sexual practices. The U.S. Department of Health and Human Services guidelines now recommend ART for all HIV-infected individuals for the prevention of transmission of HIV (both for heterosexual transmission and for other transmission risks). (Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Section accessed 5/16/13)

In the observational studies that have been reported to date, the follow-up time on ART was short relative to the lifetime duration of treatment that will be required of persons who start ART. Most patients who initiated ART did so at CD4+ counts <200 cells/mm^3, when clinical symptoms may have provided a greater impetus for adherence. It is essential to obtain reliable information about the comparative long-term transmission benefits and behavioral risks associated with ART, particularly when it is initiated at higher CD4+ cell levels.

ART does not eliminate transmission risk: An important research finding is that genital HIV shedding may not be fully suppressed among people receiving ART, even those with undetectable plasma viral loads, suggesting that ART may not completely eliminate transmission risk. In addition, the phenomenon of nonadherence means that not everyone prescribed ART will achieve reduced infectiousness. Healthcare providers should counsel patients on ART that the risk of transmission is not zero and that patients on ART have transmitted HIV to a partner, even when the patients had undetectable plasma HIV levels. Recommendations to women with HIV should stress the importance of consistent condom use to decrease HIV transmission risk.

Pre-exposure prophylaxis (PrEP) (see Table 3-9): The rationale for PrEP grows out of successful HIV prevention with use of ART prophylaxis for infants born to HIV-1–infected women and from nonhuman primate studies demonstrating that ARVs given prior to high-dose mucosal simian HIV challenge can provide partial or even full protection against infection (*PLoS Med* 2008:5:e28). PrEP offers advantages over post-exposure prophylaxis (PEP) for sexual and IDU exposures, because the efficacy of PEP declines rapidly if not initiated within

1 to 2 days after an exposure, and PEP is likely impractical for highest risk individuals (e.g., sex workers, members of HIV serodiscordant couples), who may have repeated exposures.

Providing ARVs orally to an uninfected female partner may offer some additional protection against HIV transmission from an infected male partner during attempts to conceive, but study results to date have been mixed.

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A Phase III study of daily oral TDF/FTC in uninfected MSM (iPrEX) reported a 44% overall reduction in HIV acquisition compared with placebo; effectiveness was significantly affected by adherence (*N Engl J Med* 2010;363(27):2587; *N Engl J Med* 2010;363(27):2663). In the Partners PrEP study, conducted in Kenya and Uganda among more than 1400 HIV-serodiscordant couples, the use of daily TDF or daily TDF/FTC by the uninfected partner was found to have efficacy of 67% and 75%, respectively, compared with placebo in reducing HIV transmission (with reported 97% adherence by returned pill count, but only 81% of those assigned to the active-treatment arm had detectable blood levels of the study drug) (*N Engl J Med* 2012;367(5):399). Within a subgroup of those who received TDF/FTC and whose plasma drug levels were tested, measurable concentrations of TDF were associated with a 90% reduction in risk compared with placebo. In the TDF2 trial, conducted in Botswana, TDF/FTC given to 1200 HIV uninfected heterosexual men and women reduced transmission by 62% compared with placebo, with 84% adherence by returned pill count (*N Engl J Med* 2012;367(5):423).

However, the FEM-PrEP clinical trial conducted in high-risk uninfected African women, found no efficacy with daily oral TDF/FTC (*N Engl J Med* 2012;367(5):411; Microbicide Trials Network; 2011. Available at http://www.mtnstopshiv.org/node/3619. Accessed 9/3/2012). Medication adherence was very low in the FEM-PrEP trial; the study drug was detected in the blood of <27% of women who acquired HIV and in <38% of matched uninfected controls.

The VOICE (Vaginal and Oral Interventions to Control the Epidemic) Study was designed as a five-arm, double-blinded study in which heterosexually-active women were first randomized to receive either gel or oral PrEP, and then within each group, randomly assigned to either tenofovir 1% topical gel or placebo gel; or to oral TDF, oral TDF/FTC or oral placebo. Unfortunately, no study drug significantly reduced the risk of HIV acquisition and again adherence was low; detectable drug levels were found in less than one-third of those tested and randomized to active drug. (20th Conference on Retroviruses and opportunistic Infections, Atlanta, GA,Abstract 26LB, 2013; Microbicide Trials Network; 2011. Available at http://www.mtnstopshiv.org/node/3619. Accessed 9/3/2012). Therefore, it is likely that adherence is a key factor in the discrepant results of these studies (*AIDS* 2012;26(7):F13).

In studies of PrEP to date, safety and tolerability were excellent (although nausea and vomiting were more common in the first 1–2 months among those taking TDF/FTC) and limited resistance was observed in seroconverters. Twice-weekly and coital dosing of TDF/FTC, as well as longer-acting formulations, intravaginal rings, and new candidate ARVs, are currently being evaluated for PrEP.

In July 2012 the FDA approved a label indication for TDF/FTC for reduction of risk for sexual acquisition of HIV infection among adults, including heterosexual women. In August 2012 the CDC issued the following interim guidance for clinicians considering the use of PrEP for HIV prevention in heterosexually active adults, particularly those with known HIV-infected partners (*MMWR* 2012; 61(31):586): 1) TDF/FTC is contraindicated for PrEP in persons with unknown or positive HIV status; 2) in women and men at very high risk for acquiring HIV from penile-vaginal sex, daily doses of TDF/FTC can be safe and effective in reducing the risk of HIV infection; 3) PrEP use may be one of several options to help protect the HIV-negative partner in serodiscordant couples during attempts to conceive (*Am J Obstet Gynecol* 2011;204:488); and 4) women of reproductive age should have a documented pregnancy test before beginning PrEP and at regular intervals while being prescribed PrEP. If women become pregnant while being prescribed PrEP, providers should discuss currently available information regarding the potential risks and benefits of continuing PrEP to enable informed decision making. If a woman takes PrEP while pregnant, providers are encouraged to prospectively and anonymously submit information about the pregnancy to the Antiretroviral Use in Pregnancy Registry (http://www.apregistry.com/who.htm; accessed 9/4/2012). In addition, providers should counsel patients that the efficacy of PrEP is highly dependent on adherence and that its long-term safety in HIV-uninfected adults or following fetal exposure has not yet been determined.

PrEP should be delivered as part of a comprehensive set of prevention services, including risk-reduction and ready access to condoms. Table 3-10 summarizes current CDC guidance to health care providers providing PrEP for heterosexually active adults.

Nonoccupational Postexposure Prophylaxis

PEP may reduce likelihood of HIV infection after a high-risk exposure. Theoretically, PEP can prevent HIV transmission either by blocking initial viral infection of cells or by inhibiting viral dissemination, thereby allowing for immune clearance of a small number of already-infected cells. The data for efficacy of ARVs as PEP come primarily from a single case-control study of healthcare workers who experienced occupational HIV exposures, mostly through needlestick injuries. Those who received zidovudine had an 80% lower likelihood of becoming infected; this study, however, was limited by a small sample size, retrospective design, and other potential sources of bias. The rationale for PEP after sexual exposure is largely that the probability of infection after a single unprotected sexual exposure is similar to that after a needlestick exposure (i.e., ~0.1%; slightly higher for receptive anal intercourse). Animal models suggest that PEP may be effective for mucosal and needle exposures, particularly when used within 24–48 hours. Ethical and pragmatic considerations make it unlikely that a randomized trial of PEP will be conducted. The effectiveness of PEP is likely to be influenced by time to initiation of treatment, duration of treatment, size of inoculum, and drug resistance profile of the virus in the source individual. Although the risks and

benefits of PEP for sexual exposure remain to be fully defined, studies suggest that provision of PEP for nonoccupational exposures is feasible (*J Infect Dis* 2001;183:707).

Considerations: If approached by anxious patients who have recently had a high-risk sexual exposure, the healthcare provider must weigh the likelihood of HIV infection in the contact, ART history if the contact is known to be HIV infected, the specific nature and timing of the exposure (initiation of PEP within 48 hours is important, given findings from animal studies and breakthrough infections with later initiation), and the possible risks of drug toxicity or side effects. CDC guidelines recommend two or three ARV medications, depending on the intensity of the exposure, for 4 weeks for occupational and nonoccupational exposures having at least moderate HIV risk (Table 3-8 and *MMWR* 2005;54:1). Other considerations should include evaluation and consideration of empiric treatment for other STIs, emergency contraception when appropriate, and possible indication for hepatitis B vaccination. Informed consent is recommended when administering PEP.

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Table 3-8		
Elements of NonOccupational Postexposure Prophylaxis Against HIV Infection		
Factors to Assess	**Considerations**	**Recommendations**
Exposure risk	**Substantial risk** for HIV exposure, defined as exposure of vagina, rectum, eye, mouth, nonintact skin, or percutaneous contact with blood, semen, vaginal secretions, rectal secretions, breast milk, or any bodily fluid contaminated with blood **Negligible risk** of HIV exposure if exposing fluid is urine, nasal secretions, saliva, sweat, or tears	**nPEP recommended** for exposures with substantial risk from a known HIV infected source **nPEP not recommended** for exposures with negligible risk, regardless of known or suspected HIV status of the source
Source of exposure	HIV infected vs. unknown HIV status (unknown HIV status of source frequently reported by persons seeking nPEP).	nPEP assessment on case-by-case basis for exposures with substantial risk from a source of unknown HIV status
Timing	nPEP efficacy for preventing HIV likely declines substantially as time since exposure elapses. Animal models indicate initiation should occur within 48–72 h	nPEP not recommended >72 h after exposure occurs

Table 3-8 continues on the next page

Table 3-8	continued

Elements of NonOccupational Postexposure Prophylaxis Against HIV Infection

Factors to Assess	Considerations	Recommendations
Initiate ARV nPEP	No evidence indicates that specific ARV agents improve efficacy for HIV prevention. In addition, no evidence indicates whether combinations of 2 vs 3 medications have different efficacy for preventing HIV. Recommended ARV medications for nPEP have been chosen on the basis of adherence and tolerability, subsequent to experience with their use for treatment of HIV infected persons.	Commonly used agents include • Efavirenz + lamivudine or emtricitabine + tenofovir or zidovudine • Atazanavir + lamivudine or emtricitabine + tenofovir (with ritonavir) or zidovudine • Lopinavir/ritonavir + lamivudine or emtricitabine + zidovudine
Testing	HIV testing at baseline is essential to confirm whether the person initiating nPEP is already HIV infected; however, nPEP should be initiated before results of HIV testing are obtained. HIV testing, including viral load and resistance testing of source, if available, should be done as well.	HIV testing at nPEP initiation and 4–6 wk, 3 mo, and 6 mo after exposure. Laboratory assessment of safety (complete blood count, liver enzymes, creatinine, as well as pregnancy testing) recommended at time of nPEP initiation and during nPEP. Additional testing for hepatitis B and C infection and STIs should be done.

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Not a substitute for risk reduction: PEP should not be administered for exposures with low transmission risk or when care is sought beyond the period of 72 hours postexposure. PEP should be considered strongly for persons who have been sexually assaulted or when a condom break during sex occurs in an HIV serodiscordant couple (especially if the positive partner is not on antiretroviral treatment or does not have an undetectable viral load). PEP is not a substitute for risk reduction and should not be considered a form of primary HIV prevention. Patients presenting for possible PEP should have reinforcement of the importance of initiating, resuming, or improving risk reduction activities.

Table 3-9

Efficacy Trials of Oral and Topical Pre-Exposure Prophylaxis

	Study Population	Location	Intervention	Outcome	Comments
CAPRISA 004	900 sexually active women	South Africa	1% topical TFV gel (dosed coitally)	39% protection with TFV gel	54% effectiveness with >80% gel adherence; high vaginal TFV concentrations needed at exposure (*Lancet* 2011; 378:279)
TDF2	1219 sexually active adults; 55% male, 45% female; 94 % unmarried; approximately 90% age 21–29 years	Botswana	Daily oral TDF/FTC	63% protection	>30% did not complete study; cannot draw definitive conclusions for women and men separately
Partners PrEP	4758 heterosexual serodiscordant couples; 38% negative-female, 68% negative-male partner; 98% married; median age 33 years	Botswana, Kenya, Rwanda, South Africa, Tanzania, Uganda, Zambia	Daily oral TDF or TDF/FTC	67% protection with TDF alone; 75% protection with TDF/ FTC	Discordant couples may be a distinct, unique population
FEM-PrEP	1951 heterosexual women at high risk of infection aged 18–35 years	Kenya, South Africa, Tanzania	Daily oral TDF/FTC	Trial discontinued for futility in April, 2011	Adherence assessment with monthly clinical samples to measure drug concentration is pending
VOICE (MTN-003)	5029 heterosexual women aged 18–45 years in high-prevalence areas	Uganda, South Africa, Zimbabwe	Daily oral TDF or daily oral TDF/FTC or daily topical TFV gel	No study drug significantly reduced the risk of HIV acquisition: HIV incidence was 5.7 per 100 person years. Effectiveness was −48.8% for TDF; −4.2% for TDF/ FTC; and 14.7% for TDF gel.	Adherence to study drugs was low: TFV was detected in 30% of the oral TDF arm; 29% in the oral TDF/FTC arm; and 25% in the TDF gel arm.

Table 3-9 continues on the next page

Table 3-9   *continued*

Efficacy Trials of Oral and Topical Pre-Exposure Prophylaxis

	Study Population	Location	Intervention	Outcome	Comments
HPTN 052	1763 heterosexual serodiscordant couples; 50% negative-female, 50% negative-male partner; 94% married; 61% aged 26–40 years	Botswana, Kenya, Malawi, South Africa, Zimbabwe, Brazil, India, Thailand	Immediate or delayed ART in HIV-infected partner	96% protection	Suppression of viraemia on therapy assured by routine monitoring

TDF = tenofovir disoproxil fumarate. TFV = tenofovir. TFV-DP = tenofovir diphosphate. FTC = emtricitabine. ART = antiretroviral therapy.

Adapted from Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health *and* Interventions to Reduce Perinatal HIV Transmission in the United States. (Note: only trials including women were included).

Table 3-10

Interim guidance for provision of PrEP for the prevention of HIV infection in heterosexually active adults who are at ongoing, very high risk for sexual acquisition of HIV infection*

Before initiating PrEP

Determine eligibility
- Document negative HIV antibody test immediately before starting PrEP medication.
- Test for acute HIV infection if patient has symptoms consistent with acute HIV infection or reports unprotected sex with an HIV-positive person in the preceding month.
- Determine if women are planning to become pregnant, are currently pregnant, or are breastfeeding.
- Confirm that patient is at ongoing, very high risk for acquiring HIV infection.
- If any sexual partner is known to be HIV-infected, determine whether receiving antiretroviral therapy; assist with linkage to care if not in care or not receiving antiretroviral therapy.
- Confirm that calculated creatinine clearance is ≥60 mL per minute (Cockcroft-Gault formula). [*Nephron* 1976;16:31]).

Other recommended actions
- Screen for hepatitis B infection; vaccinate against hepatitis B if susceptible, or treat if active infection exists, regardless of decision regarding prescribing PrEP.
- Screen and treat as needed for sexually transmitted infections (STIs).
- Disclose to women that safety for infants exposed during pregnancy is not fully assessed but no harm has been reported.
- Do not prescribe PrEP to women who are breastfeeding.

Beginning PrEP medication regimen
- Prescribe TDF/FTC (300 mg/200 mg) daily
- In general, prescribe no more than a 90-day supply, renewable only after HIV testing confirms that patient remains HIV-uninfected. For women, ensure that pregnancy test is negative or, if pregnant, that the patient has been informed about use during pregnancy.
- If active hepatitis B infection is diagnosed, consider using TDF/FTC, which may serve as both treatment of active hepatitis B infection and HIV prevention.
- Provide risk-reduction and PrEP medication–adherence counseling and condoms.

Follow-up while PrEP medication is being taken
- Every 2–3 months, perform an HIV antibody test (or fourth generation antibody/antigen test) and document negative result.
- At each follow-up visit for women, conduct a pregnancy test and document results; if pregnant, discuss continued use of PrEP with patient and prenatal-care provider.
- Evaluate and support PrEP medication adherence at each follow-up visit, more often if inconsistent adherence is identified.
- Every 2–3 months, assess risk behaviors and provide risk-reduction counseling and condoms. Assess STI symptoms and, if present, test and treat for STIs as needed.
- Every 6 months, test for bacterial STIs, even if asymptomatic, and treat as needed.
- Three months after initiation, then every 6 months while on PrEP medication, check serum creatinine and calculate creatinine clearance.

Table 3-10 continues on the next page

Table 3-10	*continued*

Interim guidance for provision of PrEP for the prevention of HIV infection in heterosexually active adults who are at ongoing, very high risk for sexual acquisition of HIV infection*

On discontinuing PrEP (at patient request, for safety concerns, or if HIV infection is acquired)

- Perform HIV test(s) to confirm whether HIV infection has occurred.
- If HIV-positive, order and document results of resistance testing, establish linkage to HIV care.
- If HIV-negative, establish linkage to risk reduction support services as indicated.
- If active hepatitis B is diagnosed at initiation of PrEP, consider appropriate medication for continued treatment of hepatitis B infection.
- If pregnant, inform prenatal-care provider of TDF/FTC use in early pregnancy and coordinate care to maintain HIV prevention during pregnancy and breastfeeding.

*E.g., those with partners known to have HIV infection.

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Possibilities and Challenges of ART-Based Prevention

A question of resources: During the past decade, ART has become available to populations worldwide—a tremendous health advance that has resulted in substantial decreases in morbidity and mortality risk for those on therapy. Nonetheless, in 2006, for each person started on ART worldwide, four were newly infected. Moreover, finite resources have limited ART availability worldwide, even for infected persons with clinical AIDS, who are most desperately at need. Implementing ART-based prevention strategies will require sufficient resources and targeted delivery to achieve a population-level impact. Pharmacovigilance systems to monitor ARV resistance will be critical for persons who become infected despite PEP or PrEP and might develop resistant virus and for those who are nonadherent to PrEP or ART.

Combination Strategies for HIV Prevention

Maximizing prevention efforts: No single standalone HIV prevention intervention is a panacea, and in the absence of a fully protective prophylactic vaccine, it is not likely that a single intervention will reverse the global epidemic. However, a number of HIV prevention strategies have been demonstrated to provide some protection against infection, thereby offering the possibility that combining several partially protective strategies might have additive or synergistic effects in reducing HIV on a population level. Analogous to the need for combination ART for treatment, researchers and clinicians are increasingly recognizing that combination HIV prevention strategies might maximize HIV prevention effects. Multicomponent packages of evidence-based biomedical, behavioral, and structural interventions must be appropriate, acceptable, and deliverable to priority subpopulations.

Population-level prevention: A core tenet of combination HIV prevention is that understanding the patterns and risks for HIV transmission at a population level guides the design of an optimal package of prevention interventions. On a population level, a combination prevention package that brings together interventions that target both HIV uninfected persons (e.g., behavioral risk reduction) and HIV infected persons (e.g., ART initiation and adherence) may achieve the greatest benefits. A key component of combination HIV prevention is increasing knowledge of HIV serostatus. For HIV infected persons, a strategy combining universal HIV testing with immediate linkage to ART has been named *Test and Linkage to Care*.

Interest in this approach was stimulated in large part by publication of a hypothetical modeling exercise in a high-prevalence African country. The results indicated that near-universal uptake of ART and optimal adherence, regardless of CD4+ cell levels, could reduce HIV incidence to <1 case per 1,000 population within 10 years of full implementation of the strategy and reduce HIV prevalence to <1% within 50 years (*Lancet* 2009;373:48). The feasibility of implementing such an approach and the realism of the original model's assumptions have been widely debated, given the challenges to date in (1) achieving high testing rates, particularly among some hard-to-reach populations; (2) addressing barriers to linking patients with HIV care; and (3) finding resources for increased testing and ART. Ongoing HIV epidemics in the United States and other high-income countries that have approximately 15 years of widely available ART are a reminder of the continued need to identify barriers to reaching HIV infected individuals who are not aware of their status. Also needed is a focus on secondary transmission risk behaviors, because ART availability alone will not curb the epidemic. Demonstration projects to increase HIV testing and triage to HIV care on a population scale are being evaluated in the Bronx, NY, and Washington, DC, as well as in international settings.

Conclusion

Prevention of HIV Remains a Critical Priority

The most effective available strategies for prevention are HIV counseling and testing, behavioral interventions that support abstinence or reduce risk taking, and condom use. While new strategies are being tested, healthcare providers must continue to assess and identify women at risk for acquiring or transmitting HIV and assist them in reducing their risk by setting and following through on achievable risk reduction plans.

4

Chapter 4:

Primary Medical Care

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Chapter 4: Primary Medical Care

Chapter 4 at a Glance

Essential Principles of Care for the HIV Infected Woman

This chapter focuses on the essential principles of care for the HIV infected woman. Cutting-edge treatment strategies currently being studied will be mentioned but not described in detail. To be truly useful, we indicate the general directions in which this field is moving and how to access updated information.

Several studies have demonstrated that positive clinical outcomes are a function of the clinician's experience in caring for HIV infected patients (*Cochrane Database Syst Rev* 2011;6:CD003938). Nonspecialists are urged to seek expert advice and consultation whenever there is any question about the best way to manage a specific patient. This is especially important in the settings of antiretroviral (ARV) treatment failure and advanced HIV disease when patients are vulnerable to multiple simultaneous opportunistic processes.

There is as yet no compelling evidence that the clinical course of HIV infection in women differs significantly from that in men, with the obvious exception of the associated gynecologic conditions and obstetric issues (described in Chapters 6 and 8). Although recent data have indicated that women may have lower HIV viral loads (VLs) than men with an equivalent degree of immunosuppression, this does not appear to confer benefit in terms of either overall survival or complication-free survival. At present, the approach to the management of HIV infected women is the same as for men. With prolonged survival now possible, general preventive and health maintenance strategies, such as smoking cessation, control of hypertension, reduction of cardiovascular (CV) risk factors, and routine screening for malignancy (cervical, breast, colon), are all part of routine care for HIV infected women.

4

Initial and Ongoing Evaluation

History and Counseling/Education

A comprehensive database is valuable to the primary caregiver in assessing a patient's current status and in formulating a management plan. At their initial encounter for HIV care, most patients are anxious and frightened. The ability to empathize, share knowledge without being patronizing, provide reassurance, and remain nonjudgmental are essential to gaining a patient's trust and obtaining accurate information (see Chapter 2, **Approach to the Patient**). The areas of exploration detailed in Table 4-1 are of particular importance in caring for patients with HIV disease and deserve special attention.

Table 4-1	
Initial HIV History	
Areas of Focus	**Areas of Exploration and Key Points**
HIV diagnosis	• When was first positive HIV test? Why was test done?
	• Can source of HIV infection be identified? Has source patient been treated for HIV? If so, are HIV medicines known? (Valuable if patient has acquired drug-resistant infection)
	• IDU? Sex with IDU or bisexual male? Trading sex for drugs, money, or shelter? Current partner(s) HIV infected or at risk? (Many women are unaware of partner's risk or HIV status.)
	• Previously tested for HIV? If prior test(s) negative, look for evidence of acute seroconversion syndrome within past 6–9 mo (e.g., flu-like syndrome, rash, lymphadenopathy).
HIV treatment history	• Pre-therapy CD4+ cell count and HIV RNA PCR quantification (i.e., VL)
	• Specific treatment history, including during pregnancy: specific drugs and regimen changes (when/why), problems with adherence, response to therapy, adverse effects, history of treatment-limiting tolerance to any agent, other barriers to taking ARVs, treatment interruptions (including after delivery)
	• History of resistance testing and availability of results
	• Past OI prophylaxis
	• HIV-related hospitalizations or any HIV-associated diagnoses
Other infectious diseases history	• Identify history of STIs: syphilis, gonorrhea, chlamydia, HSV, PID, trichomoniasis, anogenital warts
	• Identify history of other infectious diseases: TB, HAV, HBV, HCV, history of chicken pox or shingles
	• Vaccination history: usual childhood illnesses, HAV and/or HBV, pneumococcal infection and influenza, HPV
OB-GYN history (see Chapter 6)	• Date of most recent evaluation and results
	• Pap smear: history of abnormal results, date of most recent
	• Menstrual history/LMP
	• History of gynecologic problems (e.g., fibroids, endometriosis, recurrent yeast infections), previous gynecologic surgery (e.g., hysterectomy, tubal ligation, LEEP, cervical conization)
	• History of infertility or difficulty getting pregnant
	• OB history: dates and outcomes of pregnancies, OB complications, future childbearing plans and/or desires
	• Menopause: vasomotor symptoms, vaginal dryness, post-menopausal bleeding
	• Last mammogram, history of abnormal mammogram
Other pertinent medical history	• Hypertension
	• Chronic kidney disease
	• Diabetes
	• Cardiovascular disease
	• Thromboembolic disease
	• Asthma or COPD
	• Premalignant or malignant conditions (e.g., cervical, breast, colon, ovary)
	• Osteopenia and/or osteoporosis
Surgical history	• Prior surgical procedures, indications, complications

| Table 4-1 | *continued* |

Initial HIV History

Areas of Focus	Areas of Exploration and Key Points
Sexual practices	• Use of condoms (male and/or female) • Use of contraception other than condoms • Consistency of use of condoms and other contraception • Number of current sexual partners and their HIV status (if known) • Sexual activity with men, women, or both • History of anal sex
Current medications	• Prescription • OTC remedies • History of and attitude toward regular medication use • Use of nontraditional medications for HIV or other conditions • Drug allergies
Mental health history	• Past and current problems • Depression (trouble sleeping, early awakening, change in appetite, loss of interest in usual activities, anhedonia)
Family history	• Age and health of children, including HIV test results, if performed • HIV in other family members • Other medical diagnoses in family (see above list)
Social history	• Where was patient born and raised? • Where and with whom does patient live? Relationship to others in the household? • Food or housing insecurity • Childcare responsibilities • History of or current domestic violence • Presence of pets, especially reptiles (salmonellosis) and kittens (toxoplasmosis) • Extent of formal education • Occupational history and potential toxic exposures • Travel history • Cigarette, alcohol, and illicit drug use, past and current; misuse of prescription drugs
Sources of support	• To whom has the patient disclosed her diagnosis? What were the reactions? • Does the patient have friends or family to whom disclosure seems possible either now or in the future? • Other HIV infected family members or friends? • Are family or friends able to care for the patient's children in the event of acute illness? • Is the patient employed, and, if so, full or part time? Able to confide in supervisor? • Does the patient have health insurance?

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Counseling and education are important elements of the therapeutic bond; the information about HIV that the clinician shares with the patient is just as important as the information the clinician learns about the patient in the history-taking process. Because education about HIV entails conveying a large amount of information, it is best broached initially and then reintroduced and reinforced at appropriate intervals. Many patients are in a state of shock following their diagnosis or may be suffering from situational depression or fear of a partner's response. Clinicians should be kind and patient and should take adequate time with the patient; schedule at least an hour for the initial visit and schedule an early second visit. Assure patients that they will be supported and cared for. Encourage patients to develop good relationships with the office or clinic nurse and ensure that patients are able to reach someone when they have questions, complaints, or symptoms, especially when starting antiretroviral therapy (ART). Convey information in lay language at a level of complexity appropriate to the patient's ability to comprehend. Remember that a patient's formal educational level may not necessarily correlate with her ability to understand complicated medical concepts. Concepts of particular importance for review with a new patient are described in Table 4-2.

Table 4-2

HIV Information for New Patients

Topic	Areas of Discussion
HIV pathogenesis	• What are CD4+ lymphocytes and why are they important? • How does HIV infection affect CD4+ cells?
Natural history of HIV disease	• How is "AIDS" different from "HIV infection" or "HIV disease"? • Without therapy, what is the typical time course between acquisition of HIV and the development of HIV-associated problems and/or AIDS?
Monitoring activity of HIV disease	• What do CD4+ cell counts and HIV VL tests measure? • How are they used and how often will they be repeated?
Goals of HIV disease management	• What does "maintain or improve the immune system" mean and why is it a goal of therapy? • How is HIV replication controlled and why is this important? • How can medication side effects be avoided or minimized? • What are OIs and how are they prevented or treated?
Principles of HIV treatment	• Describe the value of combination therapy in preserving health and prolonging life • Underscore the importance of adherence to avoid treatment failure and the development of resistance • Discuss decision-making about starting treatment

Table 4-2	*continued*

HIV Information for New Patients

Topic	Areas of Discussion
Preventing spread of HIV infection	• Notification of sexual partners and drug use contacts • Practicing safe sex • Safer injection drug use practices, including needle exchange programs and the use of diluted bleach to sterilize injection equipment • Be informed of the prevention benefit of ART, namely, that if taken as prescribed it can substantially reduce their risk of transmitting uninfected sexual (and likely also needle-sharing) partners • Be informed about PEP and PrEP for HIV-uninfected sexual partners and under what circumstances they might consider employing either strategy
"Prevention for Positives"	• Keep bleach readily available in the household to clean up blood from accidents • Describe appropriate wound care for injuries • Reassure the patient about the difficulty of transmitting HIV to casual contacts and to family members, even in the close context of everyday family life
Health maintenance	• Cancer screening (Pap smear, mammogram, colonoscopy) • Immunizations • TB screening • Smoking cessation • Lipid screening • Diet, exercise, weight management • Dental and eye care • Bone density screening

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Lastly, because HIV is a chronic, life-threatening disease that still carries a social stigma, the clinician plays a key role in exploring mental health and psychosocial needs; helping patients identify potential sources of support; and referring patients for additional medical, psychiatric, and/or social services.

Depending on the initial history, a variety of issues may need to be explored in an ongoing fashion (at each visit or periodically). Such issues include new or worsening symptoms; interval sexual practices and other risk behaviors; interval menstrual history; a review of all medications, including complementary or over-the-counter products; adherence to ART; disclosure and/or social support issues; and others as indicated.

Physical Examination

The examination may yield clues to specific HIV-associated conditions. Perform a complete physical examination and track vital signs, particularly temperature and weight. Pay special attention to the areas outlined in Table 4-3.

Table 4-3	
Physical Examination of the HIV Infected Woman	
Area	**Key Focal Points**
General	• Evidence of wasting, often prominent at the temples • Fat redistribution syndromes, including buffalo hump, fatty deposits in neck, enlarged breasts, and truncal (visceral) obesity; may coexist with or be separate from marked subcutaneous fat loss in the extremities, face, and buttocks
Eyes	• Purplish spots of KS on conjunctival surfaces (rare in women) • Petechiae • Funduscopy: "cotton wool" spots, i.e., microinfarcts of the retinal nerve fiber layer due to occlusion of retinal capillaries • CMV retinitis: typical "eggs and ketchup" appearance of infiltrates and hemorrhages in advanced HIV disease • Visual-field deficits, common in CMV retinitis, may be uncovered with simple field testing by confrontation
Oropharynx	• No examination of an HIV infected person, regardless of disease stage, should be considered complete without a careful oral exam, which often yields the earliest physical evidence of HIV infection • Thrush: white plaques on buccal mucosa, palate, tongue, or posterior pharynx that are readily scraped off with tongue blade • Oral hairy leukoplakia: furry white plaques most often found on the lateral margins of the tongue that cannot be scraped off • Purplish spots or plaques on mucosal surfaces consistent with KS and with bacillary angiomatosis • Ulcers (HSV, CMV, aphthous)
Lymph nodes	• Generalized adenopathy: nontender or minimally tender; may wax and wane; most often related to HIV infection itself, but may also indicate lymphoma or disseminated OIs • Localized adenopathy: may be sign of malignancy or infection, e.g., enlarged axillary nodes in breast cancer, inguinal adenopathy in vulvar cancer or LGV • MAC • Extremely tender or unilaterally enlarged lymph nodes: should trigger an evaluation for specific etiology
Heart	• S3 gallop: may indicate heart failure, possible cardiomyopathy
Lungs	• Fine, dry "cellophane" rales: classic for PCP, but are a late finding and may be absent
Abdomen	• Organomegaly: may reflect disseminated infection with MAC, TB, disseminated endemic mycoses such as histoplasmosis, or lymphoma • Splenomegaly: may be associated with ITP
Pelvic examination (including digital rectal exam) (see Chapter 6)	• Genital ulcers: may reflect HSV; syphilis; other infections, including CMV, TB; aphthous or invasive vulvar cancer • Genital warts: HPV • Abnormal vaginal discharge: generally caused by infectious vaginitis (candidiasis, bacterial vaginosis, trichomoniasis)

Table 4-3	continued

Physical Examination of the HIV Infected Woman

Area	Key Focal Points
Neurologic	• Motor deficits: may reflect space-occupying lesions of the CNS, e.g., toxoplasmosis, CNS lymphoma, PML; may be due to neurosyphilis
	• Symmetrical, distal sensory deficits (especially decrease or loss of vibratory or proprioceptive sensation): typically affect feet more than hands; indicate peripheral neuropathy due to either HIV disease or drug toxicity from some nucleoside analogs (e.g., ddI or d4T)
	• Poor short-term memory, diminished concentration, sensorimotor retardation: hallmarks of AIDS dementia complex (HIV encephalopathy)
	• Dysphoric mood and flat affect: may be signs of depression
Skin	• Careful examination of skin often yields early clues about HIV infection and should be performed regularly
	• Pruritic papular eruptions: early manifestation; may be sign of bacterial folliculitis, eosinophilic folliculitis, or scabies
	• Pearly papules with central umbilication: typical of *Molluscum contagiosum*
	• Painful vesicular rash: may be HSV; in a dermatomal distribution is usually shingles (VZV)
	• Seborrheic dermatitis: may be severe; appears as greasy, scaly white, and/or erythematous areas on face, especially nasolabial fold and eyebrows; may be confined to scalp and hairline
	• Psoriasis: common scaling lesion
	• Purplish macules or plaques: may be either KS or bacillary angiomatosis; similar to appearance on mucosal surfaces; in dark-skinned individuals KS may appear more brown than purple

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Laboratory Testing and Other Monitoring

Initial HIV Diagnosis

The U.S. Centers for Disease Control and Prevention (CDC) recommends that voluntary, opt-out HIV testing be made a routine part of medical care for all patients aged 13–64 years who have been sexually active (*MMWR Recomm Rep* 2006;55(RR-14):1). Under current CDC recommendations, a separate signed consent and more extensive pretest counseling are not considered necessary. These changes are meant to simplify the process and promote universal testing; however, the need for specific consent or counseling is ultimately determined by relevant state laws.

HIV antibody tests: Standard HIV screening involves detecting antibodies to HIV, generally with an enzyme immunoassay (EIA). A reactive EIA should be followed by a confirmatory test, most commonly Western blot or, less commonly, immunofluorescence assay (IFA), which detects specific antibodies to HIV-1 proteins. CDC criteria for a positive Western blot are a band pattern indicating antibodies to two of the following proteins: p24, gp41, and gp120/160. A final diagnosis of HIV should not be given unless both screening and confirmatory tests are positive or reactive; with EIA alone the false-positive rate is 2%. In patients with infection >12 weeks after transmission, the sensitivity of this screening algorithm is 99.5%; specificity is 99.99% (*Am J Med* 2000;109(7):568).The average time from transmission to a reactive EIA is 10–14 days; seroconversion may be delayed to 3–4 weeks or longer in rare circumstances, but essentially all HIV-1 infected patients will seroconvert within 6 months (*Am J Med* 2000;109(7):568). A false-negative test can occur if testing is performed in the window period (i.e., after infection occurs but prior to the development of detectable antibodies). Agammaglobulinemia is a rare cause of a false-negative test.

The test may be reported as indeterminate if the EIA is positive but only a single band is detected by Western blot. Although the logical concern is that this result represents testing during the process of seroconversion, in most cases—particularly in low-risk individuals and low-prevalence areas—it represents the presence of cross-reactive nonspecific antibodies. With evolving seroconversion, antibody to p24 is usually the first to appear; in its absence, seroconversion is unlikely. Causes of indeterminate test results include

- Seroconversion, which can be confirmed by a quantitative virologic test with a PCR-based assay (see below);
- Advanced HIV infection with decreased titers of p24 antibodies (seroreversion is rare);
- Autoantibodies due to autoimmune or collagen vascular diseases or malignancy;
- Cross-reactive allo-antibodies from pregnancy, blood transfusions, or organ transplantation; and
- Previous receipt of an experimental HIV vaccine.

For a woman with indeterminate test results, repeat serology at 1, 2, and 6 months is recommended. Until seroconversion is ruled out, precautions should be taken to prevent HIV transmission to others. Typically, a woman in the process of seroconversion will develop a positive Western blot within 1 month. In high-risk patients or in other situations where acute infection is suspected, HIV RNA level (i.e., VL) should be obtained; this test has high sensitivity because of the generally high levels of viremia during acute infection.

HIV antigen/antibody tests: Two combination HIV antigen/antibody tests (ARCHITECT and Bio-Rad GS) have now been licensed by the U.S. Food and Drug Administration (FDA), and may be used for this purpose.

Rapid tests: Six FDA-approved rapid serologic tests are now available and usually provide results within 15–30 minutes (*FDA-Approved Rapid HIV Antibody Screening Tests*. CDC. 2008; http://www.cdc.gov/hiv/topics/testing/rapid/rt-comparison.htm. Accessed 8/1/2012). Three of the rapid tests are Clinical Laboratory Improvement Amendment (CLIA) waived, allowing point-of-care testing in clinical settings, which is particularly useful in settings where patients typically do not return for results, such as sexually transmitted infection (STI) clinics and emergency rooms, and during labor and delivery. Sensitivity and specificity are consistently >99% but positive predictive value varies depending on HIV prevalence. For this reason, positive results are considered preliminary and should always be confirmed with Western blot or IFA. For women who present to labor and delivery with undocumented HIV status and positive rapid test results, however, ARV prophylaxis should be given without delay to reduce the risk of perinatal transmission (ACOG Committee Opinion No. 418; *Obstet Gynecol* 2008;112(3):739).

In July 2012 the FDA approved the OraQuick In-Home HIV Test, a rapid home-use HIV test kit that provides a test result in 20–40 minutes and is approved for sale in stores and online to those 17 years and older. As with other rapid tests, positive tests must be confirmed by follow-up laboratory-based testing. (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm310542.htm) (http://www.oraquick.com/)

Urine test: The only currently available urine test (Calypte HIV-1 Urine EIA) is licensed for screening only and must be administered by a physician; a positive result requires confirmation by another method.

Virologic tests: Nucleic acid amplification tests—HIV DNA (qualitative) or HIV RNA (quantitative)—are used to diagnose acute HIV infection, confirm the diagnosis during the window period, and diagnose neonatal infection. HIV RNA testing is ***not*** recommended as a routine screening test for HIV because 2%–9% of people without HIV infection will have false-positive results, virtually always with low HIV RNA levels (i.e., <10,000 copies/mL [c/mL]) (*Ann Intern Med* 1999;130(1):37). Patients with acute HIV infection diagnosed by a virologic test while still antibody negative or indeterminate should undergo confirmatory serologic testing over the next 3 months. (See further discussion of HIV RNA testing on p. 92.)

Acute HIV infection should be suspected in patients with typical symptoms, including fever, pharyngitis, lymphadenopathy, and rash, particularly if these symptoms are accompanied by a high-risk exposure during the previous 3–4 weeks. Women may be less likely to perceive an exposure as high risk, particularly if they are in what they believe to be a mutually monogamous relationship.

There is evidence that pregnancy may be a time of increased risk for HIV acquisition (*Lancet* 2005;366(9492):1182). Obstetrical providers should therefore have a low threshold for retesting in pregnancy when there is concern for possible acute HIV infection. In this situation both HIV VL and HIV serology should be obtained because serology may be negative or

indeterminate. An antibody/antigen test would be appropriate to use in this circumstance as well, since the woman may be antibody negative but antigen positive.

- HIV DNA is a qualitative test used to detect intracellular virus; it is used primarily to diagnose neonatal infection. Sensitivity is >99% at all stages of infection and specificity is approximately 98%.

- Viral isolation: qualitative or quantitative cultures have been used primarily to diagnose neonatal HIV infection, but they are expensive and labor intensive and have been largely replaced by HIV DNA or HIV RNA assays.

Baseline and Interval Laboratory Evaluation

Baseline laboratory evaluation is used to establish the stage of HIV disease and determine exposure to other infectious diseases, need for vaccinations, and the presence of comorbidities that may affect the choice of HIV therapy or require specific management. Ongoing laboratory testing is needed to assess the response to therapy and monitor for adverse effects. A flow sheet, whether part of an electronic or paper health record, is an essential tool for tracking important test results and key clinical data over time. Table 4-4 outlines baseline and interval laboratory and other monitoring for women with HIV infection.

4

Table 4-4

Baseline and Interval Laboratory and Other Monitoring for Women with HIV Infection

	Entry Into Care	Before Initiating ART	ART Initiation or Change	2–8 Wks After ART Initiation/Change	Every 3–6 Mo	Every 6 Mo	Every 12 Mo	Treatment Failure	Clinically Indicated	Comments
HIV DISEASE TESTS										
CD4+ cell count	X	q 3–6 mo	X		X	q 6–12 mo in clinically stable patients with NDVL		X	X	
HIV RNA (VL)	X	q 3–6 mo	X	X	X	X		X	X	If VL is detectable at 2–8 wk, repeat q 4–8 wk until <200 c/mL, then q 3–6 mo. Interval for monitoring can be extended to q 6 mo if patient is ART adherent, has NDVL, and is clinically and immunologically stable for >2–3 y.
Resistance testing	X		X					X	X	If RT is performed at entry into care, repeat testing is optional if patient is ART naïve. RT is not possible with viral suppression and an ART switch that is due only to toxicity or for convenience.
Tropism testing			X					X	X	Perform if considering CCR5 antagonist therapy or for failure of CCR5 antagonist therapy
SAFETY/TOXICITY MONITORING										
CBC w/ differential	X	q 3–6 mo	X	If on ZDV	X				X	

Table 4-4 *continued*

Baseline and Interval Laboratory and Other Monitoring for Women with HIV Infection

	Entry Into Care	Before Initiating ART	ART Initiation or Change	2–8 Wks After ART Initiation/ Change	Every 3–6 Mo	Every 6 Mo	Every 12 Mo	Treatment Failure	Clinically Indicated	Comments
Electrolytes, BUN, creatinine	X	q 3–6 mo	X	X	X				X	Some experts recommend phosphorus measure while on TDF. Renal function assessment should include estimation of CrCl or GFR.
ALT, AST, bilirubin	X	q 3–6 mo	X	X	X				X	
Fasting glucose or hemoglobin A1C	X	If normal, q 12 mo	X	X	If last measure abnormal	If last measure normal			X	See *Diabetes Care* 2006;29:1963 for consensus guidelines for management of hyperglycemia in Type 2 DM
Fasting lipid profile	X	If normal, q 12 mo	X	Consider 4–8 wk after starting new ART		If last measure abnormal	If last measure normal		X	
Urinalysis: RBC, WBC, proteinuria, sediment levels	X		X			If on TDF	X		X	More-frequent monitoring indicated for patients with increased risk of renal insufficiency (e.g., DM, HTN)
Calculated creatinine clearance	X	Prior to initiating TDF or IDV							X	Consider at baseline, especially in Black patients, due to increased risk of HIVAN
Albumin level	X	q 12 mo					X		X	

Table 4-4 *continued*

Baseline and Interval Laboratory and Other Monitoring for Women with HIV Infection

	Entry Into Care	Before Initiating ART	ART Initiation or Change	2–8 Wks After ART Initiation/Change	Every 3–6 Mo	Every 6 Mo	Every 12 Mo	Treatment Failure	Clinically Indicated	Comments
Alkaline phosphatase level	X	q 12 mo					X		X	
Pregnancy test			If starting EFV						X	
G6PD	X									Screen for deficiency in appropriate racial or ethnic groups
HLA-B**5701 testing			If considering ABC							
COINFECTION AND COMORBIDITY TESTING										
Viral hepatitis screening (HAV, HBV, HCV)	X		If not performed at entry; if patient is not HBV immune or vaccinated						X	If HBV nonimmune, administer HBV vaccine series. Administer HAV vaccine if patient has HBsAg+ or HCV infection, is planning travel to endemic areas, is IDU, or in presence of HAV community outbreaks.
TB screening	X						X		X	Test with PPD or interferon-gamma release assay; no need to repeat if prior (+) PPD. Other testing may be indicated with potential exposure.
Syphilis serology	X						X		X	More-frequent testing may be indicated if patient engages in high-risk behavior

4

Table 4-4 *continued*

Baseline and Interval Laboratory and Other Monitoring for Women with HIV Infection

	Entry Into Care	Before Initiating ART	ART Initiation or Change	2–8 Wks After ART Initiation/Change	Every 3–6 Mo	Every 6 Mo	Every 12 Mo	Treatment Failure	Clinically Indicated	Comments
CMV and other herpes virus screening	X									CMV screening if at low risk for CMV; VZV screening if no history of chicken pox or shingles. Some experts recommend HSV-2 screening.
Toxoplasma serology	X									
STI screening (GC, chlamydia, trichomoniasis) (see http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5212a1.htm for detail on indications for more frequent testing and which testing modalities to use)	X						X		X	More-frequent testing may be indicated if patient engages in high-risk behavior
Chest X-ray	X								X	Indicated for patients with positive TB screening results. Consider at baseline in presence of underlying lung disease.
HEALTH MAINTENANCE SCREENING										
Cervical cytology	X	2x in first y of care					X			More-frequent screening is indicated if abnormal results are obtained and/or after treatment

Table 4-4 *continued*

Baseline and Interval Laboratory and Other Monitoring for Women with HIV Infection

	Entry Into Care	Before Initiating ART	ART Initiation or Change	2–8 Wks After ART Initiation/Change	Every 3–6 Mo	Every 6 Mo	Treatment Failure	Every 12 Mo	Clinically Indicated	Comments
Anal cytology/ digital rectal exam	X	2x in first y of care						X		Not currently considered standard of care, but some experts recommend a screening schedule similar to that for cervical cytology. Consider anal Pap smear in women with genital warts or abnormal cervical cytology. Evaluate abnormal results with high-resolution anoscopy.
Ophthalmologic screening						Perform dilated exam q 6–12 mo in patient with CD4+ cell count <50 cells/mm^3			X	
Depression screening	X							X	X	
Domestic violence screening	X							X	X	
Alcohol and drug use	X							X	X	
Tobacco use	X							X	X	

Table 4-4 continued

Baseline and Interval Laboratory and Other Monitoring for Women with HIV Infection

	Entry Into Care	Before Initiating ART	ART Initiation or Change	2–8 Wks After ART Initiation/ Change	Every 3–6 Mo	Every 6 Mo	Every 12 Mo	Treatment Failure	Clinically Indicated	Comments
Colonoscopy	X								X	Initiate screening at age 50; perform every 10 y, but earlier or more often if indicated by family history or prior findings
Mammography	X						X			Baseline screening at age 40 and annually thereafter (ACOG Practice Bulletin #122; Obstet Gynecol 2011;118(2 Pt 1):372). Perform individualized, periodic assessment of breast cancer risk.
Bone densitometry	X									Initiate screening at age 65; consider at age 50+ if patient has one or more risk factors for premature bone loss. Perform periodically based on prior results and ongoing risk factors for bone loss.
Global assessment for frailty, functionality, fall risk	X						X		X	Initiate screening at age 65

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

CD4+ lymphocyte count (CD4+ % and absolute CD4+ cell count): This
is a key indicator of immune function in HIV infected patients. The normal
laboratory range for the CD4+ lymphocyte percentage is 33%–60% and a
normal CD4+ cell count is 700–1400 cells/mm^3. CD4+ cell counts often drop
precipitously at the time of primary HIV infection, then usually rebound to
near-baseline levels. The natural history of HIV infection, illustrated in Figure
4-1, involves a progressive loss of CD4+ cells (approximately 60 cells per
year), with the risk of opportunistic infections (OIs) increasing as CD4+ cell
counts decrease. An adequate CD4+ response to therapy is defined as an
increase in the range of 50–150 cells/mm^3 per year until a steady-state level
is reached. If therapy is initiated at a low CD4+ cell count or at an older age,
the increase may be blunted, even with appropriate virologic suppression.

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Figure 4-1
**Natural History of HIV Infection without the Use of Antiretroviral
Therapy**
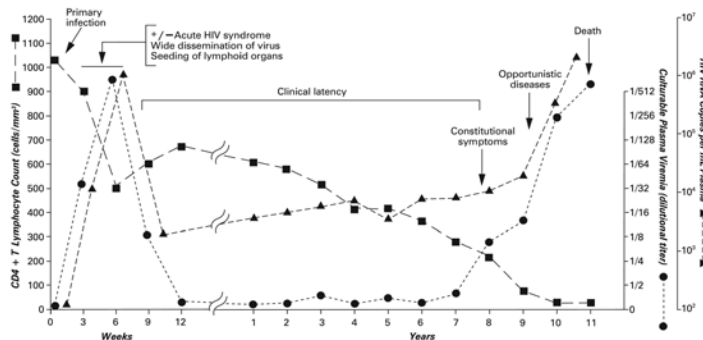
Source: © *N Engl J Med* 1993;328:327. Reprinted with permission.

The baseline CD4+ cell count is important in decisions regarding the initiation
of ART and the need for prophylaxis against specific OIs. Follow-up CD4+
cell count testing is important for determining when to start ART in untreated
patients, assessing the immunologic response to ART, and informing decisions
about the initiation or discontinuation of OI prophylaxis.

Because the CD4+ percentage is measured directly and the absolute CD4+
cell count is a calculated value, it is more useful and accurate when assessing
trends over time to focus on changes in the CD4+ percentage. Most clinicians,
however, use the absolute CD4+ cell count in clinical decision making.

Several factors may cause decreases in the absolute CD4+ cell count, including
pregnancy (due to hemodilution; the CD4+ percentage remains relatively
stable), corticosteroid use, intercurrent illness, bone-marrow suppressive
medications, and recent vaccination. HTLV-1 infection may increase the CD4+
cell count.

In general, the same laboratory should be used for serial CD4+ measurement and any value that indicates a change in patient management should trigger a retest. A 30% change in the absolute CD4+ cell count or a 3-point change (increase or decrease) in the CD4+ percentage between one test and the next is significant (i.e., a change of two standard deviations or more).

Plasma HIV RNA (VL): At baseline, VL reflects the rapidity with which HIV disease is likely to progress. Higher VLs have been repeatedly associated with a more rapid rate of disease progression.

VL is used routinely to monitor a patient's response to treatment of HIV infection, with the goal of achieving and maintaining an undetectable VL as measured by ultrasensitive assays (<20–75 c/mL, depending on the assay); however, isolated "blips" (i.e., VLs transiently detectable at low levels) can be seen in successfully treated patients and are not thought to represent viral replication or to predict virologic failure (*JAMA* 2001;286(2):171). A repeat test should be performed as quickly as possible if a patient on ART with previously undetectable VL suddenly has quantifiable virus. The U.S. Department of Health and Human Services (DHHS) *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* defines virologic failure as a confirmed VL of >200 c/mL, which eliminates most cases of apparent viremia caused by blips or assay variability (http://www.aidsinfo. nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0/. Accessed 5/16/2013).

Acute illness (e.g., bacterial pneumonia, tuberculosis (TB), herpes simplex virus (HSV), *Pneumocystis jirovecii* pneumonia [PCP]) and immunizations can cause transient increases in plasma HIV RNA for 2–4 weeks; testing should not be performed during this time. Plasma HIV RNA results usually should be verified with a repeat determination before making changes in therapy. The most frequent reason for an increase in viral load is poor adherence and any increase in viral load should prompt assessment of the patient's adherence to the prescribed ART regimen. Recent studies have shown that women have lower VLs than men at comparable CD4+ cell counts, although these VL differences tend to disappear several years after seroconversion and have not been associated with slower disease progression or longer survival (see Chapter 1, *Epidemiology*).

Several different VL assays and methodologies (e.g., reverse transcriptase PCR, branched DNA, nucleic acid sequence-based amplification) are available. The variability of VL assays is 0.3–0.5 log. Although the results of different assays correlate, absolute values differ and no standard multiplication factor exists to translate among different assays. For this reason, the same VL assay should be used to follow an individual patient longitudinally.

HIV drug-resistance testing (see also p. 110): Genotypic and phenotypic resistance assays are used to provide information on resistance to nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs); tests for integrase and fusion inhibitor resistance are available separately from several commercial laboratories. A genotypic tropism assay for predicting HIV co-receptor usage is now commercially available and may be used as an alternative to a

phenotypic tropism assay before initiation of a CCR5 antagonist-containing regimen and for evaluation of virologic failure while taking CCR5 inhibitors. The purpose of resistance assays is to inform treatment decisions in the case of possible transmitted drug resistance, virologic failure, or suboptimal VL reduction.

Resistance testing should be performed in the following circumstances:

- With acute HIV infection; 6%–16% of transmitted virus is resistant to at least one ARV, and 3%–5% is resistant to drugs from more than one ARV class (*AIDS* 2010;24(8):1203; *HIV Clin Trials* 2007;8(1):1)

- At entry into HIV care; some drug-resistance mutations can remain detectable for years in untreated infected patients (*Clin Infect Dis* 2005;40(3):468; *J Virol* 2008;82(11):5510)

- Upon initiation of ART, because of the possibility of superinfection (optional)

- At entry into prenatal care; test prior to the initiation of ART and in patients who are on therapy and have detectable VL

- If virologic failure occurs, test before or within 4 weeks of discontinuing the failing drug regimen

- If VL reduction if suboptimal

In most situations, genotypic testing is preferred over phenotypic testing because of faster turnaround time, lower cost, better sensitivity for detecting mixtures of wild-type and resistant virus, and relative ease of interpretation. Adding phenotypic to genotypic testing is generally preferred for patients with known or suspected complex drug-resistance mutation patterns, particularly with PIs. In general, resistance testing should be performed with VL >1000 c/mL. With VL >500 but <1000 c/mL, testing may be unsuccessful but should still be considered. Testing is not recommended with VL <500 c/mL because resistance assays cannot be performed consistently at such low VLs.

Hematology and chemistry panels: The effects of HIV, associated conditions, and adverse effects of drugs may involve hematologic, renal, or hepatic abnormalities.

- Complete blood count (CBC): look for leukopenia, anemia, and thrombocytopenia; lymphocyte count is needed to calculate the absolute CD4+ cell count

- Serum creatinine: increased levels may indicate HIV-associated nephropathy (HIVAN) or drug toxicity

- Abnormal liver function tests (LFTs): may reflect viral hepatitis, alcohol abuse, or drug toxicity. Abnormalities may have an impact on options for ART.

Syphilis serology: High rates of coinfection necessitate routine testing in all HIV infected patients. A reactive nontreponemal assay (rapid plasma reagin [RPR] or venereal disease reaction level [VDRL]) must be confirmed with a treponemal-specific assay (fluorescent treponemal antibody absorption test [FTA] or methoxy trifluoromethyl phenyl acetic acid).

Toxoplasmosis serology (*MMWR Recomm Rep* 2009;58(RR-4):1): Latent toxoplasmosis infection, as indicated by the presence of *Toxoplasma gondii* immunoglobulin G (IgG), may be relevant to decisions on prophylaxis and avoidance of exposure in those who are IgG negative (e.g., avoiding raw or undercooked meat, cat litter). Repeat serology is recommended in patients who were previously IgG negative and have immune reconstitution to a CD4+ cell count >100 cells/mm^3. Also repeat with a decrease in the CD4+ cell count to 100 cells/mm^3, especially if the patient is not receiving *Pneumocystis jirovecii* pneumonia (PCP) prophylaxis, which is active against toxoplasmosis. The prevalence of latent toxoplasma infection varies significantly worldwide; in the United States, the rate is approximately 30%.

CMV serology (IgG): Most HIV infected adults have latent cytomegalovirus (CMV) infection. Knowledge of CMV antibody status can guide the clinician to use CMV-negative blood products if the patient is CMV IgG negative and transfusions are required. Check serology in patients at lower risk for CMV (e.g., non-injection drug users [IDUs]) upon initiation of care (*MMWR Recomm Rep* 2009;58(RR-4):1).

Varicella serology (IgG): Check serology in patients who do not have a history of chicken pox or shingles. If the patient is varicella IgG-negative and is subsequently exposed, administer postexposure prophylaxis with varicella immune globulin (*MMWR Recomm Rep* 2009;58(RR-4):1). Consider varicella vaccination for seronegative patients at increased risk for exposure to VZV.

Hepatitis A, B, C serology (*MMWR Recomm Rep* 2009;58(RR-4):1): Hepatitis A and B serologies will identify those who are not immune and are therefore candidates for vaccination. Laboratory tests for the hepatitis viruses are listed in Table 4-5.

Table 4-5		
Laboratory Tests for Hepatitis Viruses		
Hepatitis Virus	**Laboratory Test**	**Interpretation**
A	HAV IgM Ab	Current or recent HAV infection
	HAV IgG Ab	Immunity to HAV (past infection or after vaccination)
B	HBsAg	Current (acute or chronic) HBV infection
	HBeAg	Current HBV infection with high risk of infectivity
	HBcAb	Past or present HBV infection
	HBsAb	Immunity to HBV (past infection or after vaccination)
C	HCV IgG Ab (ELISA)	Past or present HCV infection
	HCV IgG Ab (RIBA)	Confirms HCV ELISA
	HCV RNA PCR (qualitative, quantitative)	Current HCV infection
	HCV genotype in PCR+s	Useful in determining prognosis, duration of treatment of anti-HCV therapy

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Recommendations are as follows:

Hepatitis A

- Vaccinate HAV Ab-negative IDUs, women with chronic liver disease, and patients infected with hepatitis B or C

- Consider vaccine for all other HIV infected patients without prior exposure by serology

- Vaccine may not produce an adequate immune response in patients with CD4+ cell counts <350 cells/mm^3

Hepatitis B

- Provide vaccine for patients who are susceptible to infection (i.e., patients who are negative for the hepatitis B surface antigen (HbsAg), surface antibody (HbsAb), and core antibody (HBcAb)

- Offer vaccine to sex partners of persons who are HBsAg positive

- Vaccine may not produce an adequate immune response in patients with CD4+ cell counts <350 cells/mm^3

- Consider HBV DNA PCR for patients who are HBcAb positive but HBsAg and/or HBsAb negative. Most of those with isolated HBcAb are not immune and should receive a complete primary vaccination series.

- Choose ART or other potentially hepatotoxic agents carefully for women with chronic HBV (i.e., HBsAg positive or HBsAg negative but HBcAb positive with detectable HBV DNA) infection because of potential increased hepatic toxicity and the need for more-frequent assessment of LFTs

- For patients who are HBsAg positive, ART should include TDF + (FTC or 3TC) to treat both HIV and HBV infections

- In patients with HBV infection and documented cirrhosis, perform alpha-fetoprotein (AFP) and hepatic ultrasound annually to screen for hepatocellular carcinoma

Hepatitis C

- Infection status is needed to guide therapeutic decisions for possible HCV treatment

- Perform HCV antibody test at initiation of care and confirm positive HCV Ab with quantitative HCV RNA

- HIV/HCV coinfected patients may not manifest HCV antibody; consider a qualitative HCV RNA PCR test when HCV is suspected (i.e., with abnormal LFTs and negative serology)

- Women with detectable HCV should be tested for the HCV genotype

- Choose ART or other potentially hepatotoxic agents carefully for women with chronic HCV infection because of potentially increased hepatic toxicity and the need for more frequent assessment of LFTs

- Infants born to HCV infected women should be tested for HCV

- In patients with HCV infection and documented cirrhosis, perform an annual AFP and hepatic ultrasound to screen for hepatocellular carcinoma

Tuberculosis testing (*MMWR Recomm Rep* 2009;58(RR-4):1): A baseline purified protein derivative (PPD) or interferon-gamma release assay should be obtained for all patients who do not have a past history of a positive PPD. Patients who do have a history of a positive PPD should get a baseline chest X-ray (CXR). Note the following:

- A positive PPD in the setting of HIV infection is defined as >5 mm induration

- Anergy testing is not recommended

- Prior bCG vaccination is not a contraindication for PPD but may produce a positive PPD. Evaluate the patient for active TB and consider therapy for latent infection.

- With a positive PPD or interferon-gamma release assay, treat for latent TB after excluding active TB

- Repeat testing in patients with advanced HIV who were initially PPD negative but have subsequent immune reconstitution to a CD4+ cell count >200 cells/mm^3

- Close contacts of persons with active TB should be treated for latent

TB, regardless of PPD results or prior treatment for TB, but active TB must first be ruled out

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Other Laboratory Testing

Glucose-6-phosphate dehydrogenase deficiency: A relative deficiency of glucose-6-phosphate dehydrogenase (G6PD) may be found in up to 2% of African Americans and is not usually clinically significant. An absolute G6PD deficiency is occasionally found in women of Mediterranean ancestry and predisposes to hemolytic anemia with the use of certain medications, including dapsone and sulfonamides. Baseline testing will permit safe use of these drugs when needed.

Fasting blood sugar or hemoglobin A1C and lipid profile (total cholesterol, triglycerides, high-density lipoprotein, low-density lipoprotein): Both HIV and many ARVs have been associated with the development of hypertriglyceridemia and hypercholesterolemia; PIs have been linked to both new onset of and worsening of existing diabetes. Abnormal lipids should trigger a review of diet and exercise and the patient should be encouraged to make appropriate lifestyle changes. Also consider a change of HIV medications and/or anti-lipid therapy. (See *Circulation* 2005;112:3184 for the most recent recommendations.)

Urinalysis/calculated creatinine clearance: Because of an increased risk of HIV-associated nephropathy, this test is particularly important for Black HIV infected patients and patients with advanced disease or comorbid conditions. Perform prior to initiating TDF, IDV, ATV or other drugs with potential for nephrotoxicity.

Pap smear/STI screening: A Pap smear should be obtained (along with screening for gonorrhea, chlamydia and trichomoniasis) at baseline and periodically, with intervals based on prior results and/or treatment for an abnormal Pap, risk behaviors, and signs or symptoms or a diagnosis of STI (see Chapter 6, *Gynecologic Problems*).

Antiretroviral Therapy

DHHS supports several working groups of the Office of AIDS Research Advisory Council to develop and continuously update ARV treatment guidelines for adults and adolescents, children, and pregnant women. Updated recommendations are available at http://www.aidsinfo.nih.gov. The primary areas of attention in the adult and adolescent guidelines include baseline assessment, treatment goals, indications for initiation of ART, choice of the initial regimen in ART-naïve patients, drugs or combinations to be avoided, management of adverse effects and drug-drug interactions, management of treatment failure, and special ART-related considerations in specific patient populations.

This section provides an overview of the general principles of ARV treatment; current evolution of and rationale for recommendations for earlier initiation of ART; current recommendations for initiating therapy in ART-naïve individuals, with special considerations for women; and management of ART-experienced patients. For detailed information on specific ARV agents now available in the U.S., see Table 8-7 (pp. 285–298 in Chapter 8, *Pregnancy*) and Tables 13-7 to 13-9 (pp. 491–512) in Chapter 13, *Pharmacology*).

Goals of Antiretroviral Therapy

Eradication of HIV infection cannot be achieved with currently available ARV drug regimens, largely because a pool of latently infected CD4+ cells is established very early after acute infection (*Proc Natl Acad Sci USA* 1998;95(15):8869) and persists despite prolonged suppression of plasma viremia (*Nat Med* 2003;9(6):727; *Nat Med* 1999;5(5):512). Therefore, the primary goals of ART are to 1) reduce morbidity and mortality associated with HIV infection and improve quality of life; 2) restore and preserve immune function; 3) maximally and durably suppress HIV VL; and 4) prevent HIV transmission (DHHS *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*; http://www.aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0/. Accessed 8/25/2012).

Three characteristics of HIV infection have significant implications for ART:

- **Progressive immune damage:** Between the time of initial infection and the development of clinical disease, progressive immune-system damage occurs, as evidenced by a decline in CD4+ lymphocyte counts as well as by ongoing inflammation and immune activation. These changes ultimately result in vulnerability to OIs and other AIDS-defining conditions as well as in higher rates of cardiovascular and other end-organ damage. Interrupting this progression provides a major rationale for the early initiation of ART.

- **Rapid viral replication:** The half-life of HIV in plasma is less than 48 hours and turnover occurs at a rate of up to 1 billion virions per day (*Nature* 1995;373(6510):123). Lifelong therapy must be maintained to suppress viral replication and prevent disease progression.

- **High degree of inherent genetic mutability:** Mutations may develop rapidly when patients are not adherent to therapy; single mutations may confer high-level resistance to some ARV drugs and/or drug classes. Combination ART, consisting of at least two and preferably three active drugs from at least two drug classes, has been shown to have superior effectiveness in controlling viral replication, limiting the emergence of resistant virus, and reducing the risk of HIV progression and death.

When to Initiate Antiretroviral Therapy

It is now recommended that ART be initiated in all HIV-infected individuals regardless of CD4 cell count to reduce the risk of disease progression ART and to prevent of transmission of HIV. These recommendations are based on

the results of randomized controlled trials and cumulative observational cohort data that demonstrate the benefits of ART in reducing AIDS and non-AIDS associated morbidity and mortality as well as on increasing awareness that HIV-related morbidity and mortality result not only from immune deficiency but also from both the direct effects of HIV on specific organs and the indirect effects of HIV-associated inflammation on those organs. The benefit of ART in reducing transmission to others should also be considered in decisions about when to initiate therapy. The benefits of starting ART with high CD4+ cell counts and/or low viral set points should be balanced against considerations of short- or long-term adverse drug effects and the need for good adherence to lifelong therapy to prevent the development of resistance (DHHS *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*; http://www.aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0/. Accessed 5/16/2013).

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Available data indicate the following:

- Untreated HIV infection may have detrimental effects at all stages of infection

- Treatment is beneficial, even when initiated later in infection; however, later initiation may not fully reverse damage related to viral replication in the early stages of infection

- Earlier treatment may prevent the damage associated with HIV replication in early infection

- Earlier ART treatment is associated with reduced transmission to uninfected partners (*N Engl J Med* 2011; 365:493)

- Sustained viral suppression and maintenance of higher CD4+ cell counts may delay or prevent some HIV-associated but non-AIDS defining complications. Complications that may be delayed or prevented with ART include the following:

  - HIVAN: ART is associated with preserved renal function and prolonged survival (*Nephrol Dial Transplant* 2006;21(10):2809; *AIDS* 2008;22(4):481; *J Am Soc Nephrol* 2005;16(8):2412)

  - Progression of HBV/HCV infection (*Hepatology* 2009;50:1056; *BMC Res Notes* 2008;1:46; *Hepatology* 2008;48:1062)

  - CV disease: Several studies suggest that untreated HIV and viral replication may be associated with endothelial dysfunction and inflammation; that increased markers of inflammation and coagulation, as well as risk of CV events, occur with treatment interruption; and that CV disease is associated with CD4+ cell depletion. Evidence also suggests that ART may result in significant improvement of parameters associated with CV disease, including markers of inflammation, high-sensitivity C-reactive protein, and endothelial dysfunction (*J Acquir Immune Defic Syndr* 2009;52(1):25; *AIDS* 2009;23:929; *J Am Coll Cardiol* 2008;52:569; *PLoS Med* 2008;5:e203; *N Engl J Med* 2006;355:2283; *AIDS* 2009;23:1743; *AIDS* 2008;22:2409).

  - Cancer: Incidence of AIDS- and non-AIDS malignancies is increased as CD4+ cell count decreases to <350–500 cells/mm^{3}. Regardless of CD4+ cell count, there appears to be a protective effect of ART for HIV-associated malignancies (*J Acquir Immune Defic Syndr*

2009;52(1):25; *AIDS* 2009;23:1743; *AIDS* 2008;22:2143; *Clin Infect Dis* 2009;49:1109; *Lancet Oncol* 2009;10:1152).

- Neurocognitive decline: CD4+ cell count <350 cells/mm^3 is associated with higher risk for HIV-associated dementia and more-severe neurologic complications (*Ann Neurol* 2008;63:213; AIDS 2007;21:1915-1921; *AIDS Res Hum Retroviruses* 2008;24:1301)

Current recommendations for ART initiation (adapted from DHHS *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents;* http://www.aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/10/initiating-art-in-treatment-naive-patients. Accessed 5/16/2013):

- Antiretroviral therapy (ART) is recommended for all HIV-infected individuals to reduce the risk of disease progression. The strength and evidence for this recommendation vary by pretreatment CD4 cell count: CD4 count <350 cells/mm^3 (strong recommendation); CD4 count 350–500 cells/mm^3 (strong recommendation); CD4 count >500 cells/mm^3 (moderate recommendation).

- ART also is recommended for HIV-infected individuals for the prevention of transmission of HIV (strong recommendation).

- Patients starting ART should be willing and able to commit to treatment and understand the benefits and risks of therapy and the importance of adherence (strong recommendation). Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy on the basis of clinical and/or psychosocial factors.

Choosing an Initial Regimen

Factors to consider include the following (DHHS *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*):

- Comorbid conditions (e.g., cardiovascular disease, chemical dependency, liver disease, psychiatric disease, renal diseases, TB)

- Potential adverse drug effects

- Potential drug interactions with other medications

- Pregnancy or pregnancy potential

- Results of genotypic drug-resistance testing

- Female gender and pretreatment CD4+ cell count if considering NVP

- HLA-B*5701 testing if considering ABC

- Coreceptor tropism assay if considering MVC

- Patient adherence potential

- Convenience (e.g., pill burden, dosing frequency, food and fluid considerations)

The current guidelines for managing HIV in adults and adolescents offer four preferred regimens for initial therapy in ARV-naïve patients:

- Efavirenz/tenofovir/emtricitabine (EFV/TDF/FTC)

- Ritonavir-boosted atazanavir + tenofovir/emtricitabine (ATV/r + TDF/FTC)

- Ritonavir-boosted darunavir + tenofovir/emtricitabine (DRV/r + TDF/FTC)

- Raltegravir + tenofovir/emtricitabine (RAL + TDF/FTC)

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The DHHS guidelines also describe alternative and acceptable regimens, as well as combinations for which more data are needed and combinations that should be avoided. Chapter 8 of the current book covers recommendations for ART in pregnancy. Consultation with an HIV specialist is recommended for questions about treatment in specific patient situations.

In an ART-naïve patient, VL reduction to levels below the limits of assay detection usually occurs within the first 12–24 weeks of therapy. Predictors of virologic success include use of a high-potency ARV regimen, patient adherence to the treatment regimen, low baseline VL, higher baseline CD4+ cell count (>200 cells/mm^3), and rapid reduction of VL in response to treatment.

In general, studies to date have not shown differences in the virologic efficacy of ART by gender (*AIDS* 2007;21(7):835; *HIV Med* 2006;7(8):520; *Ann Intern Med* 2010;153(6):349), although several studies have suggested that gender may influence the frequency, presentation, and severity of selected ARV-related adverse events (*Expert Rev Anti Infect Ther* 2005;3(2):213). Although data are limited, evidence also suggests that women may metabolize and respond to specific medications, including ARV drugs, differently from men (*Annu Rev Pharmacol Toxicol* 2004;44:499; *Pharmacol Res* 2008;58(3-4):173; *Gend Med* 2007;4(2):106).

Results of a few studies examining metabolic complications associated with ARV use indicate that HIV infected women on ART are more likely than men to experience increases in central fat deposition and less likely than men to have triglyceride elevations (*HIV Med* 2001;2(2):84; *J Acquir Immune Defic Syndr* 2003;34(1):58). Compared with men, women have an increased risk of osteopenia and/or osteoporosis, particularly after menopause, and this risk may be exacerbated by HIV and ART (*Osteoporos Int* 2005;16(11):1345; *AIDS* 2007;21(13):1830). None of these differences, however, currently requires a change in the recommendations for treatment or monitoring in women.

Antiretroviral Agents

See Table 8-7 in Chapter 8, **HIV and Pregnancy**, for ARVs (including co-formulations) currently licensed in the United States, including formulations, dosing, and adverse effects. See Chapter 13, **Pharmacologic Considerations in HIV Infected Pregnant Patients**, for drug interactions and recommended dose adjustments with ARVs.

ARVs are now divided into six classes on the basis of their mechanism of action: NRTIs, NNRTIs, PIs, fusion inhibitors (FIs), CCR5 antagonists, and integrase strand transfer inhibitors (INSTIs). It is helpful to understand how these drug classes inhibit HIV as components of a successful combination regimen.

Nucleoside reverse transcriptase inhibitors: NRTIs were the first class of agents shown to be effective in the treatment of HIV infection. The target enzyme for this group of drugs is HIV reverse transcriptase, an RNA-dependent DNA polymerase. Class-wide adverse effects include lactic acidosis, which appears to have a female predominance. Lactic acidosis is a rare but potentially life-threatening toxicity thought to be due to mitochondrial toxicity and associated with prolonged exposure to NRTIs. It is most common with stavudine, didanosine, and zidovudine; however, it can occur with other NRTIs (*AIDS* 2007;21(18):2455).

Non-nucleoside reverse transcriptase inhibitors: NNRTIs noncompetitively inhibit HIV reverse transcriptase by binding to a site distant from the enzyme's active site. There are three first-generation NNRTIs: nevirapine, delavirdine, and efavirenz. The two second-generation agents, etravirine and rilpivirine, work against HIV that has developed some mutations to the older drugs in this class. NNRTIs are both metabolized by and induce the hepatic cytochrome P450 (CYP) enzyme system, resulting in multiple drug-drug interactions. All NNRTIs are associated with potential rash, which typically appears in the second week of dosing, usually around days 9–11. Dosing can be continued unless there is mucosal involvement, and the rash will resolve. NVP has been associated with an increased risk of symptomatic, potentially fatal, and often rash-associated liver toxicity among ARV-naïve individuals; women with higher CD4+ cell counts (>250 cells/mm^3) and/or elevated baseline transaminases appear to be at the greatest risk (*J Acquir Immune Defic Syndr* 2004;35(5):538; *Clin Infect Dis* 2008;46(6):933; *Clin Infect Dis* 2004;38 Suppl 2:S80; *J Infect Dis* 2005;192(3):545). It is not generally recommended that NVP be prescribed for ARV-naïve women who have CD4+ cell counts >250 cells/mm^3 unless there is no alternative and the benefit from NVP outweighs the risk of hepatotoxicity.

Protease inhibitors: PIs prevent maturation of virus proteins by competitively inhibiting HIV protease, an enzyme essential for cleavage of the HIV polyprotein into its separate active structural proteins; three viral enzymes (reverse transcriptase, integrase, and protease); and surface glycoproteins. When this enzyme is blocked, immature, noninfectious virus particles are produced. The other important properties of PIs are limited CNS penetration; metabolism by and complex effects on the CYP enzyme system, resulting in multiple drug-drug interactions; and an increased incidence of new diagnoses of diabetes or worsening of pre-existing diabetes.

Ritonavir, an early PI that was very difficult to tolerate at full dose, has more recently been used to enhance or boost the pharmacokinetic profiles of other PIs and other ARVs primarily metabolized by CYP 3A4, such as the CCR5 antagonist maraviroc, because it is such an effective inhibitor of CYP 3A4. RTV-boosted PI regimens that permit fewer doses and/or fewer pills

per day while achieving high PI drug levels are preferred over unboosted dosing regimens. Boosting thus facilitates adherence and helps prevent the development of resistance.

All PIs are associated with variable degrees of gastrointestinal adverse effects (nausea, diarrhea, abdominal discomfort), hyperlipidemia, hyperglycemia, and fat maldistribution (central adiposity and/or peripheral lipoatrophy). All boosted PIs should be taken with food.

Fusion inhibitors: FIs interact with HIV directly, rather than with the host cell. This interaction prevents the fusion of HIV to the cell. Because it is a protein, enfuvirtide, the first drug in this class, must be given by subcutaneous injection twice daily. The most common side effect is local injection-site reactions.

CCR5 antagonists: This is the only drug class that targets a host cellular protein rather than a viral protein. To gain access to a CD4+ cell, HIV must first bind to the CD4+ receptor, undergo a conformational change, and then bind to the CCR5 coreceptor as a prelude to virus-cell fusion. MVC, the first drug in this class, is very well tolerated but is effective only against virus that solely utilizes CCR5; it is not effective against virus that can bind to both CCR5 and the CXC chemokine receptor type 4 (CXCR4), or solely to CXCR4. A tropism assay can determine whether MVC will be effective.

Integrase strand transfer inhibitors: This is the most recently approved class of ARVs. INSTIs prevent the covalent integration of proviral DNA into cellular DNA, thus preventing the manufacture of the constituent parts of new virions by an infected cell. Raltegravir, the first drug in this class, is well tolerated and at a dose of 400 mg twice daily produces a very rapid decrease in HIV VL within the first few weeks of treatment. It has no effect on CYP 450 and therefore produces minimal drug-drug interactions. It inhibits another hepatic enzyme, UGT1, that is involved in glucuronidation. A second INSTI, elvitegravir, has been FDA approved for ART-naïve patients; it is available in a co-formulated tablet with FTC, TDF and cobicistat (a pharmokinetic enhancer) and is given once daily. Approval of a third INSTI, dolutegravir, is anticipated in the near future.

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Adherence

Medication adherence is the crucial element in successful HIV treatment. (See Chapter 5, *Adherence*.) Studies have shown that healthcare professionals are poor judges of who will and will not be adherent. For this reason, all patients initiating therapy should be educated about the importance of adherence, and adherence should be discussed repeatedly over the course of treatment to offset the effects of treatment fatigue. The most frequent reason for an increase in viral load is poor adherence and any increase in viral load should prompt assessment of the patient's adherence to the prescribed ART regimen. A potential reason for poor adherence in pregnancy is concern on the patient's or the provider's part that ARV drugs are dangerous in early pregnancy. Although multiple strategies have been employed to support and promote adherence, no data indicate which strategies are most effective.

Adverse Events Associated with Antiretroviral Therapy

Complications of particular clinical significance or concern are included in Table 4-6, with additional key information noted below. In general, decisions about management, including changes in ART, should be made in consultation with an HIV specialist.

Table 4-6	
Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects	
Adverse Effect	**Antiretroviral Agent(s)**
Bleeding events	• All PIs: ↑ spontaneous bleeding • TPV: Reports of intracranial hemorrhage. Risk factors include CNS lesions; trauma; surgery; hypertension; alcohol abuse; coagulopathy; use of anticoagulant or antiplatelet agents, including vitamin E.
Bone marrow suppression	• ZDV: Anemia, neutropenia
Cardiovascular disease	• ABC and ddI: Associated with MI in some cohort studies. Risk greatest among those with traditional CVD risk factors. • PIs: Associated with MI and stroke in some cohort studies. Risk greatest among those with traditional CVD risk factors. Limited data on newer PIs (ATV, DRV, TPV). • SQV/r, ATV/r, and LPV/r: PR interval prolongation. Risks include structural heart disease, conduction system abnormalities, cardiomyopathy, ischemic heart disease, and coadministration with other drugs that prolong PR interval. • SQV/r: QT interval prolongation in a study of healthy volunteers. Risks include underlying heart conditions, pre-existing prolonged QT or arrhythmia, or use with other QT-prolonging drugs. ECG is recommended prior to SQV initiation and should also be considered during therapy.
CNS effects	• d4T: Associated with rapidly progressive ascending neuromuscular weakness resembling Guillain-Barré syndrome (rare) • EFV: Somnolence, insomnia, abnormal dreams, dizziness, impaired concentration, depression, psychosis, suicidal ideation. Most symptoms subside or diminish after 2–4 wk. Bedtime dosing may reduce symptoms. Risk factors include history of psychiatric illness, concomitant use of agents with neuropsychiatric effects, and ↑ plasma EFV concentrations due to genetic factors or absorption (i.e., with food).
Diabetes mellitus, Insulin resistance hyperglycemia	• ZDV, d4T, and ddI • Reported for some PIs (IDV, LPV/r), but not all PIs studied • ATV +/- RTV not found to alter insulin sensitivity
Hyperlipidemia	• d4T > ZDV > ABC: ↑ LDL and TG • EFV: ↑TG, ↑LDL, ↑HDL • All RTV-boosted PIs: ↑LDL, ↑TG, ↑HDL • LPV/r = FPV/r and LPV/r > DRV/r and ATV/r

Table 4-6	*continued*

Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects

Adverse Effect	Antiretroviral Agent(s)
Gastrointestinal	• ddI, ZDV > other NRTIs: Nausea and vomiting • ddI: Pancreatitis • PIs: Diarrhea, nausea, vomiting • LPV/r > DRV/r and ATV/r; NFV (common): Diarrhea • ATV: cholelithiasis

Hepatic toxicity	• NRTIs: Reported for most
	  - ddI: Prolonged exposure linked to noncirrhotic portal hypertension, in some cases with esophageal varices
	  - ZDV, d4T, ddI: Most commonly associated with steatosis
	  - TDF, 3TC, FTC: When withdrawn, HBV coinfected patients may develop severe hepatic flare (also when HBV resistance develops)
	• NNRTIs: NVP > other NNRTIs
	  - NVP: Severe hepatic toxicity with NVP is often associated with skin rash or symptoms of hypersensitivity. For ARV-naïve patients, risk is greater for women with pre-NVP CD4+ cell count >250 cells/mm³. Overall risk is higher for women. Risk is greatest during first few months of treatment. 2-wk dose escalation of NVP reduces risk of rash and may reduce hepatotoxicity if related to hypersensitivity. NVP is contraindicated in patients with moderate to severe liver disease (Child-Pugh classification B or C).
	• All PIs: Varying degrees of drug-induced hepatitis and hepatic decompensation (and rare cases of fatalities) have been reported with all PIs
	  - TPV/r has a higher frequency of hepatic events than other PIs
	  - IDV, ATV: Jaundice due to indirect hyperbilirubinemia
	  - TPV/r: Contraindicated in patients with moderate to severe hepatic insufficiency (Child-Pugh classification B or C)
	• CCR5 antagonist: MVC

Hypersensitivity reaction (excluding rash alone or Stevens–Johnson syndrome)	• ABC: Screen for HLA-B*5701 prior to initiation; do not start ABC therapy if HLA-B*5701 is positive. Symptoms of HSR include (in descending order of frequency): fever, skin rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, respiratory symptoms. HSR worsens with continuation of ABC. Median onset, 9 d; ~90% of reactions occur within first 6 wk. Onset of rechallenge reactions is within hours of rechallenge dose. Patients, regardless of HLA-B*5701 status, should not be rechallenged with ABC if HSR is suspected. • NVP: Hypersensitivity syndrome of hepatic toxicity and rash that may be accompanied by fever, general malaise, fatigue, myalgias, arthralgias, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, granulocytopenia, lymphadenopathy, or renal dysfunction. For ARV-naïve patients, risk is greater for women with pre-NVP CD4+ cell count >250 cells/mm³. Risk is higher for women. 2-wk dose escalation of NVP reduces risk. • RAL: Rash, constitutional findings and sometimes organ dysfunction • MVC: Reported as part of a syndrome related to hepatotoxicity

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Table 4-6	*continued*

Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects

Adverse Effect	Antiretroviral Agent(s)
Lactic acidosis	• NRTIs, especially d4T, ZDV, and ddI: Insidious onset with GI prodrome, weight loss, and fatigue. May be rapidly progressive, with tachycardia, tachypnea, jaundice, muscular weakness, mental status changes, respiratory distress, pancreatitis, and organ failure. Mortality up to 50% in some case series, especially in patients with serum lactate >10 mmol/L. Increased risk: female sex, obesity. • Laboratory findings: ↑ lactate (2–5 mmol/L: correlate with symptoms; >5 mmol/L abnormal), anion gap, AST, ALT, PT, bilirubin; ↑ amylase and lipase in patients with pancreatitis; ↓ arterial pH, serum bicarbonate, serum albumin • Upon diagnosis, stop all ARV drugs until recovery
Lipodystrophy (fat maldistribution syndromes)	• Thymidine analogs (d4T > ZDV): Lipoatrophy; may be more likely when combined with EFV vs. boosted PI • EFV-, PI-, and RAL-containing regimens: Lipohypertophy (trunk fat increase) has been observed; however, a causal relationship has not been established
Myopathy and/ or elevated CPK	• ZDV: Myopathy • RAL: ↑ CPK, muscle weakness, rhabdomyolysis
Nephrotoxicity and/or urolithiasis	• TDF: ↑ serum creatinine, proteinuria, hypophosphatemia, urinary phosphate wasting, glycosuria, hypokalemia, non-anion gap metabolic acidosis; concurrent use of PI may increase risk • IDV: ↑ serum creatinine, pyuria; hydronephrosis or renal atrophy • IDV, ATV: Stone, crystal formation; adequate hydration may reduce risk • EVG (co-formulated with cobicistat): potential for new or worsening renal impairment
Osteopenia and/or osteoporosis	• TDF: Associated with greater loss of bone mineral density compared with ZDV, d4T, and ABC • Decreases in bone mineral density observed in studies of regimens containing different NRTIs combined with either NNRTIs or PIs
Peripheral neuropathy	• d4T > ddI, ddC: Peripheral neuropathy (pain and/or paresthesias, lower extremities > upper extremities); can be irreversible
Rash	• All NNRTIs • ATV, DRV, FPV • RAL: Uncommon • MVC
Stevens–Johnson syndrome and/or toxic epidermal necrolysis	• ddI, ZDV: Reported cases • NVP > DLV, EFV, ETR, RPV; females at greater risk than males • FPV, DRV, IDV, LPV/r, ATV: Reported cases • RAL: Reported cases

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Source: Adapted from *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*

Hepatotoxicity: Hepatotoxicity, generally defined as a three- to fivefold increase in serum transaminases, may occur with or without clinical hepatitis. NVP has the greatest potential for causing hepatotoxicity (up to 12%). Approximately two-thirds of NVP-associated cases of clinical hepatitis occur within the first 12 weeks of treatment; however, risk continues after this time and patients should be monitored closely for the first 18 weeks of treatment.

The initial presentation may include nonspecific gastrointestinal and flu-like symptoms. Although liver-enzyme abnormalities may or may not be present initially, this syndrome can progress rapidly to fulminant hepatic failure. Risk factors for hepatic toxicity include HBV or HCV coinfection, alcohol abuse, baseline elevated liver enzymes, and concomitant use of other hepatotoxic agents (*Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*).

Lactic acidosis: Lactic acidosis is usually seen with long-term NRTI exposure. Because the initial signs and symptoms are nonspecific, clinicians should have a high level of suspicion for this adverse effect. Routine lactate testing is not recommended; however,testing should be performed with signs or symptoms of possible lactic acidosis. ART should be stopped if clinical and laboratory manifestations are consistent with lactic acidosis. A new regimen should commence after recovery, which can take months.

Lipodystrophy (fat maldistribution syndromes): Fat accumulation is most commonly seen in the abdomen, neck (dorsocervical fat pad), and breasts. Lipoatrophy most commonly affects the face, buttocks, and extremities; risk has been associated with d4T use in particular. Women seem particularly prone to developing truncal obesity (i.e., increased abdominal girth, increased breast size). Women who perceive adverse changes in body habitus related to their ARV regimens may be at increased risk for nonadherence. It may be useful to obtain some standard measurements, such as minimum waist, maximum hip, and neck circumference at an early visit, before ART is started, and to question the patient at regular intervals about any perceived changes in body shape or changes in clothing and brassiere size. Such measurements, while inexact, are inexpensive and easier to obtain than anthropomorphic measurements, dual-emission X-ray absorptiometry, or computed tomography (CT) scans.

Management of the Treatment-Experienced Patient

In general, a distinction is made between patients with limited prior treatment and those with extensive prior treatment because those with more limited ARV experience have a greater likelihood of achieving maximal viral suppression with an appropriate change in regimen. Assessing and managing a patient with extensive prior ARV experience and treatment regimen failure is complex and expert advice is critical. Changing therapy sooner rather than later is recommended to minimize the continued selection of resistance mutations.

The DHHS Guideline Panel's overall recommendations for management of the patient whose current therapy is failing are as follows: (adapted from *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*; http://www.aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0/. Accessed 8/25/2012)

- **Evaluate virologic failure** (defined as the inability to achieve or maintain suppression of viral replication <200 c/mL): Assess the severity of the patient's HIV disease, ART history, use of concomitant medications (with consideration of possible adverse drug interactions with ARV agents), HIV RNA and CD4+ cell count trends over time, and prior drug-resistance testing results.

- **Perform drug-resistance testing:** Test for drug resistance while the patient is taking the failing ARV regimen (or within 4 weeks of treatment discontinuation). To avoid false-negative results in patients who have discontinued their treatment regimen, it may be helpful to have them restart their medications for a week or so and then obtain a resistance test.

- **Re-establish virologic suppression:** The goal of treatment for ARV-experienced patients with drug resistance who are experiencing virologic failure is to re-establish virologic suppression (e.g., HIV RNA below the current limit of detection).

- **Design a new regimen:** Use the patient's treatment history and past and current resistance test results to identify at least two, and preferably three, fully active agents to combine with an optimized background ARV regimen. A fully active agent is one that is likely to have ARV activity on the basis of the patient's treatment history, the results of drug-resistance testing, and/or the presence of a novel mechanism of action.

- **Do not add just one ARV:** In general, adding only a single, fully active ARV to a new regimen is not recommended because of the risk that resistance to this agent will develop rapidly. In patients with a high likelihood of clinical progression (e.g. CD4+ cell count <100 cells/mm^3) and limited drug options, however, adding a single drug may reduce the risk of immediate clinical progression because even transient decreases in HIV RNA and/or transient increases in CD4+ cell counts have been associated with clinical benefits.

- **Adjust goals:** For some highly ART-experienced patients, maximal virologic suppression is not possible. In these cases, ART should be continued with regimens designed to minimize toxicity, preserve CD4+ cell counts, and avoid clinical progression.

- **Avoid interruption:** Discontinuing or even briefly interrupting therapy in a patient with viremia may lead to a rapid increase in HIV RNA and a decrease in CD4+ cell count and increases the risk of clinical progression (*N Engl J Med*. 2001;344(7):472; *N Engl J Med*. 2003;349(9):837). Therefore, this strategy is not recommended.

- In the setting of virologic suppression, no consensus exists on how to define or treat immunologic failure.

Other important clinical situations besides overt virologic failure are not necessarily linked to the development of resistance, such as

- Incomplete virologic response: defined as two consecutive plasma HIV RNA levels >200 c/mL after 24 weeks; the baseline HIV RNA level may affect the time course of response and some regimens take longer than others to suppress HIV RNA levels

- Virologic rebound: defined as a confirmed detectable HIV RNA (to >200 c/mL) after virologic suppression

Treatment failure may occur for several reasons. It is important to try to distinguish among these reasons because approaches to the management of treatment failure will vary depending on the reason. In addition to patient and regimen characteristics, provider characteristics, such as inexperience in treating HIV disease, may also come into play. In some cases, the cause of treatment failure may be unknown.

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Patient characteristics:	ARV regimen characteristics:
• Higher pretreatment or baseline VL • Lower pretreatment or nadir CD4+ cell count • Prior AIDS diagnosis • Comorbidities (e.g., active substance abuse, depression) • Presence of drug-resistant virus, either transmitted or acquired • Prior treatment failure • Incomplete medication adherence and missed clinic appointments	• Drug side effects and toxicities • Suboptimal pharmacokinetics (variable absorption, metabolism, or [theoretically] penetration into reservoirs) • Food and/or fasting requirements • Bedtime dosing problems (e.g. falling asleep early, sleeping at different location from where medications are kept) • Adverse drug-drug interactions with concomitant medications • Suboptimal potency • Prescription errors

To assess virologic failure, the clinician should evaluate the following (adapted from *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*; http://www.aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0/. Accessed 8/25/2012):

- **ARV treatment history:** any changes in VL and CD4+ cell counts over time; results of prior resistance testing (if any)

- **Occurrence of HIV-related clinical events:** thorough interval history and physical exam

- **Medication-taking behavior:** adherence to recommended drug doses, dosing frequency, and food/fasting requirements; if problems are identified, address the underlying cause(s) (e.g., difficulties accessing or tolerating medications, depression, active substance abuse)

- **Tolerability of medications:** severity and duration of side effects; even minor side effects can affect adherence

- **Concomitant medications and supplements:** consider adverse drug-drug interactions

- **Comorbidities:** e.g., substance abuse

With regard to adherence, some patients do not want to disappoint their care providers and will insist that they are adherent even when they are not. Avoid putting such patients on the defensive. Refer to the facts provided by CD4+ cell count and VL load tests and encourage the patient to participate in the process of creating a new regimen or identifying supportive care

or behavioral changes that will ensure treatment success. The following management strategies may be helpful if problems with adherence are suspected or confirmed:

- If possible, simplify the ARV regimen (e.g., decrease pill count or dosing frequency)

- Provide symptomatic treatment of side effects, such as antiemetics or antidiarrheals; some patients may need scheduled antiemetics before each ARV dose until nausea abates

- Exchange one ARV for another within the same drug class (for medication intolerance)

- Exchange ARV from one drug class to another if necessary and if no prior drug resistance is suspected (for medication intolerance)

- Review recent history of gastrointestinal symptoms, such as vomiting or diarrhea, to assess the likelihood of short-term malabsorption

- Review concomitant medications and dietary supplements for possible adverse drug-drug interactions (see Chapter 13, *Pharmacologic Considerations in HIV Infected Pregnant Patients*; Drug Interactions section, Tables 14–16, *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*; http://www.aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0/. Accessed 8/25/2012) and make appropriate substitutions

- If decreased ARV exposure due to pharmacokinetic drug-drug interactions or impaired drug absorption is suspected, therapeutic drug monitoring (TDM) may be helpful

Resistance Testing

When a regimen is changed for lack of efficacy, information from resistance testing can be of pivotal importance in choosing a new regimen.

Genotypic assays: These assays determine changes in the nucleotide sequences in viral genes. Interpretation of test results requires knowledge of the mutations for which different ARV drugs select and of the potential conferred by certain mutations for cross-resistance to other drugs. The International Antiviral Society-USA maintains an updated list of significant resistance-associated mutations in the RT, PR, integrase, and envelope genes (see https://www.iasusa.org/node/128; accessed 8/25/2012). The Stanford University HIV Drug Resistance Database (see http://hivdb.stanford.edu; accessed 8/25/2012) also provides helpful guidance for interpreting genotypic resistance test results.

Genotypes are reproducible, are less expensive than phenotypes, and provide relatively rapid results (1–2 weeks). Results are reported as a three-piece string of information for each mutation detected: 1) initial associated with the wild-type amino acid (e.g., M for methionine), 2) number of the codon involved (e.g., codon 184 in reverse transcriptase), and 3) initial associated with the

amino acid coded for by the mutated codon (e.g., V for valine). Thus, the common key mutation in the RT gene that confers complete resistance to 3TC and FTC is M184V.

Phenotypic assays: These assays directly determine the amount of a medication that is required to inhibit the patient's virus. The median inhibitory concentration (IC) 50 (the drug concentration that inhibits viral replication by 50%) is calculated and the ratio of the IC50 of test and reference viruses is reported as the *fold increase* in IC50 (i.e., fold resistance). Phenotypic assays are most useful for finding agents with partial activity in patients with multiple drug resistance; this approach is more expensive and time consuming than genotypic assays. In addition, although clinically significant fold-increase cutoffs are now available for some drugs, information is incomplete regarding the specific fold increase in IC50 that is associated with drug failure.

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Limitations of resistance testing: Both phenotypic and genotypic assays are typically difficult to perform if the viral copy number is <1000 c/mL, although some specimens with >500 c/mL but <1000 c/mL can be successfully tested. The utility of these assays is also limited by an inability to detect resistant virus that makes up less than 10%–20% of the total viral population in a sample, termed *minority species*.

Furthermore, these assays will only reliably detect mutations that confer resistance to medications the patient is taking at the time the assay is performed; samples from patients who are off therapy are likely to show wild-type (sensitive) virus as the predominant circulating viral strain because it is the strain that replicates most successfully. Thus, resistance testing is insensitive to mutations secondary to selective pressure that is no longer present after a change in regimen. Virus with these mutations likely still exists as a small percentage of the circulating virus and may lead to clinical resistance if drugs that test "sensitive" are used; however, these drugs are inactive against resistant minority species, which can become dominant over time.

If the same ARV agents (or those sharing similar resistance pathways) are reinstated, early drug failure usually occurs; the virus present at failure is derived from previously archived resistant virus (*J Infect Dis* 2006;194(9):1309). Reversion to predominantly wild-type virus can occur in the first 4–6 weeks after drugs are stopped; therefore, resistance testing is of greatest value when performed before or within 4 weeks after drugs are discontinued.

Patients with pansensitive virus in the face of virologic failure should be questioned carefully but nonjudgmentally about their medication-taking behaviors. TDM can also be considered, although no data currently demonstrate that TDM improves clinical outcome.

Treatment Interruptions (Drug Holidays)

Several studies have shown that both HIV-associated and non-HIV-associated outcomes (renal, cardiac, hepatic) are worse when treatment is interrupted (*N Engl J Med* 2006;355(22):2283; *Lancet* 2006;367(9527):1981; *HIV Med* 2007;8(2):96; *AIDS* 2004;18(3):439). Therefore, long-term interruption of HIV therapy should be avoided if at all possible.

Treatment of Acute and Recent HIV Infection

The benefits of treating acute and recent (with the first 6 months) HIV infection are not completely defined. The rationale for early treatment is that it will achieve early suppression of viremia with alteration of the initial viral setpoint. This can slow disease progression rates, reduce the rate of viral mutation by suppressing viral replication, preserve immune function, and reduce the risk of viral transmission. The potential risks of initiating therapy include exposure to ART without a known clinical benefit, drug toxicities, development of drug resistance, creation of an ongoing need for strict adherence to therapy, and adverse effects on quality of life. Unanswered questions about the risks and benefits of early therapy should be addressed with patients and treatment of early HIV infection should be offered. Enrollment in clinical trials and observational studies of acute HIV should be considered.

In treating acute HIV, it is always important to use a three- or four-drug regimen that would be expected to provide complete viral suppression. In addition to considering the source of exposure and local epidemiologic information, genotypic resistance testing should be performed. In acute HIV infection, a patient's predominant virus will be the strain that was transmitted, without reversion to the wild-type (pansensitive) virus that is seen in chronically infected patients who have stopped treatment.

Treatment in Pregnancy

ART is indicated in pregnancy to reduce the risk of perinatal transmission and to treat maternal disease. Specific guidelines for optimal therapy are addressed in Chapter 8, ***HIV and Pregnancy,*** and in the DHHS guideline *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States,* available at http://aidsinfo.nih.gov/guidelines/html/3/perinatal-guidelines/0/ (accessed 5/16/2013).

Alternative or Complementary Therapy

Some patients may ask questions about alternative or complementary therapy or may indicate that they are already taking such therapy. All patients should be specifically asked about their use of such therapies because they may not consider these remedies to be medications and may not volunteer the information to a care provider. Specific complementary therapies change rapidly and their use varies widely with geography and patient demographics.

For patients who do choose such therapies, it is important to ensure that they avoid using agents with toxicities or drug interactions that overlap with their prescribed medications and that discussions about complementary or alternative therapies occur in a way that does not alienate patients from their involvement in medical care.

Presentation and Management of Opportunistic Infections and Other Conditions Associated with HIV/AIDS

4

The risk for various opportunistic processes—so called because they take advantage of a weakened immune system—is defined by the total CD4+ lymphocyte count. Opportunistic processes include OIs and certain malignancies and are similar to the diseases seen in other immunocompromised hosts, such as recipients of solid-organ transplants. AIDS was first recognized as a new entity by the characteristic pattern of opportunistic diseases—especially PCP and Kaposi's sarcoma (KS)—that were being diagnosed in young, previously healthy gay men. The pattern and sequence of OIs that are seen as the total CD4+ cell count decreases, described in Table 4-7, is so reliable that in most cases the total CD4+ cell count limits the differential diagnosis.

Table 4-7

Correlation of Complications with CD4+ Cell Counts

CD4+ Cell Count*	Infectious Complications	Noninfectious† Complications
>500 cells/mm^3	• Acute retroviral syndrome • Candida vaginitis	• PGL • Guillain-Barré syndrome • Myopathy • Aseptic meningitis
200–500 cells/mm^3	• Pneumococcal and other bacterial pneumonia • Pulmonary tuberculosis • Herpes zoster • Oropharyngeal candidiasis (thrush) • Cryptosporidiosis, self-limited • KS • Oral hairy leukoplakia	• CIN • Cervical cancer • B-cell lymphoma • Anemia • Mononeuritis multiplex • ITP • Hodgkin's lymphoma • Lymphocytic interstitial pneumonitis
<200 cells/mm^3	• PCP • Candida esophagitis • Disseminated histoplasmosis and coccidioidomycosis • Miliary/extrapulmonary TB	• Wasting • Peripheral neuropathy • HIV-associated dementia • Cardiomyopathy • Vacuolar myelopathy • Progressive polyradiculopathy • Non-Hodgkin's lymphoma

Table 4-7	*continued*

Correlation of Complications with CD4+ Cell Counts

CD4+ Cell Count*	Infectious Complications	Noninfectious† Complications
<100 cells/mm^3	• Disseminated herpes simplex • Toxoplasmosis • Cryptococcosis • Cryptosporidiosis, chronic • Microsporidiosis • PML	
<50 cells/mm^3	• CMV end-organ disease: primarily retinitis (~80–85%), GI (~15%) • Disseminated MAC	• CNS lymphoma

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

* Most complications occur with increasing frequency at lower CD4+ cell counts

† Some conditions listed as "noninfectious" are probably associated with transmissible microbes. Examples include lymphoma (Epstein-Barr virus [EBV]) and cervical cancer (human papillomavirus [HPV]).

Source: © Adapted with permission from *Medical Management of HIV Infection.* Baltimore: Johns Hopkins University School of Medicine; 2009-2010.

At CD4+ cell counts >500 cells/mm^3, illnesses are rarely associated with the patient's HIV serostatus. Non-Hodgkin's lymphoma and, rarely, mucocutaneous KS are occasional exceptions; they can occur at varying CD4+ cell counts but are more frequently diagnosed at lower values. Infections that are virulent among HIV-seronegative women, such as TB, bacterial pneumonia, and invasive cervical cancer, may occur at any CD4+ cell count but are more common and more severe as the CD4+ cell count declines.

Between 200 cells/mm^3 and 500 cells/mm^3, less-serious HIV-associated problems begin to manifest themselves, such as oral hairy leukoplakia, various skin problems, shingles, and oral or recurrent vaginal candidiasis (thrush). According to the 1993 CDC case definition, AIDS may be defined by specified OIs or by a decline in the total CD4+ cell count to below 200 cells/mm^3. This CD4+ cell count criterion acknowledges an important threshold for OI risk. PCP, the most common AIDS-defining OI, is usually diagnosed as patients approach and drift below this critical number. Other OIs, such as toxoplasmosis, cryptococcal meningitis, and disseminated histoplasmosis, tend to occur as the CD4+ cell count declines from <200 cells/mm^3 to <100 cells/mm^3. Typically, end-stage illnesses such as CNS lymphoma, CMV end-organ disease, and disseminated *Mycobacterium avium* complex (MAC), tend to occur at very low CD4+ cell counts, often less than 25–50 cells/mm^3.

Antimicrobial therapy works in concert with a patient's immune system to clear infection. Before the advent of potent combination ART, HIV-associated opportunistic diseases could not be controlled without ongoing suppressive therapy because a patient's immune function was too weak to effect that control. Once an OI was diagnosed and treated acutely (induction therapy, borrowing from the language of oncology), treatment would be continued at a lower maintenance dose or the OI would inevitably recur. "Cure" of OIs was not part of the vocabulary of HIV disease management. With potent combination ART resulting in dramatic improvement in CD4+ cell counts and immune function, however, both prophylactic and chronic suppressive OI therapies are being withdrawn successfully in responders. This has opened an entirely new era in the care of people with advanced HIV (see **Opportunistic Disease in the Era of Antiretroviral Therapy**, p. 132).

Prophylaxis of Opportunistic Infections

One of the early significant advances in the management of HIV/AIDS was the demonstration that chemoprophylaxis could prevent PCP and thereby improve survival. Before the development of potent combination ART, an important focus of the clinical research effort was to identify effective prophylactic agents for other common OIs. The success of this research was in part responsible for the slowdown in the death rate from AIDS that first became apparent near the end of 1995, just before the era of potent combination ART began.

Recommendations for prophylaxis for specific OIs depend on a number of factors (Table 4-8): the CD4+ threshold that defines the greatest risk, overall effectiveness of a given approach, risk of developing resistance, pregnancy, toxicity, and cost. The U.S. Public Health Service (USPHS)/Infectious Diseases Society of America guidelines for OI prophylaxis are updated periodically to reflect the most current understanding of disease risk and prevention. Current recommendations for initiating primary OI prophylaxis can be found on the Clinical Guidelines Portal of the AIDSinfo website (http://www.aidsinfo.nih.gov/guidelines; accessed 5/17/2013).

Table 4-8

Prophylaxis to Prevent a First Episode of Opportunistic Disease in Adults and Adolescents Infected With HIV

Pathogen	Indications	First Choice Regimen	Alternative Regimens
Pneumocystis jiroveci (formerly carinii)	**Strong recommendation:** • CD4+ cell count <200 cells/mm³ **or** • Oropharyngeal candidiasis **Moderate recommendation:** • CD4+ percentage <14% **or** • History of AIDS-defining illness **or** • CD4+ cell count >200 but <250 cells/mm³ and if CD4+ cell count monitoring every 3 mo is not possible	• TMP-SMX 1 DS or 1 SS po qd	• TMP-SMX 1 DS po tiw • Dapsone 100 mg po qd or 50 mg po bid • Dapsone 50 mg po qd + pyrimethamine 50 mg po qw + leucovorin 25 mg po qw • Dapsone 200 mg po qw + pyrimethamine 75 mg po qw + leucovorin 25 mg po qw • Aerosolized pentamidine 300 mg q mo via Respirgard II nebulizer • Atovaquone 1500 mg qd

Tuberculosis	**Strong recommendation:**
	• Screen (+) for latent TB infection but no evidence of active TB disease and no history of past treatment for active or latent TB
	  - TST reaction ≥5 mm **or**
	  - (+) Interferon gamma release assay
	• Screen (–) for latent TB infection and no evidence of active TB disease but close contact with case of active TB
	• Note: Patients with negative screening tests for latent TB and with CD4+ cell count <200 cells/mm³ and no indications for initiating empiric latent TB treatment should be retested for latent TB once they start ART and attain a CD4+ cell count ≥200 cells/mm³
		• Isoniazid 300 mg po qd or isoniazid 900 mg po biw; both with pyridoxine, 25 mg po qd x 9 mo
		• For exposure to resistant TB, consult expert
			• Rifampin 600 mg po qd x 4 mo or
			• Rifabutin (dose adjusted based on concomitant ART) x 4 mo

Toxoplasma gondii	**Strong recommendation:** • IgG antibody to toxoplasma and • CD4+ cell count <100 cells/mm³ **or** • If toxoplasma seroconversion occurs	• TMP-SMX 1 DS po qd	• TMP-SMX 1 DS po tiw • TMP-SMX 1 SS po qd • Dapsone 50 mg po qd + pyrimethamine 50 mg po qw + leucovorin 25 mg po qw • Dapsone 200 mg po qw + pyrimethamine 75 mg po qw + leucovorin 25 mg po qw

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Table 4-8 *continued*

Prophylaxis to Prevent a First Episode of Opportunistic Disease in Adults and Adolescents Infected With HIV

Pathogen	Indications	First Choice Regimen	Alternative Regimens
Mycobacterium avium complex	Strong recommendation: • CD4+ cell count <50 cells/mm³ after ruling out active MAC infection (negative clinical assessment +/–negative MAC blood cultures)	• Azithromycin 1200 mg po qw • Clarithromycin 500 mg po bid • Azithromycin 600 mg po twice weekly • Both agents are better tolerated if taken with food	• Rifabutin 300 mg po qd (dosage adjustment based on drug-drug interactions with ART; see Table 13-9, pp. 500–507) • Rule out active TB before starting rifabutin
Malaria	• Travel to disease-endemic area	• Recommendations are the same for patients with and without HIV infection • One of the following three drugs is usually recommended depending on location: atovaquone/proguanil, doxycycline, or mefloquine • Refer to the following website for the most recent recommendations based on region and drug susceptibility: http://www.cdc.gov/malaria/ (accessed 7/31/2012) • Prevent exposure with use of DEET-containing repellants and insecticide-impregnated bed nets, when indicated	
Histoplasma capsulatum	Moderate recommendation: • CD4+ cell count ≤150 cells/μL and at high risk because of occupational exposure or living in area with high rate of histoplasmosis (>10 cases/100 patient-years)	• Itraconazole 200 mg po qd	
Coccidioidomycosis	Moderate recommendation: • New (+) IgM or IgG in patients living in disease-endemic area and with CD4+ cell count <250 cells/μL	• Fluconazole 400 mg po qd	

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Source: Adapted from Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents

Regimens, doses, and indications for routine immunizations in HIV infected women are outlined in Table 4-9.

Table 4-9

Routine Immunizations for HIV Infected Women*

Vaccine	Dose and Regimen	Indications and comments
Hepatitis A	• 1 mL IM at 0, 6–12 mo (Havrix) • 1 mL IM at 0, 6–18 mo (Vaqta) • Also available in combination with HBV vaccine (Twinrix) given in 3–4 doses	• IDU, chronic liver disease, HBV or HCV infection, travel to endemic areas • Consider for all HIV infected patients who are hepatitis A antibody negative • IgG antibody response should be assessed 1 mo after vaccination; nonresponders should be revaccinated when CD4+ cell count >200 cells/µL
Hepatitis B	• Engerix B 20 mcg or Recombivax HB 10 mcg IM at 0, 1, and 6 mo • Available in combination with HAV vaccine (Twinrix) given in 3–4 doses	• Administer to patients without evidence of past or current HBV infection • In patients with isolated anti-HBc, consider screening for HBV DNA before vaccination to rule out occult chronic HBV infection • Test for anti-HBs after dose 3; repeat series should be considered for nonresponders (anti-HBs <10 IU/mL 1 mo after dose 3) and higher dose (40 mcg) booster is recommended by some experts • Some experts may delay revaccination until sustained increase in CD4+ cell count with ART if CD4+ cell count is <350 cells/mm³ when patient is first vaccinated
HPV	• Gardasil 0.5 mL IM at 0, 1–2, and 6 mo or • Cervarix 0.5 mL IM at 0, 1–2, and 6 mo	• Girls and women aged 9–26, ideally before onset of sexual activity; may consider in other groups • Safety and immunogenicity studies in HIV infected patients are ongoing
Influenza	• 0.5 mL IM annually	• All patients • Do not use live attenuated intranasal vaccine (FluMist)
Pneumococcal	• 0.5 mL IM of the polyvalent polysaccharide vaccine 13 followed by 0.5 mL IM of the polyvalent polysaccharide vaccine 23 at least 8 wk later (if CD4+ cell count <200 cells/µL, consider waiting until CD4+ cell count >200 cells/µL)	• All patients, regardless of CD4+ cell count • Moderate recommendation for re-vaccination with 23-valent vaccine ≥5 years after initial vaccination

Table 4-9	*continued*	
Routine Immunizations for HIV Infected Women*		
Vaccine	**Dose and Regimen**	**Indications and comments**
Polio	• 0.5 mL SC; 3 doses over 6–12 mo for primary immunization	• OPV contraindicated; IPV should be given if vaccine is indicated
Tetanus toxoid	• Td 0.5 mL IM; Tdap 0.5–0.75 mL IM as per package insert	• Same as for patients who are not HIV infected • Substitute single dose of Tdap at time of next booster, then Td every 10 y
Varicella	• 0.5 mL IM as two doses given 3 mo apart	• Administer if patient has CD4+ cell count >200 cells/mm³ and no evidence of immunity to varicella • *Post-exposure prophylaxis:* VZIG, 125 IU per 10 kg (maximum of 625 IU) IM, administered within 96 h after exposure to a person with active varicella or herpes zoster for patients with no evidence of immunity to varicella

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

* See Chapter 8, **HIV and Pregnancy,** for recommendations for pregnant women

Source: © Adapted from *Primary Care Guidelines for the Management of Persons Infected with Human Immunodeficiency Virus*: 2009 Update by the HIV Medicine Association of the Infectious Diseases Society of America (*Clin Infect Dis* 2009;49:651)

Common Opportunistic Infections and Other Conditions Associated with HIV

Summaries with some key points are presented below (adapted from CDC *Guidelines for Prevention and Treatment of Opportunistic Infections in HIV Infected Adults and Adolescents.* 2013). More detailed discussion is beyond the scope of this guide; specific treatment agents and alternatives and dosing regimens for acute conditions and secondary OI prophylaxis, respectively, can be found on the Clinical Guidelines Portal of the AIDSinfo website (http://www.aidsinfo.nih.gov/guidelines).

Initiation of ART as soon as possible during the course of treatment for an acute OI has been associated with longer survival, shorter time to CD4+ cell count >50 cells/mm³, and no increase in adverse effects (*PLoS One* 2009;4(5):e5575). Rapid initiation of ART will also shorten the duration of chronic maintenance (suppressive) therapy (i.e., secondary prophylaxis) for most patients as they recover immune responsiveness more quickly.

Pneumocystis jirovicii Pneumonia

Diagnosis: Because the presentation of PCP can be subtle and nonspecific, a heightened index of suspicion is warranted in appropriate circumstances. Most commonly, symptoms include the subacute onset of fever, exertional dyspnea, and nonproductive cough and chest discomfort that worsen over days to weeks.

Physical exam findings are also nonspecific. Auscultation may be entirely normal, particularly at rest with mild disease. Fine, dry "cellophane" rales may be heard with exertion. In 2%–6% of patients, PCP may present as spontaneous pneumothorax. The classic CXR findings are diffuse interstitial or perihilar infiltrates, but a wide range of CXR abnormalities is possible and radiography is normal in many cases of early disease. PCP is suggested by oxygen desaturation with exercise, which is easily measured in the office or clinic with a pulse oximeter, with the patient first at rest and then after running up a flight of steps, for example. This is particularly useful when symptoms are minimal, the patient does not appear acutely ill, and the CXR is unimpressive. Severity of illness is indicated by hypoxemia or a widened alveolar-arterial oxygen difference ($AaDO_2$) on blood gas analysis.

Other etiologies of pneumonia may have a similar presentation. The definitive diagnostic test requires histopathologic or cytologic identification of *Pneumocystis* organisms in bronchoalveolar lavage (generally preferred), induced sputum, or transbronchial or open-lung biopsy. Although induced sputum is less invasive and less expensive, it should not be attempted in the absence of expertise in both obtaining and interpreting the smear.

Treatment: The mainstay of treatment for PCP is TMP-SMX, administered intravenously or orally depending on the severity of the episode. PCP should be treated for 21 days. Patients with arterial oxygen pressure <70 mm Hg or with $AaDO_2$ >35 on room air should receive adjunctive steroids, which have been shown to decrease the incidence of ventilatory failure and death. A 21-day course of prednisone (40 mg bid x 5 days, then 20 mg bid x 5 days, followed by 20 mg qd x 11 days) is the most popular and cost-effective approach. No additional taper is required.

After completing acute therapy, the patient should begin routine daily PCP prophylaxis to prevent recurrence. PCP prophylaxis can be discontinued after ART has led to an increase in CD4+ cell count to >200 cells/mm3 for >3 months. (See **Prophylaxis of Opportunistic Infections**, p. 115.)

Candidiasis

The appearance of mucosal candidiasis is often the first clinical indication of impaired T-cell immunity in HIV infected individuals. Candida esophagitis is the second most common OI after PCP, and other mucosal forms of candidiasis (e.g, oral thrush, vaginal candidiasis) are common. Candidemia and tissue-invasive disease are rare, however.

Candida esophagitis is a serious infection that may result in significant weight loss because of odynophagia and reduced oral intake. Esophagitis should be considered when the patient describes midline substernal chest discomfort with swallowing instead of pain limited to the throat. It may occur in the absence of oropharyngeal thrush and can be diagnosed by endoscopy with visualization of lesions and histopathologic demonstration of characteristic *Candida* yeast forms and/or culture confirmation. Empiric treatment may be considered in many circumstances. If the patient's symptoms do not resolve, endoscopy with biopsy is recommended for a definitive diagnosis, as HSV and CMV infection and giant aphthous ulcers can have the same presentation.

Diagnosis: Oropharyngeal candidiasis is characterized by painless white plaques that can be easily scraped from the pharynx or buccal mucosa; severe cases will involve the tongue, gums, and lips; significant erythema may be present. Less commonly, erythematous patches without white plaques can be seen on the upper palate or tongue. Pharyngitis may be asymptomatic or may cause dysphagia or burning. Vaginal candidiasis presents similarly in HIV infected and uninfected women; however, episodes may be more severe or frequent in women with advanced immunosuppression (see Chapter 6, *Gynecologic Problems*). For oropharyngeal or vaginal candidiasis, diagnosis usually involves a consistent clinical presentation and demonstration of yeast forms on microscopy from scrapings in potassium hydroxide preparation; culture is rarely needed but can be helpful in some situations.

Treatment: The treatment of choice for esophagitis is oral fluconazole 100–400 mg po or intravenously (IV) qd or itraconazole 200 mg po qd for 14–21 days; topical agents should not be used. Oropharyngeal or vaginal candidiasis may be treated with topical or oral antifungals; topical agents are more cost-effective and avoid the risk of systemic side effects or drug-drug interactions.

Cryptococcal Meningitis

Cryptococcal meningitis may present as nothing more than the worst headache of the patient's life. Fever is common but meningismus may be minimal or absent. Altered mental status is associated with a poorer prognosis. Cranial nerve deficits and seizures are seen only in patients who present very late in the course of their infection.

When cryptococcosis occurs in the setting of HIV infection, disseminated disease is common and virtually any organ can be involved. Skin lesions resembling *Molluscum contagiosum* and isolated pulmonary infection are not infrequent.

Diagnosis: The diagnosis of cryptococcal meningitis is made by detecting cryptococcal capsular antigen in the cerebrospinal fluid (CSF). Relying upon a positive CSF India ink stain that demonstrates the organism's thick capsule is positive in only about 60%–80% of cases. Serum cryptococcal antigen is also almost always positive in cases of CNS disease and in other instances of disseminated infection. *Cryptococcus neoformans* may also be cultured from blood and CSF. When performing a diagnostic lumbar puncture, the opening pressure may be elevated, with pressures ≥25 cm H_2O occurring in most patients.

Treatment: The recommended initial standard treatment is IV amphotericin B (liposomal) combined with flucytosine for ≥2 weeks. Renal function should be monitored closely and dose adjustments made if indicated. Intracranial hypertension can be managed with frequent lumbar punctures to remove large volumes of CSF (20–30 mL at a time).

After at least 2 weeks of successful induction therapy (clinical response plus negative CSF culture on repeat lumbar puncture), amphotericin B/flucytosine may be discontinued and therapy with fluconazole 400 mg po or IV qd may be initiated and continued for 8 weeks.

Following the initial 10 weeks of therapy, initiate chronic maintenance therapy with fluconazole 200 mg qd for at least 1 year. Maintenance therapy can be discontinued in patients who have a sustained increase in CD4+ cell count to >100 cells/mm^3 for ≥3 months and suppressed HIV VL in response to ART.

Toxoplasmosis

The most common clinical presentation of *T. gondii* infection among patients with AIDS is focal encephalitis with headache, confusion, or motor weakness and fever. Physical examination may demonstrate focal neurological abnormalities, and in the absence of treatment, disease progression results in seizures, stupor, and coma.

Diagnosis: CT or magnetic resonance imaging (MRI) classically reveals one or more ring-enhancing, space-occupying lesions, although the radiographic appearance of the lesions may mimic other processes, such as primary CNS lymphoma.

Most HIV infected persons are seropositive for anti-toxoplasma IgG; absence of the antibody makes the diagnosis unlikely but not impossible. Definitive diagnosis requires a consistent clinical presentation, compatible radiographic findings, and a brain biopsy demonstrating *T. gondii* organisms. Most clinicians, however, rely initially on empiric treatment for toxoplasmosis in the absence of a likely alternative diagnosis, with confirmation of the diagnosis based on objective response (i.e., clinical and radiographic improvement). Brain biopsy is generally reserved for patients who fail to respond to specific therapy.

Treatment: The initial therapy of choice for toxoplasma encephalitis (TE) is a combination regimen consisting of pyrimethamine, sulfadiazine, and leucovorin. Acute therapy for TE should be continued for at least 6 weeks and longer if clinical or radiologic disease is extensive or if response is incomplete at 6 weeks.

After initial therapy for acute infection, chronic maintenance therapy should be administered, with the preferred regimen also a combination of pyrimethamine, sulfadiazine, and leucovorin (with slightly altered dosing), which also provides protection against PCP. Alternative regimens also provide protection against PCP, with the exception of pyrimethamine plus clindamycin. Secondary prophylaxis can be discontinued after successful initial therapy, when the patient remains without signs or symptoms of TE and her CD4+ cell count increases to >200 cells/mm^3 for >3 months in response to ART.

Tuberculosis

TB is one of the most common HIV-related OIs in the world. Because TB is virulent enough to cause disease in patients with intact immune systems, it may occur in HIV infected individuals who still have high CD4+ cell counts (*MMWR Recomm Rep* 2009;58(RR-4:1). Because rates of progression from latent to active TB are significantly increased in the setting of HIV, annual screening of all HIV infected patients is critical.

TB in HIV infected patients: In HIV infected patients with CD4+ cell counts >350 cells/mm3, TB clinically resembles TB among HIV uninfected people, with disease generally limited to the lungs. Common CXR findings include upper-lobe infiltrates with or without cavitation. In advanced HIV disease, the CXR findings of pulmonary TB are markedly different: lower-lobe, middle-lobe, interstitial, and miliary infiltrates are common whereas cavitation is less common. Marked mediastinal lymphadenopathy can also be seen.

Extrapulmonary disease is more common in the setting of HIV infection, regardless of CD4+ cell count, and is found in most TB patients with CD4+ cell counts <200 cells/mm3.

In patients with severe immunodeficiency and a high mycobacterial load, TB disease may have few symptoms. With immune reconstitution after initiation of ART, however, patients may develop acute signs and symptoms of active TB. This type of immune-reconstitution inflammatory syndrome (IRIS) can manifest as early as 7 days after starting ART.

Diagnosis: For both the PPD and interferon-gamma release assays, HIV-related immunosuppression may be associated with false-negative results. Approximately 25% of HIV infected patients with pulmonary TB disease have false-negative results (*Ann Intern Med* 2007;146:340).

If active TB Is suspected, a CXR should be obtained; sputum samples for acid-fast bacilli smear and culture should be obtained from patients with pulmonary symptoms and CXR abnormalities. A normal CXR does not exclude the possibility of active pulmonary TB; sputum samples should still be obtained if suspicion is high. The sputum smear may be negative, particularly with advanced immunosuppression and noncavitary disease, but it is not affected by HIV or immunosuppression. Drug-susceptibility testing and adjustment of the treatment regimen on the basis of the results of such testing are critical to the successful treatment of patients with TB and to preventing transmission of drug-resistant *Mycobacterium tuberculosis*.

Treatment: When active TB is diagnosed or suspected, a multi-drug anti-TB treatment regimen should be started immediately. Directly observed therapy is recommended for all patients. Until susceptibilities are known, all HIV infected patients should be treated initially with at least four drugs expected to be active on the basis of local susceptibility patterns. Treatment of drug-susceptible TB disease should include a 6-month regimen with an initial phase of INH, RIF (or rifabutin), PZA, and EMB administered for 2 months, followed by INH and RIF (or rifabutin) for 4 additional months. More-prolonged therapy is recommended for patients with a delayed response to therapy and for those with CNS disease or bone and joint TB. All patients receiving INH should

also receive pyridoxine supplementation. Expert consultation is recommended when treating TB, including when making decisions about the optimal timing of the initiation of ART. Treatment should be coordinated through the local public health department.

All close contacts of the patient—especially young children—must be evaluated for TB so that they may be treated promptly for active disease or given prophylaxis as indicated.

Herpes Simplex Virus (see Chapter 6, *Gynecologic Problems*)

Cytomegalovirus

CMV causes retinitis in 80%–85% of AIDS patients with end-organ CMV disease. Gastrointestinal disease, which can occur anywhere from the mouth to the anus, is diagnosed in another 12%–15%. Other diagnoses, such as encephalitis and pneumonitis, are uncommon (1%).

CMV retinitis can cause visual loss and progresses inexorably to blindness in the absence of ART or specific treatment. In two-thirds of patients, CMV retinitis occurs as unilateral disease at presentation; however, most patients develop bilateral disease in the absence of therapy or immune recovery. Patients may be completely asymptomatic or may complain of floaters (due to inflammatory debris), diminished acuity, or visual field defects with peripheral lesions.

Diagnosis: Diagnosis is made by visual inspection of the entire retina by an experienced ophthalmologist using dilated indirect ophthalmoscopy. Extensive disease may lead to retinal detachment, which may require surgical repair. Retinitis near critical structures such as the macula or optic nerve may cause catastrophic visual loss even when the total infected area is small.

Diagnosis of CMV colitis or esophagitis requires the presence of shallow, often large and extensive mucosal ulcerations with histopathologic evidence of characteristic intranuclear and intracytoplasmic inclusions. Culturing CMV from a biopsy or lesion is not sufficient to establish the diagnosis in the absence of histopathologic changes because CMV viremia can be present in the absence of clinical disease in persons with low CD4+ cell counts.

Treatment: The ganciclovir intraocular implant coupled with valganciclovir is the recommended treatment for CMV retinitis for immediate sight-threatening lesions. Systemic therapy has been documented to reduce morbidity in the contralateral eye. Decisions about the choice of treatment should be individualized on the basis of the location and severity of lesions, level of immunosuppression, other medications, and adherence considerations. Generally, CMV colitis or esophagitis is treated with IV ganciclovir or foscarnet or oral valganciclovir in milder disease and if able to tolerate oral therapy.

Secondary prophylaxis is recommended after CMV retinitis. The choice of agent should be made with expert consultation. Prophylaxis can be discontinued after an increase in the CD4+ cell count to >100 cells/mm^3 has been sustained for at least 3–6 months in response to ART, after ophthalmologic consultation.

Disseminated *Mycobacterium avium* Complex

Disseminated MAC presents nonspecifically with fever, weight loss, diarrhea, anemia, elevated alkaline phosphatase, and, in some cases, abdominal distention or discomfort due to organomegaly and massive intra-abdominal lymphadenopathy.

Diagnosis: Mycobacterial culture from blood, lymph-node, bone-marrow, or other normally sterile tissue or body fluid provides a definitive diagnosis; culture of sputum is not helpful.

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Treatment: Combination antimycobacterial therapy is required with two or more antimycobacterial drugs to prevent or delay the emergence of resistance. Recommended first-line agents are clarithromycin and ethambutol or azithromycin and ethambutol; some experts recommend adding a third drug for patients with CD4+ cell counts <50 cells/microliter, with high mycobacterial load or in absence of effective ART. Generally, initiation of ART in patients with disseminated MAC disease who are not already on effective ART should be delayed until after the first 2 weeks of antimycobacterial therapy have been completed to reduce the risk for drug-drug interactions, adherence problems due to pill burden, and potential IRIS.

The same drug regimen should be continued for secondary prophylaxis. This regimen can be discontinued after completion of at least a 12-month course of treatment if the CD4+ cell count increases to >100 cells/mm³ for >6 months in response to ART.

Cryptosporidiosis and Microsporidiosis

These enteric microorganisms can cause debilitating diarrhea and weight loss, often associated with severe dehydration in patients with advanced HIV disease.

Diagnosis: Cryptosporidiosis and microsporidiosis are generally diagnosed with special stool stains.

Treatment: Because no effective specific therapy exists, the mainstay of treatment is ART with immune reconstitution and supportive care (volume repletion and attempts at slowing the diarrhea). Clinical resolution (and even clearing of the organism from stool) have been documented with potent ART.

Attempts at slowing the diarrhea should be made by *adding* (not substituting) additional agents in a stepwise manner as follows:

- Diphenoxylate or loperamide, increased to their maximum dose, followed by

- Tincture of opium or paregoric, with the dose titrated gradually until the desired effect is achieved

HIV-Associated Dementia (HAD) and HIV Encephalopathy

In the pre-ART era, frank dementia was the AIDS-defining illness in up to 10% of patients. HAD is characterized by symptoms of cognitive, motor, and/or behavioral disturbances. The initial manifestations may be subtle and can be uncovered by questioning a patient carefully about short-term memory loss and difficulty concentrating. Useful questions about the latter include the ability to balance a checkbook or make change. In some patients a depressed affect may be a prominent finding, whereas unexplained seizures may bring other patients to medical attention. Psychomotor retardation—slowing of the impulses that match actions to thoughts and intentions—is another hallmark of HAD.

Diagnosis: CT and MRI scans show diffuse cortical loss with prominent sulci ("walnut sign"). A good sense of the patient's level of cognitive functioning can often be obtained at the bedside. In subtle or difficult cases, especially with a history of depression or subnormal intelligence quotient, the patient can be referred for a battery of neuropsychologic tests that demonstrate the losses characteristic of HAD. It is important to rule out other possible causes of changes in mental function (e.g., cerebrovascular disease, CNS neoplasm or other infection, severe depression, substance abuse, or metabolic/systemic disorders).

Treatment: Even patients who present with advanced dementia may demonstrate a remarkable degree of recovery with ART, so it is valuable to attempt treatment of all patients, even those initially referred for hospice or nursing home care. Because of indications that potent ART with poorer CNS penetration may predispose a patient to neurologic problems despite good suppression of HIV VL, it may be particularly useful to include agents that achieve good CSF levels.

Wasting Syndrome (aka "Slim Disease")

Although weight loss is common in HIV disease, especially in its advanced stages, the CDC surveillance definition of wasting syndrome specifically refers to involuntary weight loss that equals or exceeds 10% of the patient's baseline weight plus either diarrhea ($\geq$2 loose stools per day lasting $\geq$30 days) or chronic weakness with documented fever (intermittent or constant) for $\geq$30 days that is not attributable to a condition other than HIV itself.

Typically, wasting syndrome is accompanied by loss of muscle mass—for example, in the temporal areas—and complaints of generalized fatigue and weakness. In severe cases, the serum albumin level will be very low.

Wasting can accompany any of the typical end-stage OIs, such as disseminated MAC, or may occur by itself in the absence of any evident concomitant illness. Loss of weight, and especially loss of lean body mass, portends poorer survival.

Treatment: Initiation of effective ART is the best management strategy. Appetite stimulants, such as the progestin megestrol acetate or the marijuana derivative dronabinol, may be used, although weight gain with these agents

typically consists of fat and water rather than an increase in lean body mass. The psychological benefit of an improved appetite and some weight gain cannot be underestimated, however, even if the gain is primarily fat.

Central Nervous System Lymphoma

CNS lymphoma generally occurs at total CD4+ cell counts under 50 cells/mm^3 and is a typical end-stage complication.

Diagnosis: Symptoms include confusion, headache, memory loss, aphasia, and possible seizures without fever. Focal or nonfocal signs may be present. Definitive diagnosis is made by a brain biopsy or by CSF cytology (and possible Epstein-Barr virus [EBV] DNA in CSF) in the presence of one or more space-occupying lesions on CT or MRI scan. A presumptive diagnosis may sometimes be made by nuclear single-photon emission CT scan. Because a brain biopsy may be difficult to obtain, patients who do not respond to a trial of therapy for toxoplasmosis are often assumed to have CNS lymphoma.

Treatment: Standard therapy is radiation plus corticosteroids or methotrexate. Survival after a diagnosis of CNS lymphoma is usually very limited.

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is another end-stage complication of HIV disease, usually presenting as cognitive impairment, visual field impairment, or other focal neurologic deficit(s).

Diagnosis: PML is caused by the JC virus, which can be detected by PCR performed on CSF. An MRI scan of the brain demonstrates involvement of the white matter that can be focal or fairly diffuse but is not usually associated with either mass effect or surrounding edema. Most commonly, PML affects areas adjacent to the cortex, but lesions can be located anywhere in the brain. A definitive diagnosis is made by a brain biopsy or positive PCR, which is highly specific in the appropriate clinical context. Where these diagnostic modalities are unavailable, the typical MRI image usually suffices.

Treatment: Although no specific therapy exists for PML, this is another AIDS-associated condition that responds markedly well to potent ART. Patients can recover significant intellectual and physical functioning with ART, although not all deficits may resolve completely.

Systemic Lymphoma

HIV infected patients have an increased frequency of Hodgkin's disease, immunoblastic lymphoma, and Burkitt's lymphoma, as well as less common forms of this disease; however, the most common type of lymphoma in HIV infected patients is an aggressive non-Hodgkin's B cell lymphoma. Although lymphomas may occur at any CD4+ cell count, the prognosis is worse at lower absolute CD4+ cell counts.

A marked tendency for extranodal presentations has been observed and non-Hodgkin's lymphoma has been described over a range of unusual sites in HIV infected patients.

Diagnosis and treatment: AIDS-associated lymphoma is diagnosed and staged in the same manner as in HIV uninfected patients and the same types of combination chemotherapy are used. HIV infected patients may, however, require lower doses of chemotherapy or aggressive support with granulocyte colony-stimulating factor because of their baseline bone-marrow fragility. Advances in bone marrow transplant techniques offer new opportunities for treatment.

Chronic Hepatitis B and Hepatitis C

Many of the same behaviors that put women at risk of acquiring HIV also put them at risk for HBV and/or HCV infection. Up to 90% of HIV infected individuals have evidence of prior exposure to HBV and up to 10% have chronic HBV infection (*J Acquir Immune Defic Syndr* 1991;4(4):416; *J Infect Dis* 1991;163(5):1138). A cross-sectional analysis of a large heterogeneous group of HIV infected individuals found that 16% had HCV coinfection (*Clin Infect Dis* 2002;34(6):831), whereas among HIV infected IDUs in the United States, HCV infection rates range from 70%–95%.

Diagnosis: Both acute and chronic HBV and HCV infections are often asymptomatic or present with minimal or nonspecific symptoms such as fatigue. When present, symptoms of acute infection might include right-upper-quadrant abdominal pain, nausea, vomiting, fever, anorexia, dark urine, and jaundice. All HIV infected women should be serologically screened for HBV and HCV with HBsAg, HBsAb, HBcAb and HCV Ab at entry into care. HBV DNA should be obtained if HBsAg or HBcAb positive. Chronic HBV is defined as HBsAg positive on two occasions at least 6 months apart. Patients with chronic HBV infection should be further tested for HBV e antigen (HBeAg), antibody to HBeAg (anti-HBe), and HBV DNA. If there is an isolated HBcAb positive test and HBsAg is negative, HBV DNA testing should be considered. HCV infection is diagnosed if HCV Ab positive with detectable HCV RNA. With abnormal LFTs and negative serology, a qualitative HCV RNA PCR test should also be considered. Women with detectable HCV should be tested for HCV genotype. If acute hepatitis is suspected, screen with HAV IgM Ab, HCV Ab, and HBsAg +/- HBc IgM Ab.

HIV infection is associated with an increased risk of developing chronic HBV infection (*J Infect Dis* 1991;163(5):1138) and more rapid progression of both HBV- and HCV-related liver disease, including cirrhosis, end-stage liver disease, hepatocellular carcinoma (HCC), and fatal hepatic failure (*AIDS* 2008;22(15):1979; *Lancet* 2002;360(9349):1921). Periodic screening for HCC (every 6–12 months) with serum AFP level and ultrasound of the liver is recommended, particularly in patients with documented cirrhosis or other high-risk characteristics (e.g., older age). (*Hepatology* 2002;36(5 Suppl 1):S84). A liver biopsy to evaluate the activity and severity of hepatitis-related disease is useful to monitor progression and guide treatment decisions; decisions to perform liver biopsy should be individualized, with expert consultation.

The goals of therapy are to prevent disease progression, reduce viral hepatitis-related morbidity and mortality and, in the case of HCV infection, eradicate infection. ART may attenuate liver disease progression in persons coinfected with HBV and/or HCV by preserving or restoring immune function and reducing HIV-related immune activation and inflammation (*Hepatology* 2009;50(4):1056; *BMC Res Notes* 2008;1:46; *Haemophilia* 2009;15(2):552).

High HBV DNA levels predict progression of liver disease, development of HCC, and a reduced response to therapy. The decision to treat depends not only on the level of HBV viremia and the degree of biochemical and/or histologic disease but also on whether the patient is initiating ART.

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Treatment of HBV: ART is recommended for all HIV/HBV coinfected patients, regardless of CD4+ cell count or HBV treatment status. Regardless of the level of HBV DNA, ART must include two drugs active against HBV, preferably TDF and FTC, to reduce risk for IRIS, reduce the development of HBV drug-resistance mutations, and help to prevent the development of significant liver disease by directly suppressing HBV replication (*Hepatology* 2008;48(4):1062; *Hepatology* 2006;44(5):1110). If HIV/HBV coinfected patients do not want or are unable to take ART, treatment of active HBV (elevated alanine aminotransferase [ALT] and elevated HBV DNA >2000 IU/mL or significant fibrosis) with pegylated interferon (pegIFN) is indicated (*Guidelines for Prevention and Treatment of Opportunistic Infections in HIV infected Adults and Adolescents.* 2013).

Hepatitis C (HCV) becomes a chronic infection in about 85% of cases. Six distinct HCV genotypes have been described, with genotype 1 infection accounting for approximately 75% of all HCV infections in the United States. HCV genotyping should be performed in all HIV infected patients who are considering HCV treatment, both to guide ribavirin (RBV) dosing and because genotyping is the best predictor of response to interferon-based treatment and may therefore influence the decision to treat and/or perform a liver biopsy.

Treatment of HCV: Antiviral treatment for HCV infection should be considered for all HIV infected patients with acute or chronic HCV infection. Treatment of acute infection (<6 months from the time of HCV exposure) may prevent the development of chronic HCV infection. (*N Engl J Med* 2001;345(2):1452; *Gastroenterology* 2006;130:632). In the presence of chronic HCV infection, treatment should be considered in the following situations: HCV genotype 2 or 3 infection, HCV genotype 1 infection with a low HCV RNA level (<800,000 IU/mL), significant hepatic fibrosis (bridging fibrosis or cirrhosis), stable HIV infection not requiring ART, and cryoglobulinemic vasculitis or glomerulonephritis.

PegIFN plus RBV has been the mainstay of treatment for HCV in HIV infected patients. In HCV genotype 1–infected patients without HIV, addition of the recently FDA-approved drugs boceprevir or telaprevir significantly improves the rate of sustained virologic response; clinical trials of these drugs in HIV-infected patients are currently underway. Both boceprevir and telaprevir have significant interactions with certain ARV drugs, which may affect dosing or the ability to use these agents (see Table 13-8, p. 500). For patients with CD4+ counts <200 cells/mm^3, it may be preferable to initiate ART and delay

HCV therapy until CD4+ counts increase because of better response to HCV treatment at higher CD4+ cell counts (*Hepatology* 2009;49:1335; *J Acquir Immune Defic Syndr* 2009;52:452). Taking into account the rapid pace of HCV drug development and evolving information on drug interactions and use in the setting of HIV, treatment decisions should be made with expert consultation (http://www.aidsinfo.nih.gov/guidelines; accessed 5/17/2013).

IRIS with either HBV or HCV may manifest as dramatic increases in serum aminotransferases as CD4+ cell counts rise within the first 6–12 weeks after starting ART, with signs and symptoms of hepatitis flares.

HIV-Associated Nephropathy

In HIV infected patients, HIVAN is the most common cause of chronic kidney disease leading to end-stage kidney disease (*Kidney Int* 2004;66(3):1145). It is seen almost exclusively in Black patients and can occur at any CD4+ cell count. Ongoing viral replication appears to be directly involved in renal injury (*Nat Med* 2002;8(5):522). HIVAN is an uncommon condition in patients with suppressed viral loads (*Clin Infect Dis* 2006;43(3):377).

ART in patients with HIVAN has been associated with preserved renal function and better survival (*Nephrol Dial Transplant* 2006;21(10):2809; *J Am Soc Nephrol* 2005;16(8):2412; *AIDS* 2008;22(4):481) and therefore should be started in these patients.

Cardiovascular Disease

Cardiovascular disease is a major cause of mortality among HIV infected patients, accounting for a third of serious non-AIDS conditions and at least 10% of deaths among HIV infected patients (*AIDS* 2010;24(10):1537; *J Acquir Immune Defic Syndr* 2010;55(2):262).

In some cross-sectional studies, patients with HIV were found to have higher levels of markers of inflammation and endothelial dysfunction than HIV uninfected controls (*J Acquir Immune Defic Syndr* 2008;49(5):499; *J Acquir Immune Defic Syndr* 2009;52(1):25). In addition, several studies have found increased markers of inflammation and coagulation, as well as increased risk of cardiovascular events, following treatment interruption (*AIDS* 2009;23(8):929; *PLoS Med* 2008;5(10):e203; *N Engl J Med* 2006;355(22):2283).

ART has been associated with marked improvements in parameters associated with cardiovascular diseases, including markers of inflammation (e.g., interleukin 6 [IL-6] and high-sensitivity C-reactive protein [hsCRP]) and endothelial dysfunction (*J Am Coll Cardiol* 2008;52(7):569). Early initiation of ART is increasingly being promoted as a strategy to reduce cardiovascular disease risk (*Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*; http://www.aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0/. Accessed 8/25/2012).

Malignancies

Several population-based analyses suggest an increased incidence of non-AIDS-associated malignancies during chronic HIV infection compared with that in matched HIV uninfected controls (*J Acquir Immune Defic Syndr* 2009; 52:203). Large cohort studies mostly comprising patients receiving ART have reported a consistent link between low CD4+ cell counts (<350–500 cells/mm3) and the risk of AIDS and/or non-AIDS-defining malignancy (*J Acquir Immune Defic Syndr* 2009;52(1):203; *AIDS* 2009;23(13):1743; *Lancet Oncol* 2009; 10(12):1152; *AIDS* 2008;22(16):2143; *Clin Infect Dis* 2009;49(7):1109).

One prospective cohort study found a statistically significant relative risk of all cancers evaluated (except for anal carcinoma) in patients with CD4+ cell counts <500 cells/mm3 compared with patients with current CD4+ cell counts >500 cells/mm3 and a protective effect of ART for HIV-associated malignancies (*Lancet Oncol* 2009; 10(12):1152). The risk is particularly prominent in cancers associated with chronic viral infections (e.g., HBV, HCV, HPV, EBV, and human herpes virus-8) (*AIDS* 2009;23(17):2337; *Lancet* 2007;370(9581):59).

Anemia

Modest anemia (≥9–10 g/dL) is a hallmark of chronic HIV infection and in women of childbearing age may be complicated by menstrual blood loss. Severe anemia (≤9 g/dL) may occur as part of certain opportunistic diseases, especially MAC, disseminated histoplasmosis, and lymphoma, and may also result from drug toxicity.

Although severe anemia has been shown to be associated with poorer survival in several studies (*J Acquir Immune Defic Syndr Hum Retrovirol* 1998;19(1):29; *Semin Hematol* 2000;37(4 Suppl 6):18), initiation of ART (*J Acquir Immune Defic Syndr* 2002;29(1):54) and diagnosis and treatment of the opportunistic process are often sufficient to improve anemia in these cases.

Patients who are symptomatic with exertional dyspnea and dizziness can be transfused acutely. Most HIV infected patients gradually become anemic and unconsciously limit their activities to control symptoms. These patients can be managed with changes in ART or OI therapies known to have hematologic toxicity (e.g., ZDV, TMP-SMX). In patients whose anemia is refractory to conservative management, red blood cell production can be stimulated by using recombinant erythropoietin along with sufficient iron replacement to stimulate production of new red cells.

4

Opportunistic Disease in the Era of Antiretroviral Therapy

The impact of ART on the natural history of opportunistic diseases has been profound and the clinician must be familiar with at least the broad outline of these changes. Immune restoration in a patient on ART may be sufficient even for patients with end-stage disease to mount an inflammatory response to opportunistic pathogens. Paradoxically, this can result in worsening of an OI that has been under active treatment or in an atypical presentation of a new acute OI, generally within the first couple of months after initiating potent ART, when CD4+ cell counts have begun to improve. For example, a patient may acutely develop a tender, focal lymphadenitis due to MAC with negative blood cultures, whereas in the pre-ART era MAC would have presented as a disseminated disease with diffuse, nontender adenopathy and high-grade mycobacteremia. This seemingly paradoxical development of an OI in a patient with rising CD4+ cell counts is likely due to an inflammatory response to an OI that was subclinical or recently acquired when ART was initiated. The development of IRIS during treatment for most of the OIs has been well described. Management includes the continuation of ART plus the addition of nonsteroidal anti-inflammatory drugs or corticosteroids (especially in TB) to alleviate the inflammatory reaction.

Patients who recover pathogen-specific immunity in addition to experiencing an overall increase in the CD4+ cell count may be able to discontinue chronic suppressive (maintenance) therapy because their immune systems are now capable of containing the infection. Thus far, this has been best demonstrated for discontinuing chronic suppression of CMV retinitis. Similar phenomena have been described for other OIs, such as disseminated MAC, and there is no reason to think that other OIs will behave differently. Finally, patients with previously untreatable opportunistic processes, such as PML or cryptosporidiosis, have had clinical remissions after initiating ART.

Several studies have shown that patients receiving primary prophylaxis for PCP and MAC are at very low risk for developing these OIs if prophylaxis is withdrawn after total CD4+ cell counts have risen above the threshold risk levels for each specific OI and been sustained for at least 3–6 months. Most of these studies have been performed among patients with reasonably well-controlled HIV VLs, with most having an undetectable VL. At this point, it is clear that specific prophylaxis can be safely stopped for any OI when CD4+ cell counts have increased above the threshold of risk for ≥3 months. The USPHS guidelines on OI prophylaxis describe the data and rationale for discontinuing suppressive therapy and prophylaxis in appropriate patients. These guidelines are revised periodically (www.aidsinfo.nih.gov).

Chapter 5:

Adherence to HIV Treatment and Retention in Care

5

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Chapter 5: Adherence to HIV Treatment and Retention in Care

Chapter 5 at a Glance

Adherence to HIV Treatment and Retention in Care

With the availability of accurate HIV identification early in the course of infection and the effectiveness of combination antiretroviral (ARV) regimens, HIV infection has evolved from a uniformly progressive and fatal condition into a chronic disease. With effective antiretroviral therapy (ART), people with HIV infection now have the potential to live a near-normal lifespan with a decreased risk of transmitting the infection to others. These advances, however, have ushered in new challenges. Successful treatment requires lifelong ART. Moreover, chronic HIV care and treatment requires a level of adherence that exceeds the requirements of treatment for many other chronic illnesses because the penalties for nonadherence may be severe (e.g., viral resistance, loss of treatment options, potential for transmission of resistant virus strains). Additionally, medical and nonmedical circumstances, such as stigma, comorbidities, and short- or long-term adverse effects, may interfere with optimal adherence and retention in HIV care and treatment. This chapter addresses specific challenges to adherence and retention in comprehensive care in the setting of chronic HIV infection.

5

Goals of HIV Therapy

The primary goals of HIV therapy are to decrease the morbidity and mortality associated with HIV infection, improve quality of life, restore immune function, maximize suppression of viral load (VL), and reduce the risk of transmission of HIV to others (HHS Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*; http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed 7/20/2012).

Successful treatment: Successful HIV treatment is generally defined virologically, immunologically, and clinically as follows:

- Consistent virologic suppression below the level of detection by a sensitive assay (e.g., HIV VL <48 copies/mL)

- Increase of CD4+ cell counts to >350 cells/mm^3 or 500 cells/mm^3

- Improved clinical status

Treatment failure: Treatment failure is usually defined virologically as the inability to achieve or maintain suppression of viral replication to a VL <200 copies/mL. Suboptimal adherence is a leading cause of virologic failure (*J Infect Dis* 2010;201(5):662). Immunologic failure is more difficult to define; some patients have a persistently low CD4+ cell count while maintaining maximal VL suppression. Factors associated with poor CD4+ response include later initiation of ART, older age, and co-infection (e.g., with hepatitis C virus). Early in the course of treatment, and particularly if ART is started in advanced immunosuppression, a patient may worsen clinically if she has an underlying opportunistic infection that is "unmasked" or worsened after initiation of ART, a phenomenon known as immune-reconstitution inflammatory syndrome (see Chapter 4, *Primary Care*). This is *not* clinical failure; in general, true clinical failure occurs after both virologic and immunologic failure.

Adherence

Adherence is defined as "the extent to which a person's behavior—taking medication, following a diet, and/or executing lifestyle changes—corresponds with agreed recommendations from a healthcare provider" (World Health Organization (WHO. *Adherence to Long Term Therapies: Evidence for Action.* 2003; http://www.who.int/chp/knowledge/publications/adherence_report/ en/. Accessed 7/20/2012). The term *adherence* is preferred over *compliance* because adherence implies that the patient is involved in making decisions about her care, whereas compliance suggests that the patient is "bending to the will" of her healthcare provider (WHO. *Adherence to Long Term Therapies: Evidence for Action.* 2003).

Factors That Influence Adherence

Adherence has two components: adherence to medication and adherence to medical care, including medical visits, which is also known as retention or persistence in care. Adherence is a complex behavioral process influenced by several factors that can be categorized across five dimensions, as described in Table 5-1 (WHO. *Adherence to Long Term Therapies: Evidence for Action.* 2003). Given the complexity of adherence, several factors may result in low adherence rates. Likewise, interventions to improve adherence are most successful if they are multifaceted, addressing problems across multiple dimensions, and tailored to overcome individual or clinic-specific barriers.

Table 5-1

Factors That Influence Adherence

Dimension	Factors Affecting Adherence
Healthcare Team and System Factors	• Quality of the patient-provider relationship, including provider attitudes and healthcare-team communication style • Reimbursement and medication distribution systems • Disease management supports, including patient education and community supports • Follow-up and continuity of care • Evaluation of and interventions to improve adherence • Amount of time spent with patient
Social and Economic Factors	• Patients' competing priorities (e.g., Maslow's hierarchy of need [*Perspect Psychol Sci* 2010;5(3):292]) • Socioeconomic status • Availability and quality of social support networks • Transportation • Ability to afford healthcare services and/or medications

Table 5-1 continues on the next page

Table 5-1	*continued*

Factors That Influence Adherence

Dimension	Factors Affecting Adherence
Condition-Related Factors	• Symptom severity (adherence is usually lower when a patient is asymptomatic) • Condition-related disability (physical, psychological, cognitive, vocational) • Rate of progression and prognosis • Disease severity (patients with more advanced HIV are generally more adherent) • Commonly associated comorbidities (e.g., depression, substance abuse, co-infections)
Therapy-Related Factors	• Complexity of regimen (e.g., dosing, pill burden, dosing interval) • Restrictions (e.g., dietary, other drugs, activities) • Duration (i.e., short-term vs. lifetime; "pill fatigue" has been noted in some patients on long-term treatment) • Immediacy of beneficial effects and relief of symptoms • Side effects and availability of interventions to manage them

Patient-Related Factors	• Ability to follow instructions
	• Knowledge of and skill with self-directed health-related behaviors
	• Trust in provider and medical system
	• Degree of family dysfunction and/or chaotic lifestyle
	• Education and literacy
	• Age and lifespan factors:
	  - Children's dependency on adult
	  - Adolescents' capacity to understand risks and consequences
	  - Adults' responsibilities for work and care of children, partners, and/or parents
	• Personal or cultural beliefs regarding health and disease
	• Motivation and perceived need for treatment
	• Confidence (self-efficacy)
	• Acceptance and understanding of disease vs. negative beliefs regarding diagnosis (denial) and treatment efficacy
	• Ability to engage in illness-management behaviors
	• Perceptions, attitudes, and expectations (e.g., hopelessness, acceptance, fear of dependence, frustration, anxiety about regimen, disease-associated stigma)
	• Neurocognitive function and ability (e.g., forgetfulness, prospective memory)
	• Psychological status (e.g., stress, depression, influence of substance abuse, coping mechanisms)

Source: WHO. *Adherence to Long Term Therapies: Evidence for Action.* 2003

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Magnitude of the Adherence Problem

Medication adherence among patients suffering from chronic diseases averages 50% in developed countries (*Adherence to Long Term Therapies: Evidence for Action.* 2003; http://www.who.int/chp/knowledge/publications/ adherence_report/en/. Accessed 7/20/2012). Among patients with HIV, adherence to both medical visits and medication has been associated with decreased mortality (*Clin Infect Dis* 2007;44:1493). For patients with HIV, the consequences of medication nonadherence are devastating, which is why so much emphasis is placed on adherence to treatment. When medication doses are missed, viral resistance can emerge quickly, particularly with medications that have lower genetic barriers to resistance, such as the NNRTIs (*HIV Clin Trials* 2007;8(5):282). The early literature suggested that >95% adherence was required for success with unboosted protease inhibitors (PIs); more-recent studies of boosted PIs, however, have shown that with these more potent regimens adherence levels of 80% or greater may be sufficient (*Ann Int Med* 2000;133:21; *Ann Pharmacother* 2011;45(3):372).

The level of adherence required for treatment success depends on underlying resistance, the pattern of nonadherence, and the treatment regimen. For example, resistance is less likely to develop in a patient who is 100% adherent to a PI-based regimen, who then stops taking medication altogether for 3 months and then resumes with 100% adherence, and more likely to develop in a patient who regularly takes 60% of her NNRTI-based regimen. NNRTIs have a considerably longer half-life than other ARVs; thus, the patient with intermittent adherence is essentially taking monotherapy for prolonged periods, which increases the likelihood of developing a drug-resistant strain of HIV.

Figure 5-1 illustrates the decrease in virologic failure rates with improved adherence. Conversely, the type of ART regimen has an impact on virologic failure that correlates with intermediate levels of adherence (56%–95%). At high levels of adherence no significant differences are observed in virologic failure rates between regimens (*HIV Clin Trials* 2007;8(5):282).

Figure 5-1
Self-Reported Adherence and Virologic Failure

Source: © *HIV Clin Trials* 2007;8(5):282. Reprinted with permission.
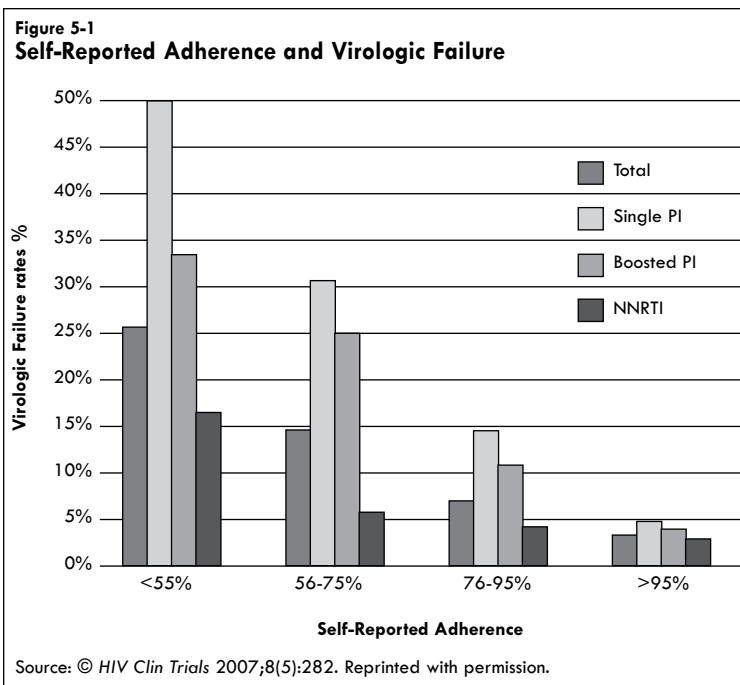
Adherence tends to decrease over time and with the initiation of subsequent ART regimens, such that adherence duration with the first regimen predicts duration with the second and third regimens (*AIDS Patient Care STDS* 2006;20(9):628). Thus, it is critical to focus on adherence to achieve viral suppression; by itself, a change in treatment regimen is not likely to be sufficient. Similarly, many patients who have had long periods of high adherence may struggle with adherence over time owing to a host of factors that may include changes in personal circumstances, such as becoming homeless or relapsing into drug abuse; changes in health insurance that make it more difficult to access medications; or changes in medical condition, such as recurrent hospitalizations, that disrupt medication-taking routines. For all of these reasons, clinicians should ask about adherence at each clinic visit.

Retention in HIV Care

Positive HIV treatment outcomes depend on early diagnosis of HIV infection, linkage to care, and retention (persistence) in care. Gaps in access or retention, such as failure to keep the first or subsequent appointments, are linked with a lack of ART utilization, disease progression, and increased mortality (*Clin Infect Dis* 2007;44:1493; *J Acquir Immune Defic Syndr* 2009;50:100). In many settings, access to HIV care and treatment, defined as no gap between HIV-related medical appointments of > 6 months within the first year, is achieved in only 50% of newly diagnosed patients (*AIDS Care* 2005;17(6):773). Likewise, it is not uncommon for established patients to drop out of HIV care. Fewer data exist regarding the numbers of HIV patients lost to follow-up. Table 5-2 outlines the factors that influence linkage to and retention in care.

Table 5-2	
Factors That Influence Linkage to and Retention in Care	
Factors Associated with Successful and/or Sustained Linkage to and Retention in Care	**Factors Associated with Unsuccessful and/or Poor Linkage to and Retention in Care**
• Co-location of services (e.g., case management, substance abuse, mental health services) • Patient-centered care (e.g., empowered patients, shared decision making) • Transition programs (e.g., from testing sites, jails, hospitalizations, adolescent-to adult-care programs, which may or may not involve the use of patient navigators)	• Untreated substance abuse and/or mental illness • Asymptomatic disease; no ART • Older age (associated with poor linkage to care) or younger age (associated with decreased retention in care) • Lack of health insurance • Longer interval between date of appointment with healthcare provider and patient's initial call to schedule the appointment • African-American race • Privacy concerns • Care-giving responsibilities • Perceived lower social support • Perceived stigma from a health care professional

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Sources: *AIDS Patient Care STDS* 2009;23(1):41; *Top HIV Med* 2008;16(5):156; *AIDS Patient Care STDs.* 2007; 21 Suppl 1:S59; *Am J Public Health.* 2000; 90 (7): 1138; *AIDS Care.* 1999; 11(3):361; *AIDS Patient Care STDs.* 2007; 21(8):584

After adjustment for clinical stage and the number of active drugs in a patient's ART regimen, the hazard ratio for developing an AIDS-defining illness or death increases as patients' number of missed clinic appointments increases, as illustrated in Figure 5-2.

Figure 5-2
Risk of Progression by Missed Visit Status

Risk of Progression (HR compared to no missed visits)

Number of Missed Visits

- 1: 2.87
- 2: 4.37
- >3: 8.19
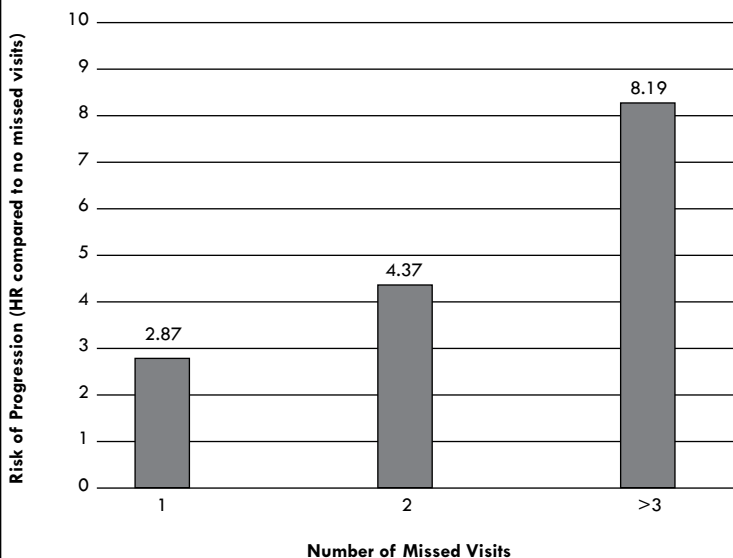
Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Source: *J Intern Med* 2007;261(3):268

5

Adherence In Women

Gender-specific factors have been noted to influence adherence and retention in care. Some studies have found that women have lower rates of adherence than men. This is not surprising given the association between family and other caretaking responsibilities and lower adherence rates (*Pediatrics* 2008;121(4):e787; *AIDS Patient Care STDS* 2009;23(4):289). Many HIV infected women are diagnosed during pregnancy and are still dealing with the implications of this diagnosis after giving birth, when the new mother becomes responsible for managing the care of a newborn, including administering ARV prophylaxis, while also managing her own health and medications. Mothers are the parents most likely to be responsible for supervising ART for an infected child. Childcare and other responsibilities, as well as postpartum physical and psychological changes, may increase the likelihood that a woman will miss doses of her own medications and may affect the provision of prophylaxis to her infant as well (*Pediatrics* 2002;110(3):e35; *J Acquir Immune Defic Syndr* 2002;30(3):311; *J Acquir Immune Defic Syndr* 2008;48(4):408).

Overview of Study Findings on Adherence in Women

- Women experience higher rates of virologic rebound than men, mostly due to nonadherence (*J Acquir Immune Defic Syndr* 2004;37(4):1470).

- Women are less likely to keep their first HIV healthcare visit appointment and to have remained in care after 2 years (*J Womens Health* 2009;18(10):1627; *J Assoc Nurses AIDS Care* 2007;18(3):33).

- Women have higher rates of mental health problems such as depression, which is associated with decreased adherence (*Psychosom Med* 2008;70(5):531; *J Gen Intern Med* 2003;18(4):248).

- Women often have a history of intimate-partner violence, which is associated with lower adherence (*AIDS Educ Prev* 2010;22(1):61; *J Adolesc Health* 2003;33(2 Suppl):39).

- Women have less knowledge of healthcare system navigation and available ancillary services (*South Med J* 2004;97(4):342).

- Nonadherence is an independent reason for the discontinuation of ART in women (*AIDS Behav* 2009; 13(1):60; *J Acquir Immune Defic Syndr* 2009;52(3):336).

- Women have multiple biological differences that influence drug tolerability and metabolism, including body weight and composition, renal clearance, and protein binding (*Pharmacol Res* 2008;58(3-4):173).

- Pregnancy may have a significant effect on many other factors that influence adherence in women (*Clin Pharmacokinet* 2004;43(15):1071).

With standardized dosing, gender-based biological differences may result in increased side effects; however, more research is needed to better delineate sex differences, particularly hormonal/biological differences that affect drug tolerability and, by extension, adherence (*J Antomicrob Chemother* 2007;60(4):724; *Gend Med* 2007;4(2):106).

Pregnancy and Adherence

Pregnancy may influence adherence to ART, particularly when pharmacokinetic interactions influence drug levels, requiring an increase in pill burden, or when medication side effects such as nausea overlap with symptoms common in pregnancy. Pregnant women, however, may be highly motivated to adhere to therapy and are more likely than nonpregnant women to be adherent to ART regimens: pregnant women report rates of perfect adherence that range from 75% to 91% (*J Acquir Immune Defic Syndr* 2008;48(4):408; *Cell Mol Biol* 2003; 49(8):1187). In the postpartum period, however, rates of adherence significantly decrease (*AIDS Patient Care STDS* 2009;23(2):101). This decrease may be due to a number of factors, including the inherent chaos of life when caring for a newborn, the additional burden of administering ARV prophylaxis during the first 6 weeks of life (which may exacerbate feelings of guilt and concerns about disclosure), and for some women the effects of postpartum depression.

Special Populations

As with men, incarceration and homelessness pose special challenges to adherence for women. Drug interruptions often occur during short jail stays. For example, even in prison systems that have discharge planning, the rate of interruption in medication regimens associated with incarceration has been reported to be 70% (*Public Health Rep* 2010;125(Suppl 1):64).

Homeless patients have inherently chaotic lifestyles. Studies have found, however, that homeless and marginally housed patients can adhere to medication (*AIDS* 2000;14(4):357). Homeless patients need additional supports to ensure access to and adherence with ARVs.

5

Adherence and Retention Assessment

Accurate assessment of adherence is challenging. Table 5-3 describes the advantages and disadvantages of direct and indirect methods of evaluating adherence. Figure 5-3 is an example of a visual analog scale for assessing adherence.

Table 5-3

Methods of Assessing Adherence

	Method	Advantages	Disadvantages
Behavioral	Self-report	• Easy • Low cost • Accessible	• Subject to recall bias • Often not standardized • Potential for over-reporting to garner provider approval
	Visual analog scale	• Low cost • Accessible • Standardized • Decreases literacy and numeracy barriers	• Subject to recall bias • Potential for over-reporting to garner provider approval

Table 5-3 continues on the next page

Table 5-3   *continued*

Methods of Assessing Adherence

	Method	Advantages	Disadvantages
Measurement of Medication Utilization	Refill history	• Low cost • Easy to implement in closed systems such as onsite pharmacy • May be part of electronic medical record	• Challenging if patients use multiple pharmacies • May not reflect actual behavior, particularly with automatic refills
	Pill counts during healthcare visits	• Low cost • Offers opportunity for education and reassurance	• Time consuming • Depends on patient bringing medications to visits • May be inaccurate (i.e., pills removed before visit)
	Pill counts by phone or in home	• Low cost if by phone • Offers opportunity for education and reassurance	• Costly if in home • May be perceived as invasive • Subject to patient availability • Subject to manipulation if by phone
	Medical Electronic Monitoring System	• More accurate • Easy to use (medication bottle caps)	• Costly • Does not reflect actual ingestion of medications • Depends on use of pills taken directly from container each time
Biologic Measurement	Therapeutic drug levels	• Easy • Minimally invasive if part of routine blood work	• Costly • Not readily available • No standardized values • Does not capture adherence between measurements if patient takes medications only just prior to visits
	Drug-specific surrogate markers: ZDV, AZT: Mean corpuscular volume ATV: Total bilirubin TDF: Alkaline phosphatase	• Part of routine monitoring • Relatively low cost	• May be influenced by effects of other pathologic process(es) • Nonspecific • Nonquantified

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Figure 5-3
Visual Analog Scale for Adherence

RED	YELLOW	GREEN
Cannot Do It At All	Somewhat Certain Can Do It	Completely Certain Can Do It

Source: © *Health Educ Research* 2005;20(1):24. Reprinted with permission.

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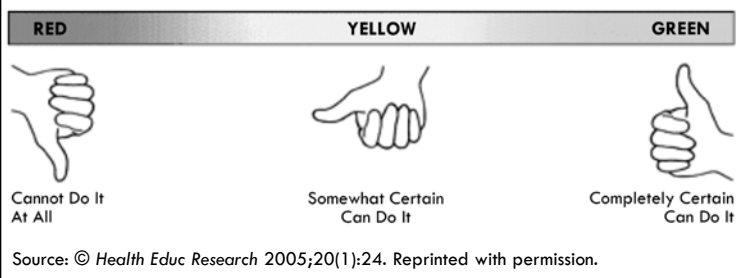
Because of cost and convenience, measuring medication adherence by direct report and visual analog scale are most commonly used by healthcare providers in clinical settings. Refill history is also very useful for clinics with onsite pharmacies, as well as for patients who are not responding as expected to HIV treatment and who report 100% adherence. Direct report should be time specific and quantified. For example, care providers should ask, "How many times in the last _____ (week, month, interval since last visit) have you missed a dose of your medicine?" This question should be followed by a nonjudgmental exploration of why the medication was missed, particularly if the patient routinely misses doses, and by brainstorming with the patient to identify ways she might overcome barriers to adherence.

Assessment of Retention in Care

Assessment of retention is important in every clinical setting. Although there is no gold standard for measuring retention in care, potential measures may include the following:

- The number of 6-month blocks during which the patient attended at least one clinic appointment over the 2-year period following an initial visit (*AIDS Patient Care STDS* 2009;23(1):41)

- Number of missed appointments

- Number of kept scheduled appointments per quarter or year

- Percentage of appointments missed

These measures provide different perspectives on appointment adherence (*AIDS Patient Care STDS* 2010;24(10):607). The rate of appointment adherence necessary for good clinical outcomes has not been quantified and may vary on the basis of stage of HIV disease and other comorbidities.

Evidence-Based Interventions to Improve Adherence

Because the factors associated with adherence are varied, the most effective interventions are multifaceted, individualized, and repeated over time. Asking about adherence at each medical visit and discussing barriers and solutions may be a key component to individualizing interventions in the context of tailoring therapy. Individualized clinic interventions, however, do not address broader provider and healthcare system issues or interventions that may significantly improve adherence across a wide group of patients. HIV treatment response rates have improved significantly in recent years as a result of increasingly potent drugs, significantly simpler drug regimens with fewer side effects, and less significant resistance among patients who are starting second- and third-line therapy (HHS Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*; http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed 7/20/2012). Combined, these factors result in lower rates of adherence being necessary to achieve viral suppression.

Even in the face of these advances in HIV care and treatment, HIV medical providers must nevertheless maintain a high level of attention to adherence and provide ongoing support to patients. The many evidence-based interventions to improve adherence have been summarized and made available online; see, for example: http://www.cdc.gov/hiv/topics/research/prs/ma-good-evidence-interventions.htm. These proven interventions can be fairly complex. Many providers practicing routine HIV clinical care take a multifaceted approach that combines evidence-based interventions, clinical experience, and common sense to maximize adherence among their patients.

Clinical Approach

It is critical to consider healthcare system factors that affect a patient's ability to access and stay in HIV care and adhere to an ART regimen. Figure 5-4 illustrates multiple factors that a healthcare provider should consider when determining the right mix of interventions (i.e., clinic/system/care provider-based/patient-based) to improve adherence to HIV care and medications (*AIDS Patient Care STDS* 2009;23(1):41). Table 5-4 describes interventions to support adherence and retention in care.

Figure 5-4
Blueprint for HIV Treatment Success

A

Retention in Care

HIV Dx → Linkage to Care → ART Receipt ↔ ART Adherence ↔ Clinical Outcomes

B

Contextual Environment
• Rural vs. urban
• Neighborhood
• Dependent care

Health Care Environment

Clinic Factors
• Clinic distance
• Appointment availability
• Waiting time

System Factors
• Mental health services
• Substance abuse services
• Case management

Provider Factors
• Trust
• Experience
• Concordance

Predisposing Factors
• Age
• Race/ethnicity
• Gender
• Poverty
• Education
• Mental Illness
• Substance abuse
• Stigma

Enabling Factors
• Insurance status
• Transportation
• Housing
• Social support
• Self efficacy

Perceived Need
• Symptoms
• Health beliefs

Linkage to Care

Retention in Care

ARV Receipt & Adherence

Clinical Outcomes
• Quality of life
• CD4+ cell count
• Plasma HIV RNA
• Opportunistic infections
• Death

Environment   **Patient characteristics**   **Health behavior**   **Outcomes**

A: Blueprint for HIV treatment success: requisite processes from initial diagnosis to long-term clinical outcomes. (*Adapted from Curr HIV/AIDS Rep* 2005;2(4):177; *AIDS* 2001;15(1):77.)

B: Adaptation of the behavioral model of health services utilization to provide a conceptual framework for evaluating the relationships between patient characteristics and their contextual and healthcare environmental factors. These relationships contribute to the health behaviors outlined in the "blueprint for HIV treatment success" that ultimately influence clinical outcomes.

Source: © *AIDS Patient Care STDS* 2009;23(1):41. Reprinted with permission.

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Table 5-4

Interventions to Support Adherence and Retention in Care

PATIENT

Help the patient become ready for therapy
- Promote the development of adaptive coping skills; identify stressors and use motivational interviewing to elicit positive coping responses
- Improve attitudes toward and perceptions of treatment
- Address patient concerns about treatment, including conspiracy theories, lack of trust in medical system
- Use clear language to discuss short- and long-term goals of therapy, side effects, and known positive outcomes; check to ensure patient understands

Minimize the effects of comorbidities
- Treat substance abuse
- Treat depression
- Consider overlapping symptoms and side effects when choosing a medication regimen

Assist the patient in taking medication as prescribed
- Tailor the regimen to patient preferences and lifestyle
- Use reminders such as telephone calls or texts and alarms
- Provide education about prescribed regimen (e.g., securing refills without gaps in access, developing contingency plans for missed doses or disruptions to daily routine, consequences of nonadherence and drug resistance)

Enhance patient supports
- Encourage the patient to enlist assistance of friends and family in promoting adherence
- Consider use of trained peer outreach workers, pharmacists, nurses, or other healthcare personnel such as health educators
- Have pill boxes, alarms, and other adherence aids available in the clinic

CLINIC/SYSTEM

Improve access to care
- Consider expanding clinic hours to include some evenings and weekends
- Develop a refill policy that minimizes interruptions in therapy; educate patients about the policy
- Use a multidisciplinary team to provide patient education and adherence support (include peers, pharmacists, and system navigators, where appropriate)

Structure clinic systems to promote adherence
- Ask about adherence in a nonjudgmental, quantitative manner at each visit
- Inquire about barriers to adherence and retention and work with patient to overcome them
- Ensure the entire clinic team is aware of and promotes adherence and retention across clinic visits
- Bilingual/bicultural staff on health care team
- Train care providers in motivational interviewing
- Support continuity of care and the building of long-term, trusting relationships between the patient and the entire healthcare team
- Develop a continuum of care that includes such support services as case management, transportation, mental health and substance abuse services, and child care
- Consider developing gender-specific programs that address the special needs of women, particularly pregnant women or those who are caring for small children

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Table 5-4	*continued*

Interventions to Support Adherence and Retention in Care

REGIMEN

Make the patient's drug regimen as simple as possible
- Consider and reduce where possible the number of doses per day and pill burden
- Account for food restrictions and requirements
- Assess the patient's willingness to take pills in front of others

Reduce side effects
- Evaluate side effects upon initiation of a medication regimen and frequently thereafter
- Educate the patient about potential side effects and proactively train her in side-effects management

Sources: *AIDS Behav* 2007;11(6 Suppl):101; *AIDS Behav* 2007;11(6 Suppl):149; *AIDS Care* 2002;14 Suppl 1:S15; *AIDS Care* 2002;14 Suppl 1:S31; *AIDS Care* 2002;14 Suppl 1:S109; *AIDS Care* 2004;16(4):446; *AIDS Care* 2005;17(8):1022; *AIDS Care* 2006;18(4):332; *AIDS Care* 2009;21(4):448; *AIDS Care* 2009;21(7):874; *AIDS Patient Care STDS* 2000;14(4):189; *AIDS Patient Care STDS* 2002;16(6):269; *AIDS Patient Care STDS* 2005;19(5):306; *AIDS Patient Care STDS* 2006;20(4):258; *AIDS Patient Care STDS* 2007;21 Suppl 1:S3; *AIDS Patient Care STDS* 2007;21 Suppl 1:S59; *AIDS Patient Care STDS* 2007;21 Suppl 1:S85; *AIDS Public Policy J* 2005;20(3-4):108; *Health Psychol* 2007;26(4):488; *J Acquir Immune Defic Syndr* 2008;47(1):62; *J Acquir Immune Defic Syndr* 2009;52 Suppl 2:S104; *J Antimicrob Chemother* 2008;62(2):246; *J Gen Intern Med* 1998;13(9):586; *J Gen Intern Med* 2002;17(5):377; *J Gen Intern Med* 2003;18(4):248; *J Urban Health* 2008;85(5):717; *Med Decis Making* 2001;21(1):17; *Qual Health Res* 2008;18(4):458

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Conclusion

Treatment success with ART depends on high rates of adherence and retention in HIV care. Assessment of facilitators and barriers to adherence and retention is important for every woman in HIV care. Interventions to address adherence and retention should be tailored to the specific needs and circumstances of each patient. Although system- and policy-related interventions are important and necessary long-term goals, patient-specific and healthcare-related interventions are suitable for everyday clinical practice.

Chapter 6:

Gynecologic Problems

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Chapter 6: Gynecologic Problems

Chapter 6 at a Glance

6

A Problem-Oriented Approach to Common Gynecologic Complaints

Gynecologic problems are common among HIV infected women and are frequently present at the time of initial presentation for evaluation and care. Minkoff and colleagues found, with prospective assessment over 1 year, that 47% of 262 HIV infected women had at least one incident gynecologic condition (*Am J Obstet Gynecol* 1999;180:824). A study of women admitted to an inpatient AIDS service revealed that although only 9% were admitted with a primary gynecologic problem, 83% had coexisting gynecologic disease when evaluated (*Clin Infect Dis* 1997;25:706). Some gynecologic issues are unrelated to a patient's serologic status, whereas others are directly related to HIV disease and associated immunosuppression. Still others are associated epidemiologically with HIV because of common risk factors such as sexual behavior or substance abuse.

Because HIV infection primarily affects women during their reproductive years, gynecologic and reproductive healthcare play an important role in the overall care of HIV infected women. With improved longevity and quality of life, gynecologic problems may be encountered more commonly or may be more prominent. With these issues in mind, the goal of this chapter is to use a problem-oriented approach in reviewing the most common gynecologic complaints together with their differential diagnosis, evaluation, management, and relationship to HIV.

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Abnormal Uterine Bleeding and Amenorrhea

What is considered "abnormal" bleeding? A normal menstrual period should occur every 21–35 days and last from 2–6 days. The average blood loss during menses is 20–60 mL, but up to 14% of healthy women have blood loss >80 mL and, as a result, are more likely to be anemic (*Comprehensive Gynecology*. 6th ed. St. Louis: Mosby; 2012). Abnormal bleeding may be of several types, described below along with the most common causes of each type.

- **Menorrhagia:** excessive or prolonged menstrual bleeding, defined as blood loss >80 mL and/or periods lasting for >7 days. Menorrhagia is most commonly caused by fibroids or by a hemostatic disorder.

- **Metrorrhagia:** light bleeding from the uterus at irregular intervals, often caused by hormonal contraception or continuous hormone replacement therapy (HRT) in the first few months after initiation. Megestrol can cause metrorrhagia. Pregnancy should be ruled out.

- **Menometrorrhagia:** heavy bleeding from the uterus at irregular intervals, commonly caused by anovulation, fibroids, or uterine or cervical neoplasm

- **Intermenstrual bleeding:** bleeding that occurs between menses or during expected times of hormonal withdrawal in women using hormonal contraception. Intermenstrual bleeding is commonly caused by polyp(s) or is breakthrough bleeding with hormonal contraception.

- **Oligomenorrhea:** bleeding that occurs at intervals >35 days. Oligomenorrhea is generally caused by ovulatory dysfunction, but may be normal with newer extended-phase oral contraceptives.

- **Polymenorrhea:** bleeding that occurs at intervals <24 days. It may indicate ovulatory dysfunction.

- **Postcoital bleeding:** vaginal bleeding noted within 24 hours of vaginal intercourse when not at the expected time of menses. This type of bleeding may indicate cervicitis. Cervical neoplasm must be ruled out.

- **Postmenopausal bleeding:** any vaginal bleeding or spotting after total cessation of menses. If a woman is on HRT, this is any bleeding that occurs at times other than expected withdrawal. Neoplasm must be ruled out.

- **Dysfunctional uterine bleeding:** excessive, noncyclic uterine bleeding that is not caused by an anatomic lesion or systemic disease. Most often, it is caused by anovulation.

- **Amenorrhea:** absence of menstrual bleeding. Primary amenorrhea is the absence of menses by age 16. Secondary amenorrhea is the absence of menses for a variable period of time—at least 3 months, but generally 6 months or longer—in a woman who has previously menstruated.

Relationship to HIV disease: Menstrual disorders are reported by 20%–30% of HIV infected women (*J Obstet Gynaecol Res* 2010;36(5):1053; *J Womens Health* 2006;15(5):591; *AIDS Patient Care STDS* 2009;23(6):463). Older controlled studies yielded conflicting evidence regarding a clinically significant direct effect of HIV or HIV-related immunosuppression on menstrual function (*J Acquir Immune Defic Syndr Hum Retrovirol* 1996;12:489; *Obstet Gynecol* 1996;87:1030; *Obstet Gynecol* 1994;83:397). Several more recent large cross-sectional and cohort studies, however, suggest that, when compared with uninfected women, HIV infected women are more likely to have amenorrhea, oligomenorrhea, and irregular periods (*J Obstet Gynaecol Res* 2010;36(5):1053; *Obstet Gynecol* 2006;108(6):1423; *Obstet Gynecol* 2006;108(6):1423) and/or that menstrual abnormalities may be more common with lower CD4+ cell counts (*J Obstet Gynaecol Res* 2010;36(5):1053; *J Acquir Immune Defic Syndr* 2000;24:68; *J Womens Health* 2006;15(5):591).

Some studies also suggest that taking antiretroviral therapy (ART) and/or having suppressed HIV RNA levels may reduce the prevalence or incidence of menstrual disorders (*J Obstet Gynaecol Res* 2010;36(5):1053; *J Womens Health* 2006;15(5):591; *AIDS Patient Care STDS* 2009;23(6):463). Analysis of data collected at 6-month intervals from women in the WIHS prospective cohort indicated no difference in the prevalence or incidence of menstrual disorders by HIV serostatus; amenorrhea and oligomenorrhea were less likely, however, in women with CD4+ cell counts >200 cells/mm^3. Both effective ART and higher CD4+ cell counts were associated with lower rates of incident menstrual abnormalities (*J Womens Health* 2006;15(5):591). In a recent cross-sectional study from Spain, approximately 75% of HIV infected women with menstrual disorders attributed the disorders to the use of ART; two-thirds of those women were <95% adherent to their antiretroviral (ARV) regimens (*AIDS Patient Care STDS* 2009;23(6):463).

Most studies of menstrual function in HIV infected women have relied on patient self-report of menstrual function; accurate determination of the cause of abnormal function, however, requires hormonal levels and potentially endometrial biopsy. In a study of HIV infected women with prolonged amenorrhea (>1 year), follicle-stimulating hormone (FSH) levels were assessed and levels >25 mIU/mL were used to define the presence of ovarian failure. More than 50% of the HIV infected women with prolonged amenorrhea, including 75% of women aged ≥45, did not have ovarian failure. After adjusting for age, HIV infected women were about threefold more likely than uninfected women to have prolonged amenorrhea without ovarian failure (*Obstet Gynecol* 2006;108(6):1423). Independent predictors of prolonged amenorrhea without ovarian failure included opiate use, low serum albumin (reflecting poor nutritional status or liver disease), and a history of AIDS-defining illness. These findings highlight the fact that amenorrhea may be incorrectly interpreted as menopause, with significant implications for patients who discontinue contraception on the basis of that presumption.

Some of the variability in previous study results may represent failure to take into account potential confounding variables. In the setting of HIV infection, those variables include age, weight loss, body mass index (BMI), chronic disease or opportunistic infections (including hepatitis), drug and alcohol abuse (*Menopause* 2007;14(5):859; *Obstet Gynecol* 2006;108(6):1423), and use of psychotherapeutic medications (*Am J Obstet Gynecol* 2003;188:881). Progestational agents used for appetite stimulation or contraception also may be related to menstrual dysfunction. Menorrhagia, or excessive menstrual blood loss, has been reported with ritonavir (*Lancet* 1999;353:811) and more recently with atazanavir (*Int J STD AIDS* 2007;18(9):651).

History, Physical Exam, Evaluation, Differential Diagnosis, and Management of Abnormal Bleeding

History

- **Characteristics of bleeding:**
  - Date of last normal menstrual period
  - Duration and frequency of menses
  - Amount of bleeding (i.e., number of pads/tampons used per day)
  - Presence of clots or associated pain/cramping
  - Duration and pattern of menstrual irregularities or amenorrhea
  - Presence of intermenstrual or postcoital bleeding
- **History of other abnormal bleeding:**
  - Gastrointestinal bleeding or bleeding from the urinary tract (vs. from a gynecologic source)
  - Easy bruising
  - Nose or gum bleed
- **History of gynecologic problems and/or other symptoms:**
  - Abnormal Pap smears
  - Uterine fibroids or polyps
  - Prior ectopic pregnancy
  - Abnormal vaginal discharge

- **Medical history:**
  - Timing of diagnosis of HIV/AIDS
  - Comorbid conditions, including hepatitis
  - Clinical symptoms of HIV
  - CD4+ cell count and viral load (VL)
  - Platelet disorders; thrombocytopenia is frequently diagnosed in patients with HIV infection, particularly those with more advanced stages of disease (*Eur J Haematol* 1992;48:168)
  - Substance abuse
  - Medications
- Sexual history: Last sexual intercourse and use of contraception and condoms

Physical Exam

- **Abdominal exam:** Presence of abdominal tenderness or mass
- **External genitalia, vagina, and cervix:** Inflammation and actively bleeding lesions (e.g., lacerations, condylomata, polyps)
- **Bimanual and rectovaginal exam:**
  - Pelvic tenderness
  - Enlarged uterus
  - Other pelvic mass

Evaluation

Further evaluation or referral is indicated based on results of the tests outlined below, severity of the problem, and response to basic management.

- **Pregnancy test** (urine or serum): All women within reproductive age range
- **Blood tests:**
  - Complete blood count (CBC)
  - Platelet count
  - Coagulation profile: with evidence of systemic bleeding, rule out coagulopathy
  - Thyroid-stimulating hormone (TSH), prolactin levels: consider with any irregular bleeding/amenorrhea without apparent cause
  - FSH, estradiol: with oligomenorrhea/amenorrhea and/or signs/symptoms of decreased estrogen production (hot flashes, vaginal atrophic changes); particularly helpful in distinguishing ovarian failure (low estradiol, high FSH) from hypothalamic amenorrhea, as with wasting (low estradiol, low/normal FSH)
- **Cervical testing:** Gonorrhea, chlamydia
- **Pelvic ultrasound:**
  - With finding of uterine enlargement, adnexal mass, significant tenderness, or positive pregnancy test
  - Transvaginal approach commonly used in evaluation of abnormal bleeding to assess endometrial thickness, especially in peri- and postmenopausal women or to look for other possible abnormalities (e.g., polyps, fibroids)
- **Endometrial biopsy:**
  - Postmenopausal bleeding
  - Prolonged amenorrhea followed by onset of irregular or heavy bleeding
  - Persistently irregular bleeding
  - Used liberally with any form of abnormal bleeding if no other cause is found and bleeding does not respond to conservative management with progestins or oral contraceptives
  - Helpful in diagnosing endometritis, endometrial hyperplasia, and uterine cancer
  - Necessary for diagnosis of cytomegalovirus (CMV) or tuberculous endometritis; alert pathologist if these are considerations

- **Pap smear:**
  - May be inadequate with active bleeding
  - Biopsy required if cervical lesion is seen

Differential Diagnosis

- **Pregnancy:**
  - Must be considered in any woman of reproductive age with irregular bleeding or amenorrhea
  - May be intrauterine or ectopic (usually tubal)
  - Bleeding with intrauterine pregnancy may indicate threatened or incomplete abortion or miscarriage
  - If later in pregnancy, may indicate serious obstetric complication
- **Anovulation:**
  - Most common cause of abnormal uterine bleeding among women of reproductive age. Women with anovulation typically have a history of menstrual irregularity.
  - Onset of heavy and prolonged bleeding may follow several months of no bleeding. Anovulatory bleeding is a diagnosis of exclusion; organic, systemic, and iatrogenic causes must be ruled out.
  - More common among perimenopausal women and adolescents soon after menarche, along with oligo-ovulation
- **Perimenopause/menopause:** Declining estrogen levels may cause irregular menses; menopause is associated with cessation of menses
- **Uterine fibroids:** Common benign uterine tumors; usually asymptomatic, but may cause heavy and/or prolonged periods
- **Adenomyosis:**
  - Migration of endometrial glands and stroma into uterine muscle (myometrium)
  - Uterus often somewhat enlarged and boggy to palpation
  - Benign condition
- **Cancer:**
  - Malignant processes in vulva, vagina, cervix, uterus, fallopian tubes, and ovaries may present with abnormal bleeding
  - Most common in postmenopausal women
  - Non-Hodgkin's lymphoma of endometrium has been reported in the setting of HIV (*Obstet Gynecol* 1997;90(4 Pt 2):697)
- **Genital tract infections:**
  - Cervicitis, endometritis, vaginitis, and vulvitis may present with abnormal vaginal bleeding or spotting
  - Aids to diagnosis include pain and/or tenderness, discharge, fever, and other signs and symptoms of infection
  - In the setting of severe immunosuppression, consider opportunistic processes, including tuberculous or CMV endometritis
- **Medical conditions:**
  - Thyroid disorders: hypothyroidism or hyperthyroidism
  - Coagulopathy, including platelet disorders
  - Cirrhosis
  - Chronic illness
  - Wasting
- **Substance abuse:** Drug use, including methadone, can lead to disturbances of the hypothalamic-pituitary axis, with resulting irregular bleeding or amenorrhea
- **Medications:** Hormonal agents: Progestational agents, such as those used for contraception (e.g., depot medroxyprogesterone acetate [DMPA], etonogestrel implant) or for appetite stimulation (e.g., megestrol acetate), frequently cause irregular vaginal bleeding. Combined estrogen-progestin contraceptive methods generally result in regular menstrual periods, although some breakthrough bleeding may occur early after initiation; inconsistent use can cause bleeding and increase

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risk for pregnancy. Consider antiretroviral agents as a potential cause of abnormal bleeding. Medications that can affect prolactin concentrations and possibly result in amenorrhea include psychotropic drugs (tricyclic antidepressants, phenothiazines, opiates) and metoclopramide. Thalidomide has also been associated with the development of secondary amenorrhea (*Eur J Dermatol* 2002;12:63).

Management of Abnormal Bleeding

Management depends on the diagnosis and on the results of testing.

- **Positive pregnancy test:** Refer to specialist. If suspect ectopic pregnancy (based on pain, HCG levels and ultrasound findings) requires urgent evaluation and treatment.
- **Suspected anovulatory bleeding:** Medical management with oral contraceptive pills or cyclic progestins: DMPA 10 mg po qd for 10–14 days each month
  - May restore regular menstruation, reduce the possibility of anemia, and protect endometrium from prolonged estrogenic stimulation, which can cause hyperplasia or neoplasia
  - Oral contraceptives also provide effective contraception but are contraindicated in heavy smokers aged >35 years and with hypertension or other cardiovascular disease, diabetes, or markedly abnormal liver function
- **Refer to specialist for:**
  - Severe bleeding and anemia
  - Pelvic mass
  - Suspected malignancy
  - Bleeding not resolved with conservative measures

Abnormal Pap Smear

In the setting of HIV infection 30%–60% of Pap smears exhibit cytologic abnormalities and 15%–40% have evidence of dysplasia; these rates are 10–11 times greater than those observed among women who are not HIV infected (*J Natl Cancer Inst Monogr* 1998;23:43).

HIV and Human Papillomavirus

The spectrum of human papillomavirus (HPV) disease includes subclinical disease, classic genital warts and other HPV-related skin lesions, lower anogenital-tract intraepithelial neoplasia, and invasive cancers of the lower genital tract and anal canal. There are >100 HPV subtypes, categorized as low, intermediate, or high risk on the basis of their oncogenic potential, though the categories are not exclusive; low-risk HPV types have been described in cervical carcinomas.

HPV is an extremely common infection. Studies suggest that more than 50% of sexually active adults have been infected with one or more genital HPV types, but most HPV infections are transient (*J Infect Dis* 1995;171:1026; *N Engl J Med* 1998;338:423). HPV VL is independently associated with HPV persistence (*J Infect Dis* 2001;184:682).

Compared with women who are not HIV infected, women with HIV have

- higher prevalence and incidence of HPV (*Int J STD AIDS* 2003;14:417; *J Infect Dis* 2001;184:682),

- higher HPV VL (*Am J Obstet Gynecol* 2002;186:21),

- longer persistence of HPV infection (*Am J Epidemiol* 2000;151:1148; *N Engl J Med* 1997;337(19):1343),

- a higher likelihood of infection with multiple HPV subtypes (*Am J Obstet Gynecol* 2002;186:21; *Acta Cytol* 2009;53:10, *Br J Cancer* 2007;96(9):1480; *Arch Virol* 2007;152:75), and

- greater prevalence of oncogenic subtypes (*Am J Obstet Gynecol* 1998;178(5):982; *J Med Virol* 1998;56:133; *Acta Cytol* 2009;53:10).

Among HIV infected women with normal cervical cytology, the rate of cervical HPV infection has been found to vary from >30% in Asia, North America, and Europe to >55% in South America, Central America, and Africa (*AIDS* 2006;20:2337).

In HIV infected women the prevalence and persistence of HPV infection increase as CD4+ cell counts decrease and HIV VL increases (*J Natl Cancer Inst* 1999;91:226; *Obstet Gynecol* 2008;111:1380). Higher HPV VLs are also associated with lower CD4+ cell counts (*Obstet Gynecol* 2000;96(3):403). Some studies have found that oncogenic HPV types may be more common with lower CD4+ cell counts and/or higher HIV VL (*J Infect Dis* 1999;179:1405; *Am J Obstet Gynecol* 1998;178(5):982; *Br J Cancer* 2007;96:1480). Immunosuppression also may increase the risk of clinically expressed (versus latent) HPV infection by approximately twofold in HIV infected women with CD4+ cell counts >500 cells/mm^3 to as much as 10-fold in women with CD4+ cell counts <200 cells/mm^3 (*Obstet Gynecol* 1995;85(5 Pt 1):680).

HIV and cervical dysplasia: Both the prevalence and incidence of abnormal Pap smears are greater among HIV infected women than among uninfected women. Abnormal cervical cytology is associated with the presence of HPV infection and the degree of immunosuppression. The frequency and severity of abnormal Pap smears, as well as histologically documented dysplasia, increase with declining CD4+ cell counts and have also been associated with higher HIV RNA levels (*Gynecol Obstet Invest* 1995;40:52; *Gynecol Oncol* 2001;80(3):350; *JAMA* 2000;282:1031; *AIDS Care* 2007;19:1052; *Obstet Gynecol* 2008;111:1388; *J Acquir Immune Defic Syndr* 2001;27:432). Increased HPV VL, seen in women with more-advanced HIV, is associated with increased frequency, severity, and incidence of cervical dysplasia (*Obstet Gynecol* 2000;96(3):403; *J Clin Microbiol* 2003;41:2763; *Am J Obstet Gynecol* 2001;184:322). HIV is also associated with more extensive and/or a larger volume of cervical involvement (*Gynecol Oncol* 1990;38:377).

Progression and regression of Pap smear abnormalities have been associated with level of immunosuppression and plasma viremia, as reflected in the CD4+ cell count and HIV VL (*J Acquir Immune Defic Syndr* 2001;27:432; *J Infect Dis* 2003;188(1):128). The incidence of invasive cervical cancer, however, is not higher among HIV infected women who are screened regularly and receive recommended treatment than among women who are not HIV infected (*Obstet Gynecol* 2004;104:1077; *Cancer* 2009;115:524).

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Invasive cervical cancer in HIV disease: In 1993, the U.S. Centers for Disease Control and Prevention (CDC) expanded the case definition of AIDS to include invasive cervical cancer (ICC). Oncogenic HPV types play a central role in the relationship between HIV and cervical cancer. Recent data from Africa indicate that in the absence of high-risk HPV, there was no increased risk for cervical cancer among HIV infected women (*J Infect Dis* 2003;188:555). In a study of ICC in both HIV infected and uninfected Kenyan women, HPV types 16 and 18 were the most common and were detected in 65% of ICCs in the HIV infected patients, with potential implications for prevention with HPV vaccines. Almost half of the cancers associated with HPV type 16 or 18 involved multiple HPV types (*Int J Cancer* 2008;122:244).

Analysis of matching data from AIDS and cancer registries in 15 regions in the United States indicates an increased risk of ICC among women with AIDS relative to HIV uninfected women (*J Natl Cancer Inst* 2009;101(16):1120); however, among women diagnosed with AIDS between 1996 (when ARVs were introduced) and 2004, ICC was not significantly increased in women with low CD4+ cell counts, a finding that may reflect the effects of active screening (*Natl Cancer Inst* 2009;101(16):1120). Other studies have found no evidence of an increased incidence of ICC among women who are screened regularly and who receive appropriate evaluation and treatment of abnormal Pap smears (*Obstet Gynecol* 2004;104:1077; *Cancer* 2009;115:524).

Cervical cancer affects HIV infected women at younger ages than it does uninfected women (about a decade earlier). Compared with other opportunistic infections (OIs), cervical cancer affects HIV infected women with more intact immune systems (*Gynecol Oncol* 2000;77:460).

HIV infected women with ICC may present at more advanced stages (especially with CD4+ cell counts <200 cells/mm^3). ICC may also behave differently in HIV infected women: it may metastasize to unusual locations (e.g., psoas muscle, clitoris, meninges), respond more poorly to standard therapy, recur more frequently and at shorter intervals, cause death more often, or progress to death more rapidly than it does in uninfected women with ICC at a similar stage (*Obstet Gynecol* 1996;88:269; *Gynecol Oncol* 1990;38:377).

HIV- and HPV-related dysplasia outside of the cervix: The association of HPV with disease outside of the cervix is also linked to persistent infection with oncogenic HPV subtypes and to the level of immunosuppression.

Compared with high-risk uninfected women, HIV infected women have about a 10-fold increase in the prevalence and incidence of vulvar (VIN), vaginal (VAIN), and perianal (PAIN) dysplasia or intraepithelial neoplasia (*Obstet Gynecol* 2006;107:1023; *AIDS* 1996;10:1641; *Gynecol Oncol* 1995;61:384; *Gynecol Oncol* 1990;38:377; *Gynecol Oncol* 1996;60:30; *Obstet Gynecol* 1994;83:205). In the WIHS cohort, VIN incidence was greater among HIV infected women and was associated with abnormal Pap smears and high- or medium-risk HPV. ART was associated with reduced VIN (*Am J Obstet Gynecol* 2004;190:1241).

Genital warts: See p. 198.

Anal HPV and/or dysplasia: Anal HPV has been reported in up to 90% of HIV infected women and is more common with lower CD4+ cell counts and in the presence of cervical HPV and/or cervical dysplasia (*Eur J Obstet Gynecol Reprod Biol* 2008;140(1):103; *J Infect Dis* 2001;183:383; *Sex Transm Dis* 2011;38(4):253). Multiple HPV types and oncogenic types are common (*Sex Transm Infect* 1999;75:172).

Abnormal anal cytology or anal squamous intraepithelial lesions (ASIL) have been reported in up to 26% of HIV infected women. Risk factors include a lower CD4+ cell count, increased HIV VL, high HPV VL, history of receptive anal intercourse, and concurrent abnormal cervical cytology (*J Natl Cancer Inst* 2001;93:843; *AIDS* 1993;7:43). Even with the use of ART, high-grade anal intraepithelial neoplasia was found in 9% of HIV infected women in a large prospective study (*AIDS* 2009;23:59).

The sensitivity of anal Pap smears appears to be similar to that of cervical cytology, although the grade of anal dysplasia may not correlate well with histology (*Int J STD AIDS* 2007;18:77).

The incidence of invasive anal cancer is seven- to 20-fold greater among women with HIV/AIDS than among women in the general population, with the highest incidence observed among women with AIDS (*J Natl Cancer Inst* 2000;92(18):1500; *J Natl Cancer Inst* 2009;101(16):1120).

Oral disease: Oral HPV infection is more common among HIV infected than uninfected women, although both the prevalence and incidence of oral HPV infection are substantially lower than cervical HPV infection (*Int J Cancer* 2007;121:143). A meta-analysis of cancer incidence in HIV infected patients indicated that cancers of the oral cavity or pharynx are 2.32 times as likely to develop in patients with HIV infection as in uninfected patients (*Lancet* 2007;370:59).

Effect of Antiretroviral Therapy on Human Papillomavirus–related Disease

Conflicting findings: The role of ART and immune reconstitution in reducing the incidence and progression of and promoting the regression of HPV infection and cervical or other abnormalities remains unclear. Conflicting findings may be related to any of a number of factors: differences in study design, screening and diagnostic protocols, virologic and immunologic parameters, duration and type of ART, length of follow-up, recruitment and referral strategies, and definitions of screening test and disease positivity.

In some studies, ART has been associated with increased regression and decreased risk of progression of cervical cytologic abnormalities and with increased regression of cervical dysplasia (*AIDS* 2002;16:1799; *AIDS* 2001;15:2157). Among women with pre-existing abnormal cervical cytology in the HERS cohort, ART was associated with enhanced HPV clearance but not with regression of abnormal Pap results (*Obstet Gynecol* 2009;113(1):26). In a study of women initiating ART, a high prevalence of cervical HPV DNA found at baseline declined over 8 months of ART (*J Acquir Immune Defic Syndr*

2009;51(3):274). In another study, with 15 months of follow-up, persistence of high-risk HPV and progression of squamous intraepithelial lesions (SIL) were comparable among three groups: women not on ART, women treated with nucleoside analogues only, and women on effective ART (*J Infect Dis* 2001;184:547).

In a more recent analysis from WIHS, the prevalence, incidence, and clearance of HPV infection and/or SILs were compared among women before and after they initiated ART. Use of effective ART and good adherence (≥95% of medications taken) were associated with a significant reduction in the prevalence and incident detection of oncogenic HPV infection and with decreased prevalence and more-rapid clearance of oncogenic HPV-positive SILs (*J Infect Dis* 2010;201(5):681). Six months of ART had no effect on anal HPV or ASIL (*J Acquir Immune Defic Syndr* 2001;28(5):422). Another analysis indicated that anal cancer was the only cancer found to be increasing in incidence among HIV infected people in the United States in the ART era (*Ann Intern Med* 2008;148(10):728). The incidence of high-grade vulvar neoplasia was not reduced with ART use (*Am J Obstet Gynecol* 2004;190:1241), even though rates of low-grade vulvar lesions and anal or genital warts did decrease with ART (*Am J Obstet Gynecol* 2004;190:1241).

Why don't HPV-related lesions respond to ART as other opportunistic illnesses do? Although there is partial restoration of immune competence with ART, this may be counteracted by increasing longevity, with increased cumulative exposure to oncogenic HPV infections and the accumulation of somatic mutations and epigenetic changes that contribute to cervical carcinogenesis. It is likely that women with higher nadir CD4+ cell counts and/or earlier intraepithelial lesions may respond best to effective ART (*J Transl Med* 2009;7:108). HIV infected women should continue to be followed closely for evidence of neoplasia in the lower genital tract, regardless of ART or VL.

Screening Tests

Cervical cytology: Cervical cytology screening programs have been associated with marked reductions in cervical cancer incidence (*Prev Med* 1986;15:582; *Ann Intern Med* 1990;113:214). It is estimated that 60% of women diagnosed with ICC have never had cervical cytology testing or have not been screened within the 5 years prior to diagnosis (NIH Consensus Statement Online 1996;43(1):1; http://consensus.nih.gov/1996/1996CervicalCancer102html. htm. Accessed 7/12/12). Because of errors in sampling or interpretation, false-negative Pap smears are associated with 30% of new cases of cervical cancer each year (NIH Consensus Statement Online 1996;43(1):1; *CA Cancer J Clin* 1995;45:305). A single Pap smear is associated with false-negative rates of 10%–25%; accuracy is significantly improved with regular periodic screening.

The accuracy of standard cervical cytology appears to be similar in both HIV infected and uninfected women (*Obstet Gynecol* 1993;81:372; *Gynecol Oncol* 1998;69:109). In the HERS cohort, HIV infected women were more likely than high-risk HIV uninfected women to have abnormal biopsy results with normal

Pap smears. Most of the HIV infected women, however, developed abnormal Paps within 1 year of the abnormal biopsy results, suggesting that current Pap smear screening guidelines are appropriate (*Clin Infect Dis* 2006;42(4):562).

If available, liquid-based Pap smears are preferred because they appear to decrease the number of inadequate smears and to reduce, but not eliminate, false-negative results; they also offer the possibility of direct HPV testing on collected specimens. Liquid-based Paps, however, are more expensive than conventional Pap tests. A review of more than 400 conventional and liquid-based cytologic screening tests in HIV infected women found that liquid-based preparations reduced the proportion of smears diagnosed as atypical squamous cells of undetermined significance (ASCUS)/atypical glandular cells of undetermined significance (AGCUS) (*Acta Cytol* 2004;48(2):165). It is believed that liquid-based cytology helped to resolve findings of "undetermined significance" into either normal or clearly abnormal results, potentially reducing the need for further evaluation.

HPV testing: HPV testing can identify both oncogenic and nononcogenic viral types. In HIV uninfected women, HPV testing for cancer-associated types is used as a triage test to stratify risk in women with a cytology diagnosis of ASCUS, in postmenopausal women with a cytology diagnosis of low-grade squamous intraepithelial lesion (LSIL), and as an adjunct to cytology for primary screening in women aged >30 years (ACOG Practice Bulletin 109; *Obstet Gynecol* 2009;114(6):1409).

The role of HPV DNA testing in HIV infected women, however, is unclear. In a WIHS substudy of HIV infected and uninfected women with normal baseline cytology, incidence of SIL was examined by baseline HPV DNA results and stratified by CD4+ cell count. Over 3 years of follow-up, incidence of any SIL was similar in both HIV infected women and HIV uninfected women with CD4+ cell counts >500 cells/mm^3 who had negative results for oncogenic HPV or all HPV, suggesting that similar cervical cancer screening practices may be applicable to both groups. On the other hand, after just 2 years of follow-up, incidence of any SIL in HIV infected women with CD4+ cell counts <500 cells/mm^3 was increased, even among women with negative results for any HPV, suggesting that a closer screening strategy may be needed for women with lower CD4+ cell counts (*JAMA* 2005;293(12):1471).

The 2006 American Society for Colposcopy and Cervical Pathology (ASCCP) Consensus Guidelines endorse the option of reflex high-risk HPV testing for triage of ASCUS on Pap smear irrespective of HIV status (*Am J Obstet Gynecol* 2007;197(4):346). CDC guidelines, however, although based on limited and conflicting data, recommend routine colposcopy or repeat cytology in 6–12 months for HIV infected women with ASCUS and colposcopy for a higher-grade abnormality (Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents (http://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/343/hpv; accessed 5/17/2013). In two prospective studies of HIV infected women with ASCUS, approximately 30% of participants had evidence of oncogenic HPV, a finding that would support the use of HPV testing in this population if HPV testing remained highly sensitive (*J Womens Health* 2004;13:147; *J Low Genit Tract Dis* 2004;8:298). One of these studies,

however, reported a sensitivity of HPV testing of 100% for the detection of cervical intraepithelial neoplasia (CIN) 2 or higher (*J Low Genit Tract Dis* 2004;8:298); the other study reported a sensitivity of only 50% for detecting high-grade CIN (*J Womens Health* 2004;13:147).

Currently, CDC and the American Congress of Obstetricians and Gynecologists (ACOG) do not recommend HPV testing for triage of HIV infected women with abnormal cytology results, for follow-up after treatment for CIN, or to lengthen screening intervals (Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents (http://aidsinfo. nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/343/hpv; accessed 5/17/2013); ACOG Practice Bulletin 117; *Obstet Gynecol* 2010;116(6):1492).

A study examining HPV DNA testing as a primary screening method for cervical dysplasia in 94 HIV infected women found that HPV DNA testing identified high-grade cervical dysplasia more accurately than Pap smear (*Gynecol Oncol* 1999;75(3):427). Further study is needed regarding a potential role for HPV DNA testing for primary screening in the setting of HIV, especially given the high rates of HPV infection in HIV infected women.

Recommendations for cytologic and other screening and colposcopy:
Pap smear results are reported according to the Bethesda System (*JAMA* 2002;287(16):2114), outlined in Table 6-1.

Table 6-1	
Pap Smear Results: Bethesda System	
Specimen adequacy	• Satisfactory for evaluation: note presence/absence of endocervical transformation zone component • Unsatisfactory for evaluation: specify reason
General categorization	• Negative for intraepithelial lesion or malignancy • Epithelial cell abnormality • Other

Interpretation and/or result	• Negative for intraepithelial lesion or malignancy
	  - Infections
	  - Reactive changes (inflammation, radiation)
	  - Atrophy
	• Epithelial cell abnormalities
	  - ASC
	  - ASCUS
	  - ASC-H
	  - LSIL, including HPV changes and mild dysplasia, CIN 1
	  - HSIL, including moderate and severe dysplasia, CIN 2, CIN 3
	  - Squamous cell carcinoma
	  - Glandular cell abnormalities
	• Other
	  - Endometrial cells in a woman aged ≥40 years

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Suggested frequency of Pap smears:

- Normal Pap: once yearly
- ASC/LSIL, evaluated and followed without treatment: every 6 months
- Following treatment of preinvasive lesions: every 3–4 months for first year, then every 6 months

Evaluation of abnormal results: Women with HIV infection should be screened with cervical cytology twice in the first year after diagnosis of HIV and, if results are normal, annually thereafter (Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents (http://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/343/hpv; accessed 5/17/2013); ACOG Practice Bulletin 109; *Obstet Gynecol* 2009;114:1409). More-frequent Pap smears should be considered with an abnormal Pap smear that is followed conservatively (after colposcopic evaluation to rule out HSIL), with HPV infection, and after treatment for cervical dysplasia.

Although adolescents with HIV have a higher incidence of cervical dysplasia than uninfected adolescents, the incidence of high-grade abnormalities appears to be low (*J Low Genit Tract Dis* 2008;12:199; *J Infect Dis* 2004;190:1413; *Am J Obstet Gynecol* 2009;200:149.e1). Cytologic surveillance in adolescents with HIV should be the same as that recommended for adults.

Pap smear results are reported according to the Bethesda System (see Table 6-1). Abnormal Pap smears (ASCUS or worse) require further evaluation with colposcopy and biopsy of abnormal areas for histologic confirmation and to confirm or exclude a high-grade cervical lesion. The 2006 ASCCP Consensus Guidelines recommend that ASCUS on Pap trigger the use of reflex high-risk HPV testing for triage to colposcopy (HPV positive) vs. short-term cytologic follow-up (HPV negative) for both HIV infected and uninfected women (*Am J Obstet Gynecol* 2007;197(4):346). Current CDC guidelines recommend colposcopy or repeat cytology in 6–12 months for all HIV infected women with ASCUS (Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents (http://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/343/hpv; accessed 5/17/2013), irrespective of CD4+ cell count, HIV VL, or ART. Currently, ACOG states that HIV infected women with ASCUS may be monitored with repeat cytology alone or referred for colposcopy (ACOG Practice Bulletin 117; *Obstet Gynecol* 2010;116(6):1492).

Indications for colposcopy of the cervix include

- cytologic abnormality: atypia or greater, including ASC and atypical glandular cells (AGC);
- history of untreated abnormal Pap smear;
- repeat colposcopy in women with AGC not otherwise specified (AGC-NOS) if the initial evaluation is negative and follow-up cytology is abnormal; and
- evidence of HPV infection (consider).

Consider periodic colposcopy

- after treatment of cervical dysplasia, particularly with recurrence or persistence of cytologic abnormalities;

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- with ASCUS or LSIL after ruling out a high-grade lesion; and
- with cytologic progression of ASCUS or LSIL that is being followed conservatively.

The finding of ASC represents the mildest Pap smear abnormality. ASC is stratified into two categories: ASCUS and ASC-H. In the general population, 5%–17% of women with ASC have underlying CIN 2–3 and approximately 0.1% have invasive cancer (*J Natl Cancer Inst* 2001;93:293), whereas 24%–92% of women with ASC-H have CIN 2–3 confirmed with biopsy (*JAMA* 2002;287(16):2120). HIV infected women with ASCUS are approximately twice as likely to have underlying dysplasia as are uninfected women (*Obstet Gynecol* 1996;87:515). Immunosuppression does not appear to increase the frequency of dysplasia associated with ASCUS on Pap (*Gynecol Oncol* 1999;75(1):118).

It remains unclear whether HIV infected women with mild cytologic abnormalities are at a similar or increased risk for clinically significant disease (i.e., HSIL or worse) compared with uninfected women. In a cross-sectional study of HIV infected and uninfected women with ASCUS and LSIL, HIV infected women were no more likely to have CIN 2 or higher on biopsy than were uninfected women (*Obstet Gynecol* 2008;112:238). Other studies have shown that with ASCUS or LSIL on Pap and no histologic evidence of high-grade CIN, the absolute risk of progression to CIN 2 or higher is approximately 12% (*Obstet Gynecol* 2005;106(3):525) and that CIN 1 infrequently progresses to more advanced disease (*AIDS* 2004;18:109).

The risk of underlying pathology with a diagnosis of AGC is significant. The 2001 Bethesda System stratifies AGC into three categories: AGC, either endocervical, endometrial, or NOS; AGC, favor neoplasia; and endocervical adenocarcinoma in situ (AIS). Various studies have found that 9%–54% of women with AGC have CIN on biopsy, 0%–8% have AIS on biopsy, and up to 9% have invasive cancer (*JAMA* 2002;287(16):2120). The risk of a significant abnormality increases with the severity of the AGC reading. Colposcopy, as well as endocervical sampling, is indicated with any AGC on Pap. Endometrial sampling is indicated in women aged >35 years and in younger women with AGC who have unexplained vaginal bleeding (*JAMA* 2002;287(16):2120). Women who have AGC, favor neoplasia, or endocervical AIS should undergo a diagnostic excisional procedure (e.g., cervical conization) if the initial evaluation is negative for invasive cancer (*JAMA* 2002;287(16):2120).

Even in high-resource areas, screening for cervical dysplasia in the setting of HIV can be challenging. Women receiving gynecologic and primary HIV care at the same location are more likely to have had Pap-smear screening within the previous year (*J Acquir Immune Defic Syndr* 2001;27:463); however, despite high rates of HPV and CIN, many women with HIV do not engage in the recommended annual Pap testing (*J Womens Health* 2008;17(10):1609; *J Acquir Immune Defic Syndr* 2009;51(4):430).

Vaginal and vulvar screening: Careful visual inspection of the vagina and vulva should be performed at least annually; look for evidence of HPV infection (e.g., warts, hyperpigmented or hyperkeratotic lesions). Consider

vaginal cytology and careful examination and/or colposcopy of the entire lower genital tract (vagina, vulva, and perianal region) with any of the following: visible evidence of cervical, vaginal, or vulvar HPV infection; current CIN or history of CIN; or cervical, vaginal, or vulvar cancer.

Continued vaginal cytologic surveillance is warranted in HIV infected women who have a history of CIN 2 or greater who undergo hysterectomy (ACOG Practice Bulletin 117; *Obstet Gynecol* 2010;116(6):1492). Abnormal vaginal cytology should be evaluated with colposcopy +/− Lugol's iodine, with biopsy of abnormal areas. Persistent ulcer or mass of concern for possible cancer should be biopsied.

Anal screening: Question patients at least annually about such symptoms as rectal bleeding and/or pain and perform an annual digital rectal exam to detect mass on palpation.

The role of anal cytology remains unclear pending further screening and treatment studies; recommendations for routine anal Pap smear screening are not currently part of national guidelines. If anal cytology is performed, it is critical to refer for further evaluation of abnormal screening (e.g., high-resolution anoscopy, biopsy) and treatment.

At a minimum, consider anal cytology in women with a history of abnormal cervical cytology and/or genital warts.

The approach suggested by experts in this field is similar to recommendations for cervical Pap-smear screening: perform an anal Pap as part of the initial evaluation; if results are normal, repeat in 6 months and annually thereafter. More-frequent anal Pap smears should be considered with a previous abnormal anal Pap smear and after treatment for anal dysplasia. Anal Pap smears with ASCUS or SIL should be evaluated with high-resolution anoscopy and biopsy.

Anal Pap smears are performed by inserting a moistened Dacron swab 1−1.5 inches into the anal canal and rotating it while slowly withdrawing it over 15−20 seconds and maintaining contact with the mucosa. Both rectal columnar and anal squamous cells must be obtained to have an adequate specimen. The swab should then be vigorously shaken in liquid-based cytology media.

Management of Cervical and Other Lower-Genital-Tract Dysplasia

Management of abnormal Pap smears is outlined in Table 6-2. The purpose of colposcopy is to identify abnormal areas and their extent for targeted biopsy. The results of Pap smear plus colposcopy and/or biopsy are used to determine the need for treatment, follow-up, or further evaluation.

Treatment is recommended with documentation of a high-grade cervical lesion on biopsy; standard excisional or ablative treatment is recommended. Cryotherapy has had the highest rate of recurrence and should be avoided if other treatment methods are available. Close observation should be considered for management of CIN 1 and CIN 2 in HIV-infected adolescents. Hysterectomy should be used as treatment for high-grade cervical dysplasia

only after excluding invasive cancer with an excisional treatment and in general should not be used as a primary treatment. It is generally reserved for persistent or recurrent high-grade disease. Hysterectomy as treatment for recurrent or persistent cervical dysplasia has also been associated with significant rates of vaginal recurrence (*Am J Obstet Gynecol* 2002;186:880).

HIV infected women have an increased incidence (>50%) of recurrence of cervical lesions after treatment (*Int J STD AIDS* 2006;17(8):507), particularly with any of the following:

- Positive surgical margins with a loop electrosurgical excision procedure or cervical conization (present in >40% of HIV infected women) (*Am J Obstet Gynecol* 1999;181(6):1395; *Gynecol Oncol* 2005;96(1):112; *Int J Gynaecol Obstet* 2009;104:100)

- Glandular involvement (*Int J Gynaecol Obstet* 2009;104:100)

- Greater level of immunosuppression (*Gynecol Oncol* 1999;74:428; *J Obstet Gynaecol* 2008;28(3):327)

- Absence of suppressive ART (*Am J Obstet Gynecol* 2001;184(4):538)

Most recurrences appear to be low-grade disease, which may be associated with new HPV infections (*J Low Genit Tract Dis* 2007;11:90), but re-excision may be necessary in some cases (*Gynecol Oncol* 1999;74:428; *Anticancer Res* 2007;27:1795). Follow-up with cervical cytology alone or cytology and colposcopy together at 6-month intervals during the first year after treatment is recommended (*Am J Obstet Gynecol* 2007;197(4):346).

After treatment for cervical dysplasia, abstinence should be emphasized until complete healing has occurred because treatment has been shown to dramatically increase genital-tract HIV shedding, which may increase risk for sexual transmission of HIV (*Am J Obstet Gynecol* 2001;184(3):279).

Table 6-2

Recommended Management for Abnormal Pap Smear*

Pap Smear Result	Management
Unsatisfactory	• Repeat Pap smear
Partially obscuring (inflammation)	• Evaluate for infection • Consider repeat Pap smear
Epithelial Cell Abnormalities	

Atypical glandular cells	• Colposcopy, endocervical sampling
	• Endometrial sampling if aged >35 y or with abnormal bleeding
	• If AGC, favor neoplasia: cervical conization if initial evaluation is negative
	• If AGC-NOS:
	  - Consider cervical conization
	  - If observation is elected, repeat Pap smear and/or colposcopy in 6 mo
	  - If persistent reading of AGC, proceed to diagnostic excision

Table 6-2	*continued*

Recommended Management for Abnormal Pap Smear*

Pap Smear Result	Management
Atypical squamous cells (ASCUS and ASCUS-H)	• Colposcopy (repeat cytology alone in 6–12 mo can be considered for ASCUS) • Biopsy if indicated • Endocervical sampling if unsatisfactory colposcopy • Follow with Pap smear every 6 mo • Consider repeat colposcopy annually if Pap smear is unchanged • May resume annual Pap smears after two successive negative results
Low-grade squamous intraepithelial lesion (LSIL, CIN 1)	• Colposcopy • Biopsy if indicated • Endocervical sampling if unsatisfactory colposcopy • Follow with Pap smear every 6 mo • Consider annual repeat colposcopy if Pap smear is unchanged
High-grade squamous intraepithelial lesion (HSIL, CIN 2–3, carcinoma in situ)	• Colposcopy • Biopsy • Endocervical sampling • Treat with loop excision or conization • If evaluation is negative, consider diagnostic excision • If close follow-up is elected, repeat Pap smear and colposcopy in 6 mo • Proceed to excisional procedure with repeat reading of HSIL
Invasive carcinoma	• Colposcopy with biopsy or conization for diagnosis • Treat confirmed invasive disease with surgery or radiation • Referral to gynecologic oncologist

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

*Management should be based on histologic findings when biopsy is performed

Management of other lower-anogenital-tract dysplasia: Women with documented vaginal, vulvar, or anal dysplasia should be managed in consultation with a specialist. Treatment options include observation, excision, cavitational ultrasonic surgical aspiration, or laser vaporization; 5-FU has been used successfully to treat vulvar and vaginal lesions and small studies suggest a possible role for topical 1% cidofovir gel with lower-genital-tract HPV-related lesions (*J Med Virol* 2001;64:195; *Clin Infect Dis* 2001;33:597). Regardless of the type of treatment, recurrence rates are higher in HIV infected women than in uninfected women and close follow-up is needed (*Dis Colon Rectum* 2002;45:453).

Prevention of Human Papillomavirus Infection

HPV vaccine: Use of the HPV vaccine is an issue of concern in HIV infected adolescents, a significant percentage of whom were infected perinatally. Although the safety of the HPV quadrivalent vaccine has been demonstrated in HIV infected children, the efficacy of currently available HPV vaccines in HIV infected women or girls has not yet been established (*J Acquir Immune Defic Syndr* 2010;55(2):197). Given existing evidence that the vaccine is safe and immunogenic, and because of the potential benefit in preventing HPV-associated disease and cancer in HIV-infected women, either the bivalent or quadrivalent HPV vaccine is recommended for HIV-infected females aged 13 through 26 years. (MMWR *Recomm Rep* 2007;56(RR-2):1; *Obstet Gynecol* 2010;116;800; Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents (http://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-oi-prevention-and-treatment-guidelines/343/hpv; accessed 5/17/2013)).

Condoms: Consistent and correct use of condoms has been associated with a reduced risk of acquiring genital HPV infection (including genital warts), CIN, and cervical cancer (*N Engl J Med* 2006;354:2645; *Cancer Epidemiol Biomarkers Prev* 2006;15:326; *Sex Transm Dis* 2002;29:725), although data are limited in the HIV setting.

Genital Ulcers

The presence of genital ulcers in HIV infected patients increases HIV shedding, which may increase the risk of HIV transmission to partners and also increases vulnerability to HIV acquisition (*Curr Infect Dis Rep* 2008;10:505). History, physical examination, and evaluation for patients with HIV ulcers are outlined below.

History, Physical Exam, Evaluation, and Differential Diagnosis

History

- Duration and location of lesion(s)
- Previous history of genital ulcers, syphilis, or genital herpes
- Associated symptoms, e.g., pain, pruritus, fever
- Medications and timing of ulcers relative to initiation of new medication
- Sexual history (including condom use)
- CD4+ cell count
- HIV VL

Physical Examination

- Dimensions and location of lesion(s)
- Presence of pigmentation, edema, erythema, or induration
- Presence of associated exudate or tenderness
- Presence of oral lesions
- Associated lymphadenopathy or rash

Evaluation

- Syphilis serology or darkfield examination
- Culture or PCR from lesion for herpes simplex virus (HSV); in some circumstances (e.g., genital ulcers and negative evaluation), consider type-specific HSV antibody test
- Biopsy with unclear diagnosis, lack of response to treatment: consider special stains (e.g., CMV acid-fast bacillus)
- Culture for *Haemophilus ducreyi*: not widely available commercially; diagnosis of chancroid generally made with typical clinical presentation, after excluding syphilis and HSV

Differential Diagnosis

- Infectious causes
  - HSV
  - Syphilis
  - Chancroid
  - CMV
  - Other (lymphogranuloma venereum, granuloma inguinale, TB)

- Noninfectious causes
  - Inflammatory conditions (Crohn's disease, Behçet's syndrome, hidradenitis suppurativa)
  - Neoplasia
  - Drug reaction
  - Trauma
  - Aphthous genital ulcerations

Herpes Simplex Virus

HSV is the most prevalent infectious cause of genital ulcers in the United States. Two distinct serotypes exist: HSV-1 and HSV-2; most cases of recurrent genital herpes (60%–95%) are caused by HSV-2, but HSV-1 is causing an increasing proportion of first episodes of anogenital herpes in some populations, including young women (*Sex Transm Infect* 2009;85:416). Since the late 1970s, the seroprevalence of HSV-2 infection has increased by 30%; infection is detectable in 21.9% of people aged ≥12 years nationwide (*N Engl J Med* 1997;337(16):1105). Most people with HSV-2 do not know they are infected because they have mild or unrecognized symptoms; they may, however, shed virus intermittently in the genital tract and transmit infection to their sexual partners. Age-adjusted HSV-2 prevalence is significantly higher among women than men (*J Infect Dis* 2002;185(8):1019). Viral shedding and sexual transmission can occur during asymptomatic periods.

HSV in HIV infected patients: Approximately 70% of HIV infected patients are co-infected with HSV-2 (*JAMA* 2006;296:964). More-frequent, prolonged, and/or severe episodes are common with progressive immunosuppression and lesions may be atypical in appearance or location.

HSV viral shedding, which increases with declining CD4+ cell counts (*Ann Intern Med* 1995;123:845) and higher plasma HIV VL (*Clin Infect Dis* 2003;36:207), may be more common in women who use oral contraceptives or DMPA and in women with severe vitamin A deficiency (*J Infect Dis* 2000;181:58). Most viral shedding is asymptomatic.

Although ART reduces the severity and frequency of symptomatic genital herpes, HIV infected women have comparatively more genital ulcers, and frequent subclinical shedding still occurs among women on ART (*J Infect Dis* 2004;190:693; *AIDS* 2006;20:1051). HSV is associated with increased risk for HIV transmission and/or acquisition (*Lancet* 1994;343:255) and HIV disease progression is increased by HSV-2 infection (*PLoS One* 2010;5:e9973). Higher levels of cervical HSV have been associated with increased HIV shedding in the genital tract (*AIDS* 2002;16:2425) and plasma HIV VL is increased during HSV reactivation (*J Infect Dis* 2002;186:1718)

Diagnosis: Lesions typically present as painful vesicles that ulcerate and heal without scarring. Primary infection is often associated with systemic symptoms (fever, photophobia, headache); duration of lesions and viral shedding are more prolonged with primary infection. After the primary episode, latency is established in sacral dorsal root ganglia. Recurrent episodes occur with variable frequency and are associated with more localized lesions and shorter duration than primary or nonprimary first episodes.

Nonprimary first-episode herpes, which is often milder and shorter in duration, is diagnosed with antibodies to HSV-2 or HSV-1 in patients who present with symptoms but have no previous clinical symptoms of HSV.

Treatment: Recommended HSV treatment regimens are outlined in Table 6-3. HIV infected women often need higher doses and longer courses of treatment, particularly with more advanced immunosuppression, and they may benefit from suppressive therapy. Daily suppressive therapy reduces the frequency of recurrences by ≥75% among patients who suffer from six or more HSV recurrences per year. Suppressive therapy reduces but does not eliminate viral shedding. Suppressive or episodic therapy with oral antiviral agents is effective in decreasing genital ulcers and genital HSV-2 shedding as well as genital HIV shedding and plasma HIV VL among co-infected women (*AIDS* 2009;23:461; *J Acquir Immune Defic Syndr* 2008;49:77; *N Engl J Med* 2007;356:790; *AIDS* 2006;20:2305; *Int J STD AIDS* 2002;13(1):12; *J Infect Dis* 2003;188:1009). Daily HSV suppressive therapy in HSV-2/HIV co-infected persons was not associated with reduced HIV transmission to HIV uninfected sexual partners, despite a reduction in HIV VL and occurrence of genital ulcers due to HSV-2 (*N Engl J Med* 2010;362(5):427). Clinical manifestations of genital herpes might worsen during immune reconstitution after initiation of ART.

Table 6-3	
Recommended Treatment for Herpes Simplex Virus	
Indication	**Treatment Options**
First clinical episode	• Acyclovir 400 mg po tid x 7–10 d or 200 mg po 5x/d x 7–10 d • Famciclovir 250 mg po tid x 7–10 d • Valacyclovir 1 g po bid x 7–10 d
Recurrent episodes	• Acyclovir 400 mg po tid x 5–10 d • Famciclovir 500 mg po bid x 5–10 d • Valacyclovir 1 g po bid x 5–10 d
Daily suppressive therapy	• Acyclovir 400–800 mg po bid–tid • Famciclovir 500 mg po bid • Valacyclovir 500 mg po bid
Severe disease	• Acyclovir 5–10 mg/kg body weight IV q8h x 2–7 d or until clinical improvement is observed • Follow with oral antiviral therapy to complete at least 10 d total therapy
Acyclovir-resistant HSV	• Intravenous foscarnet: 40 mg/kg IV q8h or 60 mg/kg IV q12h until clinical resolution • Intravenous cidofovir: 5 mg/kg q wk • Topical cidofovir gel 1%: apply to lesions qd x 5 consecutive days • Topical imiquimod: apply to lesions qd x 5 consecutive days

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Source: *MMWR Recomm Rep* 2010;59(RR-12):1

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Acyclovir resistance: Suspect acyclovir resistance if lesions persist or recur in a patient on antiviral treatment; obtain a viral isolate for sensitivity testing (*Arch Intern Med* 2003;163:76). Acyclovir-resistant HSV strains are cross-resistant to valacyclovir and usually to famciclovir. The prevalence of resistant HSV in immunocompromised patients has remained stable at approximately 4%–7% (*Clin Microbiol Rev* 2003;16:114). Most of these isolates are susceptible to intravenous (IV) foscarnet or topical cidofovir. Factors associated with acyclovir resistance are low CD4+ cell counts and long-term exposure to acyclovir. Results of a study of immunocompromised but HIV uninfected patients showed that daily suppressive antiviral therapy was less likely than episodic therapy during outbreaks to be associated with the development of acyclovir-resistant HSV (*J Infect Dis* 2007;196:266).

Syphilis

Syphilis is a systemic disease caused by infection with *Treponema pallidum*.

Syphilis in HIV infected patients: HIV infected patients may have abnormal serologic test results (unusually high titers, false negatives, delayed seroreactivity). Generally, however, serologic tests can be interpreted in the usual manner. If clinical findings suggest syphilis but serology is nonreactive, then biopsy, darkfield examination, or PCR of lesion material should be considered.

The clinical presentation of syphilis is very variable at all stages; atypical manifestations may be seen in the setting of HIV disease. HIV infected patients with primary syphilis are more likely than HIV uninfected patients to have multiple ulcers and those with secondary syphilis are more likely to have concomitant genital ulcers (*Sex Transm Dis* 2001;28:158; *MMWR Recomm Rep* 2010;59(RR-12):1).

The CDC recommends annual screening for syphilis among sexually active HIV infected women, with more-frequent screening if indicated by symptoms or risk behaviors (*MMWR Recomm Rep* 2010;59(RR-12):1). Although some study results indicate no influence of HIV serostatus on rates of successful syphilis treatment (*Sex Transm Dis* 2006;33:151), others indicate significantly more treatment failures or a longer median time to successful serologic response in HIV infected patients (*Sex Transm Infect* 2007;83(2):97; *Int J STD AIDS* 2007;18:814). Close follow-up after treatment is essential.

Neurosyphilis should be considered in the differential diagnosis of neurologic signs or symptoms in HIV infected patients, who may be at increased risk for neurologic complications in early syphilis (*MMWR Morb Mortal Wkly Rep* 2007;56:625). Clinical and cerebrospinal fluid (CSF) abnormalities consistent with neurosyphilis are most likely in HIV infected patients who have been diagnosed with syphilis and have a CD4+ cell count of $\leq$350 cells/mm^3 and/or a rapid plasma reagin (RPR) titer of $\geq$1:32 (*J Infect Dis* 2004;189:369; *Sex Transm Dis* 2007;34:141; *Clin Infect Dis* 2009;49:162).

Diagnosis: Definitive methods for diagnosing early syphilis are darkfield examination and PCR (not commercially available) of lesion exudate or tissue. Presumptive diagnosis is possible using two types of serologic tests: nontreponemal (venereal disease reaction level or RPR) and a confirmatory treponemal test (fluorescent treponemal antibody absorption test, microhemagglutination-*T. pallidum*, various enzyme immunoassays [EIAs], and chemiluminescence immunoassays). Nontreponemal antibody titers usually correlate with disease activity and are used to assess treatment response. Serial assessment during follow-up after treatment should use the same type of nontreponemal test.

Treatment: Recommended management strategies are outlined in Table 6-4. ART may improve clinical outcomes in patients co-infected with HIV and syphilis (*Clin Infect Dis* 2008;47:893; *AIDS* 2008;22:1145; *Clin Infect Dis* 2008;47:258).

Table 6-4

Recommended Treatment of Syphilis

Syphilis Stage	Treatment
Primary, secondary, and early latent	• Benzathine penicillin G, 2.4 million units IM (single dose) • CSF examination indicated with neurologic signs/symptoms • Routine CSF exam not associated with improved clinical outcomes • If penicillin-allergic: consider skin testing and PCN desensitization if positive
Late latent, unknown duration, and tertiary	• Benzathine penicillin G, 7.2 million units IM; administer as 2.4 million units q wk x 3 wk • CSF examination indicated with neurologic signs/symptoms • Routine CSF exam not associated with improved clinical outcomes
Neurosyphilis	• Aqueous crystalline penicillin G, 18–24 million units qd; administer as 3–4 million units IV q4h or by continuous infusion x 10–14 d • Some recommend benzathine penicillin 2.4 million units IM q wk x 1–3 wk after completion of IV regimen

Recommended Follow-up for Management of Syphilis

Syphilis Stage	Treatment
Primary, secondary	• HIV infected patients: clinical and serologic evaluation for treatment failure at 3, 6, 9, 12, and 24 mo after treatment • Treatment failure (with signs or symptoms that persist or recur or sustained fourfold increase in nontreponemal test titer): CSF examination; if CSF exam is negative, retreat with benzathine penicillin G, 2.4 million units IM q wk x 3 wk; consider same for patients whose titers do not decrease fourfold within 6–12 mo
Latent	• HIV infected patients: clinical and serologic evaluation at 6, 12, 18, and 24 mo after treatment • With development of clinical symptoms, fourfold rise in titers, or titers that do not decrease fourfold between 12 and 24 mo after evaluation, perform CSF examination and follow with appropriate treatment
Neurosyphilis	• Repeat CSF examination q 6 mo until cell count is normal • Consider retreatment if cell count has not decreased after 6 mo or if CSF is not entirely normal after 2 y • Limited data suggest that changes in CSF parameters might occur more slowly in HIV infected patients, especially those with more advanced immunosuppression (AIDS 2008;22:1145)

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Source: *MMWR Recomm Rep* 2010;59(RR-12):1

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Chancroid

Chancroid is caused by infection with *Haemophilus ducreyi*, which is endemic in some areas of the United States and also occurs in discrete outbreaks. Ten percent of patients with chancroid are co-infected with *T. pallidum* or HSV.

Chancroid in HIV infected patients: Response to treatment may be diminished in HIV infected patients, who may require longer or repeated courses of therapy and may be at increased risk for treatment failure.

Diagnosis: The initial presentation typically consists of a tender papule that becomes pustular and then ulcerative; the ulcer is usually well demarcated, with ragged, undermined edges. Definitive diagnosis requires the identification of *H. ducreyi* on special culture media (not widely available; sensitivity <80%). No U.S. Food and Drug Administration (FDA)-cleared PCR test for *H. ducreyi* is available in the United States. A probable diagnosis can be made if the patient has one or more painful ulcers, no evidence of *T. pallidum* or HSV infection is apparent, and the clinical presentation (appearance of ulcers and regional lymphadenopathy) is typical for chancroid.

Treatment: In HIV infected patients, single-dose therapies should be used only if follow-up can be ensured. Recommended regimens include the following (*MMWR Recomm Rep* 2010;59(RR-12):1):

- Azithromycin 1 g po (single dose), *or*
- Ceftriaxone 250 mg intramuscularly (IM) (single dose), *or*
- Ciprofloxacin 500 mg po bid x 3 days, *or*
- Erythromycin base 500 mg po 4x/day x 7 days

Cytomegalovirus

CMV should be suspected with genital ulcers in severely immunocompromised patients. Cervical shedding of CMV is associated with low CD4+ cell counts (*J Acquir Immune Defic Syndr Hum Retrovirol* 1997;15:341).

Diagnosis: Biopsy of lesion with immunohistochemical stains is required.

Treatment: Ganciclovir 5 mg/kg IV bid x 3–4 weeks or foscarnet 60 mg/kg IV q8h or 90 mg/kg q12h for 3–4 weeks.

Other Infectious Causes of Genital Ulcers

Lymphogranuloma venereum: Infection is rare in the United States and is associated with tender, usually unilateral inguinal or femoral lymphadenopathy, proctocolitis, or rectal fistulas/strictures. Diagnosis is made with serology and exclusion of other causes. Treatment is a 3-week course of doxycycline or erythromycin. HIV infected patients may require more-prolonged treatment and resolution of symptoms may be delayed.

Granuloma inguinale (donovanosis): Infection is rare in the United States. It is associated with painless, progressive ulcers that bleed easily on contact, without regional lymphadenopathy. Diagnosis is made with biopsy or tissue-crush preparation. Treatment options are doxycycline, azithromycin,

ciprofloxacin, erythromycin, or trimethoprim-sulfamethoxazole, taken for 3 weeks or until all lesions are healed. The CDC recommends considering the addition of aminoglycoside to the treatment regimen in HIV infected patients.

Tuberculosis: Genital TB is generally a secondary manifestation of primary disease, usually pulmonary. In the United States, the incidence of genital disease is <1%. Diagnosis is made with biopsy. Genital TB should be treated in the same manner as extrapulmonary disease; expert consultation is necessary (*Eur J Obstet Gynecol* Reprod Biol 1998;80(2):227).

Noninfectious Causes of Genital Ulcers

Crohn's disease: This disease is easy to misdiagnose because its principal clinical features (fever, abdominal pain, diarrhea, fatigability, weight loss) are often found in patients with HIV infection. Crohn's disease may also present with genital ulcers, rectal fissures, perirectal abscesses, or intestinal fistulas. Sigmoidoscopy or barium enema is essential in making this diagnosis. Manage with expert consultation.

Behçet's syndrome: This is a multisystem disorder that presents with recurrent oral and genital ulcerations as well as uveitis, arthritis, and vasculitis. Vaginal ulcers are usually painless, whereas lesions on the external genitalia are generally painful. Ulcers range between 2 mm and 10 mm in diameter and can be shallow or deep, with a central yellowish necrotic base. A single lesion or crops of lesions may be evident. Diagnosis is established on the basis of the clinical presentation and biopsy. Treatment consists of topical or systemic corticosteroids.

Hidradenitis suppurativa: This is a chronic, refractory condition involving the skin, subcutaneous tissues, and apocrine glands. Lesions are painful and are associated with a foul-smelling discharge. Eventually a deep-seated chronic infection of the apocrine glands develops, with multiple draining abscesses and sinuses. A biopsy is necessary to establish the diagnosis. In the early stages of disease, treatment options include antibiotics, anti-androgens, and retinoids. Treatment of advanced disease requires surgical intervention (*Dermatol Clin* 2010;28:779).

Neoplasia: Any nonhealing genital ulcer must be biopsied to rule out a neoplastic process, including squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, melanoma, lymphoma, and Kaposi's sarcoma. Refer to an oncologist for management.

Drug reaction: Genital ulcers have been described as a rare side effect of treatment with zalcitabine and foscarnet.

Trauma: Consider with a history of traumatic injury and the possibility of sexual violence.

Aphthous genital ulcerations: Aphthous genital ulcers have no identifiable specific etiology (typical or opportunistic organism) and are similar to aphthous ulcers seen in the gastrointestinal tract (*J Acquir Immune Defic Syndr Hum Retrovirol* 1996;13(4):343). Most patients with these types of ulcers

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are significantly immunosuppressed (median CD4+ cell count 50 cells/mm³). Oro-esophageal ulcers coexist in about one-third of cases, and one-fifth are associated with genital fistula formation.

The lesions can be painful, multiple, deep, and extensive (1–6 cm). Associated morbidity includes immobility, bleeding, and superinfection. Most have been reported to be chronic and/or recurrent or relapsing.

Treatment: After standard evaluation for other causes, consider empiric therapy for HSV. If empiric therapy fails, systemic steroids (prednisone 40–60 mg/day for 1–2 weeks, then taper) have been moderately successful. There has been one report of successful treatment of oral aphthous ulcers with ART (*Int J Infect Dis* 2007;11(3):278).

Thalidomide: Thalidomide 200 mg qd x 2–4 weeks has been used to treat similar ulcers in the oropharynx or esophagus, with complete healing in 55%–73% of cases (*N Engl J Med* 1997;336:1487; *J Infect Dis* 1999;180:61). There are anecdotal reports of similar success in treating genital aphthous ulcers. **WARNING:** Thalidomide is a powerful teratogen and should be used by women of reproductive age only after appropriate counseling and pregnancy testing and in the setting of reliable contraception or abstinence.

Vaginal Discharge

Abnormal vaginal discharge is a common gynecologic complaint among women, including HIV infected women.

History, Physical Exam, Evaluation, and Differential Diagnosis

History

- Duration and characteristics of discharge
- Associated symptoms (e.g., pruritus, malodor, burning, pelvic pain)
- Associations with menstrual cycle
- Sexual history, including condom and other contraceptive use
- History of sexually transmitted diseases
- History of douching
- Recent antibiotic use
- CD4+ cell count
- HIV VL
- Medications

Physical Exam

- Complete genital inspection and bimanual pelvic examination
- Document characteristics and amount of discharge as well as presence of erythema, edema, and tenderness

Evaluation

- Saline wet mount
- 10% potassium hydroxide (KOH) preparation
- Vaginal pH determination
- Test for gonorrhea and chlamydia
- Perform fungal culture if indicated (signs/symptoms of yeast infection with negative findings on microscopy; chronic/recurrent yeast infections)

Differential Diagnosis

- Bacterial vaginosis (BV)
- Vulvovaginal candidiasis
- Trichomoniasis
- Gonorrhea
- Chlamydia
- Other causes of abnormal vaginal discharge

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Bacterial Vaginosis

BV is the most prevalent cause of vaginal discharge or malodor. It results from the replacement of normal *Lactobacillus*-dominant vaginal flora with mixed flora, including anaerobic bacteria, *Gardnerella vaginalis*, and *Mycoplasma hominis*. It is associated with increased rates of several obstetric and gynecologic complications, including pelvic inflammatory disease (PID), postabortion and posthysterectomy infections, and preterm labor. BV increases the risk of HIV-1 acquisition in women (*AIDS* 2008;22(12):1493; *J Infect Dis* 2005;192(8):1372) and increases HIV-1 shedding in the genital tract (*J Infect Dis* 2005;191(1):25).

Bacterial vaginosis in HIV infected patients: Data conflict on whether HIV infection is associated with increased BV prevalence compared with high-risk uninfected women (*Obstet Gynecol* 2001;98(4):656; *J Acquir Immune Defic Syndr* 2006;43:161). One study found both increased prevalence of BV and increased bacterial persistence in HIV infected women; increased persistence could result in higher prevalence, but not necessarily more frequent infections (*Obstet Gynecol* 2001;98(4):656). Prevalence, persistence, and severity all increase as CD4+ cell counts decrease (*Obstet Gynecol* 2001;98(4):656; *Clin Infect Dis* 1999;29:1145; *Sex Transm Dis* 1999;26:143). Use of ARVs has been associated with lower BV prevalence (*Infect Dis Obstet Gynecol* 2001;9:133).

Diagnosis: Standard diagnosis is made by clinical criteria and requires the presence of three of the following: 1) homogeneous grayish or yellowish discharge that may coat vaginal walls; 2) clue cells on microscopic examination; 3) vaginal pH >4.5; and/or 4) a positive whiff test (i.e., fishy odor of discharge before or after addition of 10% KOH).

Treatment: Treatment is indicated for women who have symptoms of BV. No current data suggest that screening and treatment of asymptomatic women reduces obstetric or gynecologic complications. A Pap smear report of "bacterial flora shift suggestive of BV" does not indicate treatment, but does indicate the need to question the patient about signs or symptoms.

Recommended regimens include the following (*MMWR Recomm Rep* 2010;59(RR-12):1):

- Metronidazole 500 mg po bid x 7 days (avoid alcohol during treatment and for 24 hours after completion), **or**
- Clindamycin cream 2%, 5 g intravaginally qhs x 7 days (oil based and may weaken latex condoms and diaphragms), **or**
- Metronidazole gel 0.75%, 5 g intravaginally qd x 5 days

Alternative regimens include the following (*MMWR Recomm Rep* 2010;59(RR-12):1):

- Tinidazole 2 g qd x 2 days, **or**
- Tinidazole 1 g qd x 5 days, **or**
- Clindamycin 300 mg po bid x 7 days, **or**
- Clindamycin ovules 100 g intravaginally qhs x 3 days

Vulvovaginal Candidiasis

Vulvovaginal candidiasis (VVC) is most commonly caused by infection with *Candida albicans*; however, the prevalence of infections due to non-*albicans* species is increasing. Up to 75% of all women will have at least one episode of candidiasis and 40%–45% will have two or more episodes; fewer than 5% of women experience recurrent episodes of candidiasis.

Typical symptoms are a thick, white discharge and pruritus; other symptoms include vulvar burning, vaginal soreness, dyspareunia, and external dysuria.

Vulvovaginal candidiasis in HIV infected patients: VVC is associated with increased HIV seroconversion in women who are not HIV infected and with increased genital tract HIV in HIV infected women (*Sex Transm Dis* 2008;35(11):946; *J Acquir Immune Defic Syndr* 2008;48(2):203).

Prevalence among HIV-infected women is 3%–15%; most studies suggest no significant difference in the prevalence of infection between relatively immunocompetent HIV infected women and uninfected controls. Analysis of longitudinal data from HERS indicated that VVC occurred with higher incidence and greater persistence, but not greater severity, among HIV infected women compared with uninfected women. A lower CD4+ cell count and higher VL were associated with VVC (*Clin Infect Dis* 1999;29:1145; *Obstet Gynecol* 2003;101:548). More-frequent use of antibiotics is a possible confounding factor for HIV infected women and pregnancy is a predisposing factor for candidiasis irrespective of HIV status.

Most studies show increased rates of vaginal, rectal, and oral colonization in HIV infected women, particularly with declining immune function (*J Acquir Immune Defic Syndr* 2006;43:161; *J Infect Dis* 2003;188:118; *Obstet Gynecol* 1997;90(2):252; *Obstet Gynecol* 2003;101:548). In HIV infected women, 26%–27% of vaginal isolates are non-*albicans* strains (*Clin Infect Dis* 1998;27:1161); although the most common strain is C. *glabrata*, data conflict on the proportion of non-*albicans* strains in HIV infected women compared with uninfected women. No association has been found between strain diversity and HIV progression.

Diagnosis: Diagnosis is made by identifying budding yeast or pseudohyphae on a wet mount, KOH preparation, or Gram stain of vaginal discharge. Positive identification can also be accomplished with culture. In general, wet mount and KOH are used as point-of-care tests if microscopy is available. Culture is usually reserved for cases of unclear diagnosis or for species identification in recurrent and/or persistent cases.

Treatment: Table 6-5 details recommended treatment regimens. In general, conventional antifungal therapies are less effective with non-*albicans* species; 10–14 days of therapy with a non-fluconazole azole drug is recommended as first-line therapy.

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Table 6-5	
Management of Vulvovaginal Candidiasis	
Agent	**Dosing and Notes**
Topical Azoles	
Butoconazole	• 2% cream* 5 g vaginally x 3 d • 2% single-dose bioadhesive 5 g: one vaginal application
Clotrimazole	• 1% cream* 5 g vaginally x 7–14 d • 2% cream* 5 g vaginally x 3 d
Miconazole	• 2% cream* 5 g vaginally x 7 d • 4% cream* 5 g vaginally x 3 d • 200 mg vaginal suppository* qd x 3 d • 100 mg vaginal suppository* qd x 7 d • 1200 mg vaginal suppository* (one application)
Tioconazole	• 6.5% ointment* 5 g vaginally (one application)
Terconazole	• 0.4% cream* 5 g vaginally x 7 d • 0.8% cream* 5 g vaginally x 3 d • 80 mg vaginal suppository qd x 3 d
Oral Agent	
Fluconazole	• 150 mg single dose po; avoid concomitant use with terfenadine, astemizole, and cisapride secondary to cardiotoxicity

Table 6-5	*continued*

Management of Vulvovaginal Candidiasis

Agent	Dosing and Notes
Other Agents	
Nystatin	• 100,000-unit vaginal tablet qd x 14 d; less effective than other treatments
Gentian violet	• 1% for vaginal application q7d x 4; messy; may be useful in chronic or recurrent cases; causes mucosal exfoliation; encourage abstinence during treatment; reinforce condom use
Boric acid	• 600 mg intravaginal capsules qd x 14 d; may be useful in chronic or recurrent cases; encourage abstinence during treatment; reinforce condom use

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

*Available over the counter

Source: *MMWR Recomm Rep* 2010;59(RR-12):1

Special treatment considerations for HIV infected women

• Topical therapies may be more effective when given for at least 7 days; fluconazole may be more effective when given in two sequential 150-mg doses 3 days apart (*Adv Stud Med* 2005;5:403)

• Consider prophylactic use of topical antifungals when antibiotics are given

• Long-term prophylactic therapy with fluconazole at a dose of 200 mg weekly has been found effective in reducing colonization with *C. albicans* and symptomatic vulvovaginal candidiasis in HIV infected women, but this regimen is not recommended for routine primary prophylaxis in HIV infected women (*Clin Infect Dis* 2001;33:1069; *MMWR Recomm Rep* 2010;59(RR-12):1). Consider in selected cases with recurrent vaginal candidiasis.

Azole resistance: There is some concern that extensive use of oral azoles may promote azole resistance and possibly limit the use of these agents for other HIV-related indications. Information about reduced azole susceptibility is limited but suggests that it is relatively uncommon with *C. albicans* isolates, with no evidence of a progressive reduction in susceptibility over time. Among non-*albicans* isolates, reduced susceptibility occurs frequently and is more common among HIV-seropositive women (*J Infect Dis* 2001;183(2):286; *Rev Iberoam Micol* 2004;21(4):177; *Ann Intern Med* 1997;126:689). No current data suggest that intermittent therapy with a single dose of fluconazole increases the development of azole resistance. Weekly prophylaxis with fluconazole has been associated with the infrequent development of resistance (*Ann Intern Med* 1997;126:689). Nevertheless, long-term treatment with fluconazole may select for more resistant and difficult-to-treat non-*albicans* species and should be used with caution.

Recurrent Candidiasis

Four or more symptomatic episodes of candidiasis per year are considered recurrent candidiasis. Evaluation includes identification and/or elimination (if possible) of predisposing factors that may include uncontrolled diabetes, corticosteroid use, topical or systemic antibiotics, spermicides (conflicting data), tight-fitting synthetic underwear, douching, pregnancy, and immunosuppression.

Diagnosis: Fungal culture may be needed if the diagnosis is unclear, symptoms are recurrent or persistent, and wet mount and/or KOH or Gram stain are negative. Speciation and/or susceptibility testing may be required.

Treatment: Management options include the following:

- Longer duration of standard treatment regimen (e.g., 7–14 days of topical therapy; fluconazole 100 mg, 150 mg, or 200 mg every third day for total of three doses)

- Chronic intermittent therapy (e.g., with perimenstrual episodes)

- Restriction of orogenital and/or anogenital sexual contact (anecdotal evidence only; double-blind, placebo-controlled trials of topical therapy for male sexual partners showed no benefit [*Sexually Transmitted Diseases*. 4th ed. New York: McGraw Hill; 2008])

- Possible role for boric acid vaginal capsules and gentian violet (*Gynecol Obstet Invest* 2010;70:306)

- Maintenance therapy, comprising an initial intensive regimen followed by one of the following maintenance regimens for at least 6 months: fluconazole 100, 150, or 200 mg po weekly (avoid concomitant use with terfenadine, astemizole, cisapride secondary to cardiotoxicity) *or* clotrimazole 500 mg vaginal suppository weekly

- Immune reconstitution: ART initiation has potential benefit if indicated (*J Infect Dis* 1999;180:448)

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Trichomoniasis

Trichomoniasis is caused by infection with *Trichomonas vaginalis*. Clinical features include profuse, malodorous, often frothy, yellow-green discharge and vulvar irritation, which may be accompanied by urinary symptoms or dyspareunia and signs of inflammation (i.e., vaginal erythema, "strawberry" vagina, cervix with punctate hemorrhages). In chronic cases, infection may be asymptomatic.

Trichomoniasis in HIV infected patients: In HIV infected women *T. vaginalis* infection increases genital HIV shedding and possibly sexual and perinatal transmission. Treatment of *T. vaginalis* has been shown to reduce HIV shedding (*J Infect Dis* 2003;187:375; *J Infect Dis* 2001;183:1017; *Sex Transm Dis* 2009;36:11; *J Perinatol* 2010;30(11):717). Trichomoniasis has also been associated with an increased risk of HIV acquisition (*J Infect Dis* 2008;197:548; *J Infect Dis* 2007;195:698).

In HIV infected women, trichomoniasis prevalence is 5%–23% and incidence is 10%–17% (*Am J Obstet Gynecol* 1999;180:824; *Am J Trop Med Hyg* 1998;58:495); however, studies have not shown increased prevalence, incidence, persistence, or recurrence in HIV infected women compared with either uninfected women or HIV infected women with lower CD4+ cell counts (*Clin Infect Dis* 2002;34:1406; *J Acquir Immune Defic Syndr* 2006;43(2):161).

Results of a study from South Africa indicated that trichomoniasis was associated with a significantly higher risk of PID, specifically in women with HIV (*Clin Infect Dis* 2002;34(4):519).

Diagnosis: Diagnosis is made with a variety of methods: saline wet mount (motile trichomonads seen in 50%–70% of culture-positive cases), Pap smear (60%–70% sensitivity; false positives not uncommon), culture (95% sensitivity), PCR, DNA probes, and monoclonal antibodies. Point-of-care testing with wet mount is the preferred method if microscopy is available. Other methods are useful in the absence of microscopy or with consistent symptoms and a negative wet mount result.

Treatment: Recommended regimens are outlined in Table 6-6. If sex partners are treated simultaneously, cure rates of >90% can be expected. Topical metronidazole has been found to be less effective than the oral preparation (*MMWR Recomm Rep* 2010;59(RR-12):1).

Table 6-6

Treatment of Trichomoniasis

Drug	Dosage	Comments
Metronidazole	500 mg po bid x 7 d	• More effective than single-dose metronidazole regimen in setting of HIV (*J Acquir Immune Defic Syndr* 2010;55:565) • Avoid alcohol during treatment and for 24 h after completion of therapy • Treat sex partners with same regimen; avoid intercourse until therapy is complete and patient and partner are asymptomatic
Metronidazole	2 g po (single dose)	• Avoid alcohol during treatment and for 24 h after completion of therapy • Treat sex partners with same regimen; avoid intercourse until therapy is complete and patient and partner are asymptomatic
Tinidazole	2 g po (single dose)	• No studies have evaluated tinidazole treatment in women co-infected with HIV and *T. vaginalis* • Avoid alcohol during treatment and for 72 h after completion of therapy • Treat sex partners with same regimen; avoid intercourse until therapy is complete and patient and partner are asymptomatic

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Source: *MMWR Recomm Rep* 2010;59(RR-12):1

Three months after completion of treatment, consider rescreening HIV infected women, regardless of symptoms, given the high proportion of recurrent or persistent infection and the association between HIV and *T. vaginalis* infection (*Sex Transm Dis* 2000;27:284; *Clin Infect Dis* 2008;46:994; *Ann Intern Med* 2006;145:564).

Resistance: Low-level metronidazole resistance has been identified in 2%–5% of cases of vaginal trichomoniasis (*Antimicrob Agents Chemother* 2006;50:4209), but high-level resistance occurs only rarely. Organisms with decreased susceptibility usually respond to tinidazole or to higher doses of metronidazole. If treatment failure occurs with either regimen, re-treat with metronidazole 500 mg po twice a day for 7 days. If treatment failure occurs repeatedly, treat with metronidazole or tinidazole 2 g po once a day for 5 days. Patients with documented infection (with re-infection excluded) who have not responded to these measures should be managed in consultation with an expert.

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Gonorrhea

Gonorrhea is caused by infection with *Neisseria gonorrhoeae*. Infection is commonly asymptomatic but vaginal discharge may be present. If untreated, 10%–20% of infected women develop PID. The urethra is the primary site of colonization after hysterectomy. Gonorrhea may also cause rectal infection, pharyngitis, and (rarely) disseminated infection.

Gonorrhea in HIV infected patients: There are no differences in prevalence, clinical presentation, diagnosis, or treatment between HIV infected and uninfected patients.

Diagnosis: Diagnosis is made by nucleic acid amplification tests (NAATs) of endocervical, vaginal, or urine specimens; by nucleic acid hybridization tests of endocervical or urethral (after hysterectomy) specimens; or through culture of the endocervix or urethra (after hysterectomy). The sensitivity of NAATs for the detection of *N. gonorrhoeae* in genital and nongenital anatomic sites is superior to culture but varies by NAAT type. The NAAT may detect gonorrhea and chlamydia simultaneously. Because nonculture tests cannot provide antimicrobial susceptibility results, in cases of suspected or documented treatment failure, clinicians should perform both culture and antimicrobial susceptibility testing (*MMWR Recomm Rep* 2010;59(RR-12):1).

Treatment: *N. gonorrhoeae* has the ability to develop antibiotic resistance, which makes it a moving target for treatment. In the United States, as of April 2007, quinolones are no longer recommended for the treatment of gonorrhea and associated conditions; cephalosporins are the only antimicrobial class currently recommended and available (*MMWR Recomm Rep* 2010;59(RR-12):1). In the United States, minimum inhibitory concentrations of *N. gonorrhoeae* to cephalosporins have been increasing—particularly for cefixime—though no resistant cases have been seen yet. The CDC is now recommending treatment of gonorrhea with single-dose ceftriaxone 250 mg IM and the *preferential* co-treatment of chlamydia with single-dose azithromycin 1 g po, instead of 1 week of doxycycline, because azithromycin

offers coverage of both gonorrhea and chlamydia (*MMWR Morb Mortal Wkly Rep* 2011;60(26):873). The CDC's website (http://www.cdc.gov/std/gisp) and state health departments can provide the most current information on gonorrhea treatment.

For uncomplicated gonococcal infections of the cervix, urethra, and rectum, the following regimens are recommended (*MMWR Recomm Rep* 2010;59(RR-12):1), with rescreening 3 months after treatment:

- Single-dose ceftriaxone 250 mg IM; **or**, if not an option,
- Single-dose cefixime 400 mg po (less effective for pharyngeal infection); **or**
- Single-dose injectable cephalosporin regimen **plus**, for presumptive chlamydia treatment, single-dose azithromycin 1 g po (preferred) **or**, if azithromycin is not an option, doxycycline 100 mg po bid for 7 days; **or**
- Alternative single-dose injectable cephalosporin regimens: ceftizoxime 500 mg IM, cefoxitin 2 g IM with probenecid 1 g po, and cefotaxime 500 mg IM (efficacy for pharyngeal infection is less certain)

It is recommended that women be treated for chlamydia presumptively, particularly in areas with high rates of co-infection, or where there is no chlamydia testing, and/or when a patient may not return for test results. Avoid the use of doxycycline or quinolones in pregnancy.

Treatment of sex partners: Sex partners should be treated for both gonorrhea and chlamydia if their last sexual contact with the patient was within 60 days before the diagnosis or onset of symptoms. If a patient's most recent sexual contact occurred more than 60 days before the onset of symptoms, her most recent partner should be treated. Intercourse should be avoided until treatment is completed and symptoms have resolved.

Culture and susceptibility testing are recommended after apparent treatment failure with the standard regimen; persistent positive test results with or without persistent symptoms indicate treatment failure.

Chlamydia

Chlamydia is caused by infection with *Chlamydia trachomatis.* Asymptomatic infection is common, but clinical presentation may include abnormal discharge and/or symptoms of urethritis. If untreated, 10%–40% of infected women develop PID.

Chlamydia in HIV infected patients: There are no differences in prevalence, clinical presentation, diagnosis, or treatment between HIV infected and uninfected women.

Diagnosis: NAATs, cell culture, direct immunofluorescence, EIA, and nucleic acid hybridization tests are available for the detection of C. *trachomatis* on endocervical specimens. NAATs have the highest sensitivity and can also be used with urine. Some NAATs are cleared for use with vaginal swab specimens, which can be collected by the provider or self-collected by the patient. Self-collected vaginal swab specimens perform well compared with

other approved specimens using NAATs (*Sex Transm Dis* 2005;32:725; *Int J STD AIDS* 2008;19:507) and are well accepted by women. NAATs may also be used to detect C. *trachomatis* at rectal and oropharyngeal sites and have demonstrated improved sensitivity and specificity compared with culture at these sites (*Sex Transm Dis* 2008;35:637; *J Clin Microbiol* 2010;48:1827; *J Clin Microbiol* 2009;47:902).

Treatment: Recommended regimens include the following (*MMWR Recomm Rep* 2010;59(RR-12):1), with rescreening 3 months after completion of treatment:

- Single-dose azithromycin 1 g po, *or*
- Doxycycline 100 mg po bid x 7 days (avoid in pregnancy)

Alternative regimens include the following:

- Erythromycin base 500 mg po 4x/day x 7 days, *or*
- Erythromycin ethylsuccinate 800 mg po 4x/day x 7 days, *or*
- Ofloxacin 300 mg po bid x 7 days (avoid in pregnancy), *or*
- Levofloxacin 500 mg po x 7 days (avoid in pregnancy)

Recommendations for the management of chlamydia in sex partners are the same as for gonorrhea (see above).

Other Causes of Abnormal Vaginal Discharge

Abnormal vaginal discharge may have several other potential causes.

Atrophic vaginitis: This condition, which is related to estrogen deficiency, is characterized by irritative symptoms, vaginal dryness, and dyspareunia. The vaginal epithelium appears thin and a watery discharge may be present. Treat with either topical or oral estrogen.

Foreign body: If suspected, a careful speculum exam should be performed to identify retained tampons, toilet paper, etc.

Local irritants: Remove possible offending agents, including spermicides, vaginal medications, toilet-paper dye, hygiene sprays, soap, detergent, douches, etc.

Pelvic and/or Lower Abdominal Pain

Abdominopelvic pain can be classified as acute, chronic, or cyclic. Acute pain is typically sudden in onset and short in duration, whereas chronic pain is of at least 6 months' duration. Cyclic pain is associated with the menstrual cycle.

History, Physical Exam, Evaluation, and Differential Diagnosis

History

- Characteristics of pain:
  - onset rapid or gradual
  - character crampy, colicky, sharp, or dull
  - location generalized or localized
  - duration
  - severity
  - radiation of pain
  - constant or intermittent

- Associated symptoms:
  - abnormal vaginal bleeding or discharge
  - gastrointestinal symptoms (e.g., nausea/vomiting, anorexia, constipation, diarrhea)
  - urinary symptoms (e.g., dysuria, frequency, urgency, hematuria)
  - fever or chills

- History of other medical conditions
- Surgical history
- Gynecologic history:
  - date of last menstrual period
  - use of contraception and condoms
  - history of sexually transmitted infections (STIs)

- Medications
- CD4+ cell counts
- HIV VL

Physical Exam

- Obtain complete set of vital signs
- Focus on abdominal and pelvic findings
- Abdominal exam should evaluate
  - presence and character of bowel sounds
  - presence of distention
  - suprapubic or costovertebral angle tenderness
  - other abdominal tenderness, including location, presence of rebound, and guarding
  - presence of mass or organomegaly
- Pelvic exam should determine
  - presence of abnormal bleeding or discharge
  - reproducibility and location of tenderness (e.g., uterine, adnexal, or cervical motion tenderness)
- Presence of a palpable abdominal or pelvic mass

Evaluation

- Pregnancy test
- Laboratory tests
  - CBC with differential
  - sedimentation rate or C-reactive protein
  - chemistry panel
  - others as indicated

- Wet mount and/or STI testing
- Urinalysis and urine culture
- Stool studies (cultures, evaluation for ova and parasites, *Clostridium difficile* toxin assay), if indicated by gastrointestinal (GI) symptomatology
- Pelvic ultrasound, computed tomography (CT) scans, if indicated
- Blood cultures for bacteria and/or *Mycobacterium avium*, if indicated

Differential Diagnosis

Differential diagnosis includes but is not limited to
- Pregnancy
- PID
- Ruptured/hemorrhagic ovarian cyst
- Ovarian torsion
- Uterine leiomyomas (fibroids)
- Endometriosis
- Dysmenorrhea
- Mittelschmerz
- Gastrointestinal pathology
- Urinary tract pathology
- Medication-related pathology

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Pregnancy (see Chapter 8)

Refer as indicated. With pain and a positive pregnancy test with or without bleeding, suspect ectopic pregnancy; urgent evaluation is indicated.

Pelvic Inflammatory Disease

PID is an upper-genital-tract infection, usually polymicrobial in nature. Sexually transmitted organisms, including *N. gonorrhea* and *C. trachomatis*, are implicated in most cases of PID; BV-associated organisms are also commonly present. CMV, *M. hominis*, *Ureaplasma urealyticum*, and *M. genitalium* may be associated with some cases of PID (*Sex Transm Infect* 2005;81:463; *Sex Transm Infect* 2007;83:319; *Clin Infect Dis* 2009;48:417). Symptoms may be virtually absent or mild and nonspecific (e.g., abnormal bleeding, dyspareunia, vaginal discharge; less commonly, right-upper-quadrant pleuritic pain secondary to perihepatitis).

PID in HIV infected patients: Several studies have found an increased seroprevalence of HIV in patients hospitalized with PID (*Am J Obstet Gynecol* 1990;163:1135; *J Reprod Med* 1991;36:122). An analysis of hysterectomy specimens from HIV infected and uninfected women, matched for surgical indication, found chronic endometritis twice as commonly in the specimens from HIV infected women as in those from uninfected women; some degree of abnormal uterine bleeding had occurred in all cases (*Infect Dis Obstet Gynecol* 1998;6:186). The clinical presentation of PID in HIV infected women may be more severe or otherwise altered (e.g., lower white blood cell counts) (*Obstet Gynecol* 1997;89:65; *J Infect Dis* 1998;178:1352; *Am J Obstet Gynecol* 1995;172:919; *Obstet Gynecol* 2000;95:525). In studies from Africa, more-

severe illness, including tubo-ovarian abscess, and longer hospital stays were found in women with significant immunosuppression (*Am J Obstet Gynecol* 1995;172:919; *J Infect Dis* 1998;178:1352).

HIV infected and uninfected women respond equally well to standard parenteral and oral antibiotic regimens (*Obstet Gynecol* 2006;107:807; *Am J Obstet Gynecol* 1999;181:1374). The microbiology of infection and the response to standard antibiotic regimens are similar in HIV infected and uninfected women, although one study found that mycoplasmas and streptococci were more likely to be isolated from HIV infected women (*Obstet Gynecol* 2000;95:525). Some studies have reported a greater need for surgical intervention in HIV infected women (*Obstet Gynecol* 1993;82:765).

CMV, cryptococcosis, and tuberculosis may cause upper-genital-tract infection in rare cases and should be considered in appropriate clinical situations (*Infect Dis Obstet Gynecol* 2009;2009:745060; *Int J Gynecol Pathol* 2008;27(1):37).

Diagnosis: The current minimum CDC-recommended criteria for diagnosis of PID are cervical motion tenderness **or** uterine tenderness **or** adnexal tenderness (*MMWR Recomm Rep* 2010;59(RR-12):1). Because PID is difficult to diagnose and has the potential to cause long-term complications, empiric therapy should be initiated if these criteria are present and no other cause for symptoms is identified.

Criteria that enhance diagnostic specificity include
- oral temperature >101°F (>38.3°C),
- abnormal mucopurulent cervical or vaginal discharge,
- elevated erythrocyte sedimentation rate,
- elevated C-reactive protein,
- documented cervical gonorrhea or chlamydia infection, and
- elevated white blood cells on saline wet mount of vaginal secretions.

In patients who are severely ill and/or when diagnosis is uncertain, the most specific criteria for diagnosis of PID are
- endometritis on endometrial biopsy;
- tubo-ovarian complex, **or** thickened, fluid-filled tubes on transvaginal ultrasound or magnetic resonance imaging (MRI), **or** Doppler studies suggesting pelvic infection (e.g., tubal hyperemia); and
- laparoscopic abnormalities consistent with PID.

Treatment: The decision to treat with oral vs. parenteral antibiotics (Table 6-7) should be individualized, as should the decision to hospitalize an HIV infected patient with PID for treatment. Indications for hospitalization include
- inadequate response to outpatient therapy;
- uncertain diagnosis (surgical emergency cannot be excluded);
- pregnancy;
- inability to tolerate or follow outpatient regimen;

- tubo-ovarian abscess or other evidence of severe illness, nausea and vomiting, or high fever; and
- consider with immunosuppression or other significant comorbidity: low CD4+ cell count, clinical AIDS, on immunosuppressive drugs.

Table 6-7

Parenteral Regimens for Treatment of Pelvic Inflammatory Disease

Regimen A	Cefotetan 2 g IV q 12 h + doxycycline 100 mg po or IV q 12 h **or** Cefoxitin 2 g IV q 6 h + doxycycline 100 mg po or IV q 12 h	• Parenteral therapy may be discontinued 24 h after evidence of clinical improvement • Oral therapy with doxycycline 100 mg bid should continue through completion of 14 days of therapy • When tubo-ovarian abscess is present, clindamycin 450 mg orally 4x/d **or** metronidazole 500 mg bid + doxycycline can be used for continued therapy rather than doxycycline alone; this regimen provides more effective anaerobic coverage
Regimen B	Clindamycin 900 mg IV q 8 h + gentamicin loading dose IV or IM (2 mg/kg of body weight), followed by maintenance dose (1.5 mg/kg) q 8 h (Single daily dosing of gentamicin 3–5 mg/kg may be substituted)	• Parenteral therapy may be discontinued 24 h after evidence of clinical improvement • Oral therapy with doxycycline 100 mg bid or clindamycin 450 mg po 4x/d should continue through completion of a total of 14 d of therapy • When tubo-ovarian abscess is present, clindamycin should be continued, rather than doxycycline, to provide more effective anaerobic coverage

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Source: *MMWR Recomm Rep* 2010;59(RR-12):1; see same for alternative oral and parenteral regimens

Oral Regimens

- Ceftriaxone 250 mg IM in a single dose + doxycycline 100 mg po bid x 14 days +/- metronidazole 500 mg po bid x 14 days, **or**

- Cefoxitin 2 g IM in a single dose + probenecid 1 g po administered concurrently in a single dose + doxycycline 100 mg po bid x 14 days +/- metronidazole 500 mg po bid x 14 days, **or**

- Other parenteral third-generation cephalosporin (e.g., ceftizoxime or cefotaxime) + doxycycline 100 mg po bid x 14 days +/- metronidazole 500 mg po bid x 14 days

Sexual partners of women diagnosed with PID should be evaluated and treated presumptively for gonorrhea and chlamydia if the couple have had sexual contact within the 60 days preceding the onset of symptoms.

Other Causes of Pelvic and/or Lower Abdominal Pain

Ruptured/hemorrhagic ovarian cyst: A ruptured cyst can cause acute pelvic/abdominal pain. Bleeding associated with rupture is usually self-limited but may require surgical intervention.

Ovarian torsion: Torsion can cause acute, severe, unilateral lower-abdominal/pelvic pain, often with a history of previous similar episodes. A palpable adnexal mass is often present. Surgical intervention is required.

Uterine leiomyomas (fibroids): Fibroids may cause pain with rapid enlargement, degeneration, or torsion. Referral to a gynecologic specialist is indicated for management.

Endometriosis: This condition can cause acute or chronic pain and usually includes secondary dysmenorrhea and/or dyspareunia. Referral to a gynecologic specialist is indicated if endometriosis is suspected.

Dysmenorrhea: This cyclic pain with menses affects about 50% of all menstruating women. Primary dysmenorrhea is menstrual pain in the absence of pelvic pathology; secondary dysmenorrhea is associated with underlying pathology, such as endometriosis. Treatment of primary dysmenorrhea consists of nonsteroidal anti-inflammatory drugs (NSAIDs), which are 80% effective, or oral contraceptive pills, which are 90% effective. Treatment of secondary dysmenorrhea is directed at the specific underlying problem.

Mittelschmerz: This pain with ovulation is generally self-limited and is managed with NSAIDs.

Gastrointestinal pathology: Opportunistic infections, including cryptosporidia, CMV, and *M. avium* may cause chronic diarrhea in patients with AIDS; clinical features usually include abdominal pain. Other types of GI pathology include

- appendicitis;
- diverticulitis, with pain generally localized to the left lower quadrant (usually seen at older ages);
- irritable bowel syndrome, in which pain is usually intermittent, cramp-like, more common in the left lower quadrant, and exacerbated by certain foods;
- inflammatory bowel disease;
- infectious enterocolitis, with pain, cramping, and diarrhea; and
- obstruction, with colicky pain, distention, vomiting, and obstipation.

Urinary tract pathology: Pathology of the urinary tract may include renal and/or ureteral stones, cystitis, and pyelonephritis. Urinalysis and urine culture should identify the presence of infection, which should be treated on the basis of microbial sensitivities. Renal or ureteral stones are generally associated with severe, often colicky pain and hematuria; ultrasound or other imaging of the urinary tract may show partial obstruction. The patient generally needs IV fluids, pain control, and possibly lithotripsy. Referral to a urologic specialist is indicated.

Medication-related pathology: Indinavir may cause renal stones; didanosine may cause pancreatitis.

Pelvic Mass

A pelvic mass may be detected by the patient or may be felt on abdominal or pelvic exam. Symptoms vary; a mass often may occur without any symptoms.

History, Physical Exam, Evaluation, and Differential Diagnosis

History

- Presence and duration of associated symptoms
- Pain
- Abnormal vaginal bleeding or discharge
- Urinary symptoms (e.g., frequency, urinary retention)
- Gastrointestinal symptoms (e.g., nausea, vomiting, constipation, diarrhea, bloating)
- Constitutional symptoms (e.g., fever, chills, sweats, weight loss or gain)

Physical Exam

- Vital signs
- Constitutional signs
- Complete abdominal and pelvic examination, with particular attention given to
  - Size, location, mobility, and characteristics of the mass if palpable
    ° With functional ovarian cysts, a normal ovary may be up to 5 cm–6 cm in size for a woman in the reproductive age range
    ° A palpable ovary in a postmenopausal woman may be abnormal and requires further evaluation
- Signs of ascites
- Lymph node survey

Evaluation

- Pregnancy test if premenopausal
- Laboratory tests
  - CBC with differential
  - chemistry panel
  - tumor markers if indicated (e.g., carcino-embryonic antigen, Ca-125; tests for these markers produce frequent false positives and false negatives and should be used only in conjunction with other diagnostic procedures)
- Radiologic studies as indicated
  - pelvic ultrasound (transabdominal and/or transvaginal): generally the first diagnostic modality employed in evaluating pelvic anatomy; concerning characteristics include a complex or solid mass and the presence of ascites
  - CT and/or MRI: if indicated; CT and/or MRI are better than ultrasound at imaging the GI tract, retroperitoneal lymphadenopathy, and liver
- Additional evaluation (e.g., laparoscopy, colonoscopy): refer to appropriate specialists

Differential Diagnosis

- **Ectopic pregnancy:** primary consideration in the setting of an adnexal mass and a positive pregnancy test; urgent evaluation is indicated
- **Ovarian functional cysts:** most-common ovarian masses found among women of reproductive age; usually less than 5 cm–6 cm in size; resolution occurs spontaneously in 1–3 months
- **Uterine leiomyomas (fibroids):** often asymptomatic, but may be associated with heavy and/or prolonged menses, urinary frequency, or sensation of pelvic pressure
- **Endometrioma:** consider in women with a documented or suspected history of endometriosis
- **Hydrosalpinx/pyosalpinx and tubo-ovarian abscess:** consider in women with a history and exam suggestive of PID; initial management is with broad-spectrum antibiotics, even if the patient is asymptomatic
- **Benign or malignant ovarian neoplasm:** surgical intervention required
  - no evidence of increased prevalence in HIV infected women, although anecdotal reports suggest ovarian cancer may present at a more advanced stage, with a poorer response to cytoreductive surgery and chemotherapy (*Obstet Gynecol Surv* 1996;51:679)
  - non-Hodgkin's lymphoma of the ovary in an HIV infected woman has been described (*Obstet Gynecol* 1996;88:706)
- **Retroperitoneal lymphadenopathy:** may present as a pelvic mass; possible causes include tuberculosis, lymphoma
- **Gastrointestinal masses:** includes diverticular abscess and bowel malignancy

Note: In general, the presence of a pelvic or abdominal mass requires expert consultation and referral to an appropriate specialist.

Urinary Symptoms

Urinary symptoms are common complaints in both HIV infected and uninfected women. Causes of symptoms include both lower and upper urinary tract disease.

History, Physical Exam, Evaluation, and Differential Diagnosis and Management

History

- Duration and severity of urinary symptoms:
  - dysuria
  - pain with urination
  - frequency
  - urgency
  - hematuria
  - nocturia
  - incontinence
- Associated symptoms:
  - pain, suprapubic or flank
  - fever
  - chills
  - weight loss
- Other medical conditions (e.g., diabetes, sickle-cell disease)

- Surgical history
- Medications (increased risk of renal toxicity with TDF, IDV, ATV)
- CD4+ cell count and VL

Physical Exam

- Vital signs
- Abdominal exam: document presence of suprapubic, flank, or costovertebral angle tenderness
- Pelvic exam: document presence of vulvar sores/ulcers, vaginal atrophic changes or discharge, palpable pelvic mass or tenderness

Evaluation

- Microscopic exam of urine (midstream, clean-catch urinalysis) or catheterized specimen (contamination from vaginal discharge or bleeding may occur if a simple voided specimen is collected)
- Urine culture and sensitivity
- Gonorrhea and chlamydia testing, if indicated
- Urine cytology: consider in women aged >50 y who present with irritative symptoms or hematuria and negative culture
- Urine for acid-fast bacillus (AFB) culture; purified protein derivative (PPD) or interferon gamma release assay, if urinary TB is suspected
- Urinary tract imaging (if indicated; consider if stones, urinary tract anomalies, or urinary TB is suspected)
  - CT
  - ultrasound
  - intravenous pyelogram
- Other tests: cystoscopy, urodynamics—refer to appropriate specialist

Differential Diagnosis and Management

- **Bacterial urinary tract infection:** lower tract (cystitis) or upper tract (pyelonephritis); may be asymptomatic; clinical signs and symptoms cannot reliably distinguish between upper- and lower-tract infection
  - **Cystitis** is classically characterized by the presence of dull, suprapubic pain. Typical associated symptoms include dysuria, urinary frequency and urgency, and occasionally hematuria.
    ° *Vulvar dysuria* is the sensation of burning when urine flows over the vulva and can be misdiagnosed as a urinary tract infection; it is often caused by active herpetic or other vulvar lesions
  - **Pyelonephritis** is associated with flank or costovertebral pain and tenderness to percussion. Typical systemic signs and symptoms include fever, chills, nausea, vomiting, and tachycardia. Treat with appropriate antibiotics; severe pyelonephritis requires hospitalization for IV antibiotics and hydration.
- **Urethral syndrome:** dysuria, frequency with negative urine culture
  - Rule out urethritis due to gonorrheal or chlamydial infection
- **Renal and/or ureteral stones:** characterized by severe, colicky pain
  - Stones are usually associated with urinary stasis or chronic infection, although they may be related to metabolic abnormalities such as gout or to problems with calcium homeostasis
  - Atazanavir and indinavir therapy increase the risk for stones
  - IV hydration and pain control are often required; surgical intervention is sometimes needed
- **Interstitial cystitis:** symptoms include severe urinary frequency and urgency (urinating as often as every 15 minutes daytime and nighttime) as well as suprapubic or perineal discomfort before, during, and after urination
  - Refer to a urologic specialist for definitive evaluation

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- **Urinary tuberculosis:** one of the most common sites of extrapulmonary TB
  - Consider with gross or microscopic hematuria and pyuria with negative bacterial culture; manage with expert consultation
- **Tumors:** most common presenting complaint is gross or microscopic hematuria; hematuria without identifiable etiology (e.g., infection) requires referral to a urologist
- **Urinary incontinence:** can be caused by many factors, including anatomic displacements related to aging and childbearing; bladder muscle (detrusor) instability; neurologic disease; infection; fistulas secondary to surgical injury, radiation, or cancer; and some medications
  - Review medication list
  - Rule out infection with culture and "overflow" incontinence secondary to an overdistended bladder with postvoid catheterization for residual urine determination
  - Further evaluation requires referral to a urogynecologist or urologist
  - Management depends on etiology and is beyond the scope of this manual; expert consultation is recommended
- **Urinary retention:** may be caused by obstruction, neurologic disorders, or certain medications (e.g., antihistamines, antidepressants, antipsychotics, opiates, antispasmodics, terbutaline, over-the-counter cold remedies)
- **HIV-associated nephropathy:** presents with nephrotic syndrome and progressive renal failure; may have symptoms of increased urination, excessive thirst, and fatigue
  - If untreated, may lead to end-stage renal disease
  - Risk is increased in African Americans and injection drug users
  - Usually occurs with advanced disease and, generally, CD4+ cell count <200 cells/mm^3

Genital Warts

Genital warts are a common manifestation of HPV infection. HPV types 6 and 11 are usually the cause of visible genital warts. Oncogenic types (i.e., 16, 18, 31, 33, and 35) are occasionally found in visible warts and have been associated with squamous intraepithelial neoplasia of the external genitalia (see **Abnormal Pap Smear**, p. 160).

HIV infected women are more likely to have HPV co-infection, and both the prevalence and incidence of genital warts are greater in infected than uninfected women. Increased immunosuppression is associated with an increased prevalence and incidence of warts, larger or more numerous warts, poorer response to therapy for genital warts, and more frequent recurrences after treatment (*Sex Transm Dis* 2002;29:427; *Sex Transm Dis* 2002;29:121; *Lancet* 2002;359(9301):108; *AIDS* 2008;22:1213). ART and immune reconstitution have been associated with a decreased incidence of warts after treatment (*Am J Obstet Gynecol* 2004;190:1241). Squamous cell carcinomas that arise in or resemble genital warts may occur more commonly in the setting of immunosuppression, making confirmation of the diagnosis with biopsy more often necessary.

History, Physical Exam, and Evaluation

History

- Location of warts
- Duration
- Presence of associated symptoms (e.g., itching, irritation, pain, bleeding)
- History of prior occurrences of similar lesions and their treatment
- History of abnormal Pap smear results

Physical Exam

- Perform a complete examination of the external genitalia, vagina, cervix, and perianal region. Increasingly, HPV disease is found in the oral cavity, which should be examined as well.
- Document the location, size, and characteristics of warts
  - Genital warts can present as cauliflower-shaped growths (condyloma acuminata); smooth, dome-shaped, skin-colored papules; keratotic warts with a thick horny layer; or flat or slightly raised flat-topped papules

Evaluation

- **Biopsy:** Biopsy of the lesion and histopathologic confirmation of the diagnosis are always indicated in the following situations:
  - Diagnosis is uncertain
  - Warts do not respond to therapy
  - Lesions worsen during therapy
  - Warts are pigmented, indurated, fixed, or ulcerated
- Typical condyloma acuminata are diagnosed by inspection and do not require biopsy, although current CDC guidelines suggest biopsy when the patient is immunocompromised
- **Colposcopy:** Colposcopy and directed biopsies of the entire lower genital tract should be considered in HIV infected women with evidence of HPV infection
  - Perform colposcopy and biopsy to rule out the presence of HSIL before initiating treatment of cervical warts

Treatment: The primary goal of treatment is the removal of symptomatic lesions. When left untreated, visible warts may resolve spontaneously, may remain unchanged, or may increase in number or size. There is no evidence that currently available therapies eradicate HPV, affect the natural history of infection, or affect the subsequent development of cervical cancer. Infectivity may or may not be decreased by the removal of visible warts.

The choice of treatment modality depends on the number, size, and location of warts. When the lesions are few in number and fairly small in size, a topical agent may be employed. Table 6-8 presents provider-applied and patient-administered regimens recommended by the CDC (*MMWR Recomm Rep* 2010;59(RR-12):1). Intralesional interferon is an alternative to the therapies listed below, but it is expensive and associated with a high frequency of systemic side effects. Efficacy data are limited for the two other alternatives, photodynamic therapy and topical cidofovir.

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Most treatment modalities are associated with mild to moderate discomfort and local irritation. Persistent hypo- or hyperpigmentation is common after ablative therapies and can occur with imiquimod. Rarely, scarring or chronic pain can occur at the treatment site. Warts located on moist surfaces respond best to topical treatment.

Most genital warts respond within 3 months of therapy. The treatment method should be changed if a patient has not improved substantially after a complete course of treatment or if side effects are severe. Data are limited on combining modalities, which does not necessarily increase efficacy but may increase complications.

Recurrence rates are significant with all modalities; frequent follow-up will allow retreatment when new warts are small and few in number. When the number of warts is large or the lesions are very extensive, consider referral for possible laser or excisional surgery.

Table 6-8

Recommended Management of Genital Warts

Provider-applied	Patient-applied
TCA or BCA: • Weekly application if necessary • Remove excess acid with talc powder, baking soda, or liquid soap	**Podofilox 0.5% solution or gel:** • Apply bid x 3 d, then 4 d of no therapy • May repeat application for up to four cycles • Should be limited to 0.5 mL/d and <10 cm² area of warts • Avoid during pregnancy
Cryotherapy with liquid nitrogen or cryoprobe: • Repeat every 1–2 wk	**Imiquimod 5% cream:** • Apply 3x/wk for up to 16 wk • Treated area should be washed with mild soap and water 6–10 h after application • Avoid during pregnancy
Podophyllin resin 10%–25%: • Weekly application if necessary • Limit application to <0.5 mL of podophyllin or <10 cm² of warts per session • Preparation should be thoroughly washed off 1–4 h after application to reduce local irritation • Avoid use on mucosal surfaces or with any open wounds or lesions because of concern about potential systemic absorption and toxicity • Avoid during pregnancy	**Sinecatechins 15% ointment:** • Apply tid (0.5 cm strand of ointment to each wart) • Do not continue past 16 wk • Do not wash off after use • Avoid sexual contact while ointment is on skin • Not currently recommended for HIV infected women because of lack of safety/efficacy data in HIV setting • Avoid during pregnancy
Surgical removal: Laser or excision	

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Source: *MMWR Recomm Rep* 2010;59(RR-12):1

Genital Masses and/or Nodules

Genital masses or nodules are relatively common complaints among women in general and may be associated with pain or discomfort or with no symptoms at all. All genital masses or nodules, however, require careful evaluation for appropriate diagnosis and management.

History, Physical Exam, Evaluation, and Differential Diagnosis and Management

History

- Duration
- Changes in size or appearance
- Associated symptoms (e.g., pain, tenderness, itching, edema)
- History of similar nodules and their treatment
- Sexual history, including the presence of similar lesions on partner's genitals
- Medications
- CD4+ cell count and VL

Physical Exam

- Document anatomic location, number, and size of nodules
- Presence of associated edema, erythema, induration, fluctuance, tenderness, discharge, or bleeding

Evaluation

- Biopsy indicated if etiology is unclear
- Culture abscess contents

Differential Diagnosis and Management (*JAMA* 2003;290:1001)

- Bartholin's abscess or cyst
- Genital warts (see p. 198)
- *Molluscum contagiosum*
- Subepithelial cysts, folliculitis
- Tumors, other masses

Bartholin's Abscess or Cyst

Bartholin's glands are normally nonpalpable and located deep in the perineum at the 5 o'clock and 7 o'clock positions in the entrance to the vagina. Obstruction of a Bartholin's duct by nonspecific inflammation, infection (e.g., gonorrhea or chlamydia), or trauma can lead to the formation of an exquisitely tender abscess. Treatment consists of incision and drainage. Often a residual Bartholin cyst is present after the resolution of infection. This does not require treatment unless it becomes repeatedly infected, is growing, or is otherwise symptomatic. The differential diagnosis of a new-onset mass in the Bartholin's region in women aged >40 years must include malignancy.

Molluscum contagiosum

Molluscum contagiosum is an asymptomatic viral disease that primarily affects the skin of the vulva, although in immunosuppressed patients it can present as a generalized skin disease. It is spread through sexual and nonsexual close contact. Clinical presentation is small nodules or domed papules, usually 1 mm–5 mm in diameter; more mature nodules appear to have an umbilicated center. This disease tends to be self-limited; however, the disease course may be complicated by repeat infection and autoinoculation of the virus.

***Molluscum contagiosum* in HIV infected patients:** This disease affects 5%–10% of HIV infected patients. Extensive, severe lesions that respond poorly to therapy are common, particularly with more advanced immunosuppression. Unresponsive lesions have been found to regress with ART (*Indian J Dermatol* 2009;54(2):180; *Eur J Dermatol* 1999;9:211), but they have also been reported as a manifestation of immune reconstitution syndrome (*Dermatol Online J* 2007;13(2):6).

Treatment: Treatment consists of serial applications of liquid nitrogen or removal of nodules with a dermal curet and chemical cauterization of the base with 85% trichloroacetic acid or ferric subsulfate. Successful eradication with systemic interferon has been reported in an immunocompromised patient (*Dermatology* 2008;217(3):196).

Cysts and Folliculitis

Several benign processes in the genital area may present as a mass or nodule and are self-limited, requiring no or limited specific treatment. These are generally small and minimally symptomatic and can usually be diagnosed on the basis of typical appearance.

Tumors and Other Masses

A biopsy is required for suspected tumors and other masses; expert consultation is indicated.

Genital Itching and/or Irritation

Genital itching and irritation are among the most common gynecologic complaints in both HIV infected and uninfected women.

History, Physical Exam, Evaluation, and Differential Diagnosis and Management

History

- Duration, location, and severity of pruritus/irritation
- Associated symptoms (e.g., erythema, edema, vulvar burning, dysuria, dyspareunia, vaginal discharge)
- Prior episodes of similar symptoms and treatment
- Exposure to particular agents coincident with onset of symptoms (see **Allergic and/or Irritative Reaction**, p. 204)
- Presence of similar symptoms or a recent diagnosis of genital tract infection in close contacts
- Medications, including antibiotics
- CD4+ cell count
- HIV VL

Physical Exam

- Physical appearance and distribution of any lesions on irritated area (e.g., diffuse rash, papular or vesicular lesions, skin burrows)
- Associated findings, including erythema, edema, tenderness, or vaginal discharge
- More thorough inspection of the skin over the whole body may be indicated if a more generalized process is suspected (e.g., scabies, allergic reaction to detergent)

Evaluation

- Fungal culture and/or KOH preparation is indicated if fungal infection is suspected
- HSV culture: herpes may appear atypically and should be ruled out in the presence of vesicular lesions, unexplained abrasions, fissuring, or if warranted by history
- Other cultures/saline wet mount, if indicated by exam findings
- Skin scrapings: the skin papule is scraped with a needle and the crust is placed under a drop of mineral oil on a slide; eggs, parasites, or fecal pellets microscopically visualized by this technique are diagnostic of scabies or pubic lice. A biopsy should be considered if other diagnostic tests are negative or with lack of response to treatment.

Differential Diagnosis and Management (*JAMA* 2003;290:1001)

- Fungal infection
- Allergic and/or irritative reaction
- Scabies
- Pediculosis pubis
- Other: vaginitis or cervicitis, vulvar atrophic changes, vulvar dystrophy

Fungal Infection

Although the primary symptom associated with fungal infections is itching, women also complain of vulvar burning, dysuria, and dyspareunia, particularly with the involvement of vulvar skin. Examination often reveals edema, erythema, and excoriation; when extensive skin involvement is present, pustular lesions may be found to extend beyond the line of erythema.

Diagnosis: Fungal infection is diagnosed through KOH preparation or fungal culture.

Treatment: The infection is treated with the topical application of an antifungal preparation (see **Vulvovaginal Candidiasis**, p. 182).

Allergic and/or Irritative Reaction

Contact dermatitis frequently affects the vulvar skin, particularly the intertriginous areas. Etiologic agents include urine or feces, latex, semen, and cosmetic or therapeutic agents, including vaginal contraceptives, lubricants, sprays, perfumes, douches, fabric dyes, fabric softeners, synthetic fibers, bleaches, soaps, chlorine, dyes in toilet tissues, and local anesthetic creams. Severe cases of dermatitis may be due to poison ivy or poison oak. Typical symptoms are itching, vulvar burning, and tenderness.

Diagnosis: Examination of the skin reveals erythema, edema, and inflammation; the skin may be weeping and eczematoid. Secondary infection may occur.

Treatment: Remove the offending agent. Severe lesions may be treated with wet compresses of Burow's solution diluted 1:20 for 30 minutes several times a day. If possible, the vulva should be dried with cool air from a hair dryer following application of the compresses. Lubricating agents such as Eucerin cream or petroleum jelly can help reduce the itching. Nonmedicated baby powders can be used to facilitate vulvar dryness. Symptomatic relief can be achieved with hydrocortisone (0.5%–1%) or fluorinated corticosteroid (Valisone 0.1% or Synalar 0.01%) lotions or creams applied to the skin two to three times a day for a few days. Dermatitis due to poison ivy or poison oak may require treatment with systemic corticosteroids. The use of white cotton undergarments is advisable, and tight-fitting clothing should be avoided.

Scabies

Scabies is a parasitic infection produced by the itch mite *Sarcoptes scabiei*. It is sexually acquired in adults. The main reported symptom is severe, intermittent itching that tends to be more intense at night.

Diagnosis: Lesions can present as vesicles, papules, or burrows; although any area of skin may be affected, hands, wrists, breasts, vulva, and buttocks are most often affected. HIV infected and other immunosuppressed patients are at increased risk for crusted or Norwegian scabies, a disseminated dermatologic infection, which can appear classically as hyperkeratotic, nonpruritic lesions; as crusting with pruritus; as a pruritic, papular dermatitis; or as lesions resembling psoriasis (*South Med J* 1994;87:352).

Treatment: The CDC-recommended treatment for scabies is permethrin cream (5%) applied to all areas of the body from the neck down and washed off after 8–14 hours *or* ivermectin 200 mcg/kg po, repeated in 2 weeks (*MMWR Recomm Rep* 2010;59(RR-12):1). An alternative regimen is lindane (1%) 1 oz of lotion or 30 g of cream applied to all areas of the body from the neck down and washed off thoroughly after 8 hours. Lindane should not be used by pregnant or lactating women and should not be used after a bath.

Itching may persist for days following treatment; antihistamine therapy should be considered for symptomatic relief. Bedding and clothing should be decontaminated (machine washed or dry cleaned) or removed from body contact for at least 72 hours. Norwegian scabies should be managed in consultation with an expert.

Pediculosis Pubis

Pediculosis pubis is caused by infestation with the crab louse *Phthirus pubis*, or pubic louse. Transmission is by close contact, but the louse can also be acquired from bedding or towels. This infection is usually confined to the hairy areas of the vulva, although eyelids are occasionally infested. The presenting symptom is constant itching in the pubic area.

Diagnosis: Eggs, adult lice, and fecal material can be seen upon close examination, without magnification. The diagnosis can be definitively established by microscopic visualization, as described above.

6

Treatment: The CDC-recommended treatment is permethrin 1% cream rinse *or* pyrethrins with piperonyl butoxide applied to affected areas and washed off after 10 minutes (*MMWR Recomm Rep* 2010;59(RR-12):1). Alternative regimens include malathion 0.5% lotion applied for 8–12 hours and then washed off *or* ivermectin 250 mcg/kg orally, repeated in 2 weeks if symptoms do not resolve.

Patients should be reexamined in 1 week; re-treat if lice or eggs are seen at the hair–skin junction. All clothing and bedding must be decontaminated (i.e., either dry cleaned or machine washed and dried using the hot setting) or removed from body contact for at least 72 hours. Close household contacts and recent sexual contacts (i.e., within the previous month) should be treated.

Other: Vaginitis or Cervicitis, Vulvar Atrophic Changes, Vulvar Dystrophy

Diagnosis: based on exam findings and the results of cultures and/or saline wet mount when indicated. A biopsy may be needed if lesions are seen (scaly, hypertrophic, fissures).

Treatment: indicated if another infectious process is identified; topical estrogen for atrophic vaginitis and/or vulvitis; topical steroid therapy empirically for suspected vulvar dystrophy or other dermatosis, with biopsy if symptoms or lesions do not resolve.

Breast Lump

A clinical breast exam should be part of the routine physical examination for all HIV infected women and should be performed on an at least an annual basis. The presence of a breast lump always requires further evaluation, depending on the factors listed below.

History, Physical Exam, Evaluation, and Differential Diagnosis and Management

History

- Palpable by the patient?
- Duration of lump
- Any associated symptoms (e.g., tenderness, nipple discharge or bleeding, cyclic pain)
- Changes in characteristics of the lump (e.g., increase in size)
- Menstrual phase or menopausal status
- History of previous breast lumps
- Family history of breast disease, cancer, or history of genetic screening showing BRCA-1 or BRCA-2 mutation
- Mammogram history

Physical Exam

- Examination of both breasts: symmetry, contour, and general appearance of the breasts; presence of edema, erythema, skin dimpling, or nipple retraction
- Presence and size of dominant masses; nodularity, tenderness, mobility
- Nipple discharge, including color; evidence of blood
- Lymph node survey: lymphadenopathy, axillary and supraclavicular

Evaluation

- Mammogram should be performed with any persistent palpable mass or other suspicious changes in the breast (e.g., bloody nipple discharge, skin retraction)
  - Negative mammogram alone is not sufficient to rule out malignant pathology in a patient with a palpable breast mass or bloody nipple discharge; further evaluation and a possible biopsy are indicated
- Ultrasound is most helpful to distinguish cystic and solid masses
  - Useful initial test in younger women when a simple cyst is suspected
- Needle aspiration for cystic lesion
  - Fluid can be discarded if clear and if mass disappears
  - Otherwise, send fluid for cytology; biopsy may be needed
- Biopsy is indicated in cases of a dominant mass, even with normal mammographic findings, or suspicious nonpalpable mammographic findings

Differential Diagnosis and Management

- Fibrocystic changes
- Fat maldistribution syndrome
- Breast abscess and/or mastitis
- Benign breast tumor
- Breast cancer

Fibrocystic Changes

Fibrocystic changes are typically found among women aged 30–50 years.

Diagnosis: Fibrocystic changes usually present as breast nodularity associated with cyclic bilateral pain or tenderness that is worse premenstrually. Breast engorgement, increased density, and cyst formation are common and vary with the menstrual-cycle phase.

Treatment: The pain/discomfort associated with this condition can be relieved by wearing a brassiere that gives adequate support. Analgesics can aid in symptomatic relief. Some women have reported improvement of symptoms with vitamin E (400 IU per day) and a decrease in caffeine consumption. Oral contraceptives are known to decrease benign breast disease. The appearance of a persistent dominant mass requires a biopsy.

6

Fat Maldistribution Syndrome

HIV or antiretroviral treatment may affect breast tissue, resulting in gynecomastia or increased fatty deposition (*Breast J* 2002;8:234).

Breast Abscess and/or Mastitis

This condition usually presents with tender breasts with evidence of inflammation (redness, swelling). If an abscess is present, a fluctuant mass may be palpated; fever may be present. The etiology is generally bacterial, but tuberculous mastitis and/or abscess should be considered in appropriate circumstances. This condition is most commonly, but not exclusively, seen in lactating women.

Treatment: Antibiotics, incision and drainage of abscess. Consider a biopsy and/or other diagnostic tests with nonresponse to treatment.

Benign Breast Tumor

The most frequently diagnosed benign tumors of the breast are fibroadenomas, which are usually found in women aged 20–35 years. Typically, masses are about 2 cm–3 cm in diameter, although they can become much larger. Examination reveals a firm, smooth, rubbery mass that is freely mobile. Inflammation, skin dimpling, and nipple retraction are absent. On mammographic examination, the mass appears smooth with well-defined margins.

Diagnosis: Definitive diagnosis is established by means of a biopsy.

Treatment: A fibroadenoma may simply be observed; however, a large, growing, or otherwise suspicious mass should be surgically excised.

Breast Cancer

The incidence of breast cancer increases with age. Risk factors include a positive family history, early menarche, late menopause, and nulliparity or late childbearing. If a palpable mass is present, it is usually firm and nontender, with irregular margins; it may be fixed to skin or underlying tissue.

Diagnosis: Definitive diagnosis is established by means of a needle or open biopsy; referral to a surgeon is indicated.

Breast cancer in HIV infected patients: There is no apparent increase in the incidence of breast cancer among HIV infected women; however, breast cancer in the setting of HIV infection may occur at a relatively early age, may be more likely to be bilateral and to have unusual histology, and may be more aggressive, with early metastatic spread and poor outcome. Most cases occur in women with CD4+ cell counts above 200 cells/mm3. Kaposi's sarcoma and non-Hodgkin's lymphoma may also be localized to the breast in women with AIDS (*Breast J* 2002;8:234; *Cancer Invest* 2002;20:452).

Sexual Dysfunction

When the validated Female Sexual Function Index (FSFI) was administered to women in the WIHS cohort, HIV infected women reported more sexual problems than uninfected women. Lower sexual function was also associated with menopause, symptoms of depression, or not being in a relationship. Women with CD4+ cell counts <200 cells/mm3 also reported lower sexual functioning than did women with higher CD4+ cell counts (*J Acquir Immune Defic Syndr* 2010;54(4):360). In another study of the responses of clinically stable women with HIV to the FSFI, one-third reported sexual dysfunction. The major determinant was self-perceived body changes; there were no significant associations with sex hormones, CDC stage, CD4+ cell count, HIV RNA level, or cumulative exposure to ARV drugs (*Antivir Ther* 2009;14(1):85).

Clinicians should proactively address issues related to sexual function and related concerns. Signs and symptoms of menopause (see below) and depression should be assessed and, when indicated, appropriate interventions implemented. Treatment of depression with selective serotonin reuptake inhibitors (SSRIs) is also a common cause of decreased libido or inability to reach orgasm. Because of the possible association with body image and a potential relationship with medication adherence, concerns about changes in body appearance should be addressed when a patient is starting ART and at regular intervals during the course of therapy.

Menopause

Menopause is defined as the permanent cessation of menstruation caused by the loss of ovarian function. The mean age at which women undergo menopause is genetically predetermined; in the United States, the average age of menopause onset is 51–52. As HIV infected women live longer, and as greater numbers of women who are nearing menopause or are postmenopausal become infected, it is increasingly important to consider and address issues related to menopause.

History, Physical Exam, and Evaluation

History

- Last menstrual period
- Recent menstrual pattern (i.e., cycle length, duration, amount of flow)
- Any irregular or intermenstrual bleeding or spotting
- Hot flashes
- Genitourinary dryness/atrophy
- Decreased libido
- Anxiety
- Irritability
- Sleep disturbances
- Depression
- Difficulty with memory
- Urinary symptoms

Physical Exam

- Vagina appears smoother in contour, "drier"
- May be more easily traumatized and more vulnerable to infection

Evaluation

- If indicated, confirmation of menopause can be provided by an elevated serum FSH level and a low estradiol level

Menopause in patients with HIV infection: Although data regarding the effect of HIV on the age at menopause are not conclusive, studies suggest that the mean age at menopause for HIV infected women is 3–4 years younger than that for uninfected women (*J Womens Health* 2007;16:1402). Several factors associated with earlier menopause are common among women with HIV, including smoking, substance abuse, African-American race, lower socioeconomic level, and low relative body weight, and may factor into the earlier onset of menopause (*Menopause Int* 2008;14:163). CD4+ cell count<200 cells/mm3 has also been associated with an earlier onset of menopause (*Clin Infect Dis* 2005;41:1517; *Int J STD AIDS* 2011;22(2):67).

Among women in the WIHS cohort, age at menopause was not affected by HIV status, but amenorrhea lasting longer than 12 months was more common among HIV infected women than among uninfected women. Predictors of ovarian failure included lower BMI and lower serum albumin (*Obstet Gynecol*

2006;108:1423). In a cross-sectional analysis of 429 HIV infected and uninfected women (median age 45 years), HIV infected women on ART had approximately a twofold increase in estradiol levels across the menopause transition, with a potential increased likelihood of abnormal perimenopausal bleeding (*Menopause* 2007;14(5):859).

Women are at increased risk for osteoporosis compared with men, and this risk increases after menopause. Recent studies suggest a potential association between HIV infection, ART, and loss of bone density (*J Acquir Immune Defic Syndr* 2003;33:281). Low bone mineral density has been found to be more prevalent among women with HIV approaching menopause than among uninfected women (*Menopause* 2009;16:199). Results of a population-based case-control study indicated that, even among women with normal bone mineral density, HIV infected women reported significantly more history of fragility fractures than did women in the control group (*Osteoporos Int* 2007;18:1345).

Studies have also found that more than 60% of HIV infected patients are vitamin D insufficient or deficient; in addition to known risk factors, the association of renal insufficiency with the use of some ARV agents is consistent with both HIV-related and treatment-mediated alterations in vitamin D metabolism (*Clin Infect Dis* 2011;52(3):396). Data regarding osteoporosis treatment in HIV infected women are lacking. Nonetheless, standard suggestions can be made for treatment and prevention: increase physical activity, stop smoking, and take calcium and vitamin D supplements. Small studies confirm the benefits and safety of alendronate therapy in HIV infected patients (*AIDS* 2007;21:657).

Management

Hormone replacement therapy (combined estrogen-progestin replacement therapy): Currently, the recommendation is to use HRT to treat menopausal symptoms at the lowest effective dose for the shortest duration needed, with periodic evaluation of the need for continued use.

A variety of estrogen and progestin formulations are available. Estrogen can be given orally, transdermally, or topically; progesterone and/or progestin is generally administered orally or by transdermal patch. These agents can be given on a continuous (daily) basis or cyclically (estrogen given daily and progestin 12–14 days per month). Combined oral and transdermal regimens are available and improve adherence.

The benefits and risks associated with HRT have been studied extensively among HIV uninfected women. HRT is known to ameliorate symptoms of vasomotor instability (e.g., hot flashes, sleep disturbances, irritability) and urogenital atrophy (e.g., vaginal dryness, dyspareunia); it is also associated with a decreased risk of colon cancer, osteoporosis, and osteoporosis-related fractures (*JAMA* 2002;288:321). A recent position paper from the United Kingdom National Osteoporosis Society concluded that HRT has a role to play in the management of osteoporosis in postmenopausal women aged <60 years (*Menopause Int* 2011;17(2):63).

The results of a large, randomized, placebo-controlled study of combined estrogen-progestin therapy (at higher doses than are generally used today and in women with a mean age of 63 years) found a small but statistically significant increase in the incidence of breast cancer, dementia, stroke, pulmonary embolism, and cardiovascular disease (*JAMA* 2002;288:321; *JAMA* 2003;289:2717; *JAMA* 2003;289:3243). An increased risk of endometrial cancer was seen in women treated with estrogen only, which is not recommended for women who still have a uterus.

Because of the higher prevalence of active liver disease in patients co-infected with HIV and hepatitis B or C and a potential increased risk for cardiovascular disease associated with the metabolic changes that occur with long-term ART, HRT may be associated with increased risk in the setting of HIV infection and should be used only if the benefit is felt to outweigh the risk.

Alternatives to Hormone Replacement Therapy

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- Progestin-only regimens (medroxyprogesterone acetate 10–30 mg qd or norethindrone 1–5 mg qd) may help relieve hot flashes; the health effects of long-term therapy are unknown

- SSRIs may help relieve hot flashes

- Nonhormonal lubricants and/or moisturizers or local/topical estrogen formulations may be used to manage urogenital atrophy

- Bisphosphonates (e.g., alendronate, ibandronate) may be used for the prevention or treatment of osteoporosis

- Selective estrogen receptor modulators (raloxifene 60 mg po daily) offer bone benefit without evidence of breast or endometrial stimulation. They are also FDA indicated for breast cancer prophylaxis in high-risk postmenopausal women. These drugs have no effect on hot flashes, pose a small increased risk of venous thromboembolism (VTE), and are contraindicated in women with a history of VTE.

Health Maintenance Issues

Regardless of coexisting medical problems and even in the absence of gynecologic symptoms, regular gynecologic evaluation and other recommended health screening tests are important to identify potential problems that require further evaluation and treatment.

Gynecologic Evaluation

Perform annually and as indicated by the presence of symptoms, need for follow-up of ongoing problems, exposure to STIs, development of abnormal Pap smear, or other need for referral based on primary care evaluation.

Pap Smears

Perform twice within the first year of HIV diagnosis and then annually. More-frequent screening may be indicated with a history of abnormal Pap smear, HPV infection, and/or after treatment for cervical dysplasia.

Screening for Sexually Transmitted Infections

- Screen annually for syphilis and if neurologic signs and symptoms develop

- Screen annually for gonorrhea, chlamydia, and trichomoniasis in sexually active women. Screen as indicated by the presence of relevant symptoms or exam findings and with a recent change in sexual partners and/or a history of STI in the sexual partner. Screen periodically as indicated by sexual practices (e.g., commercial sex work, multiple sex partners, inconsistent use of condoms) or on patient request.

Mammography

ACOG recommends baseline mammography beginning at age 40 and then every 1–2 years until age 50, with annual screening thereafter (ACOG Committee Opinion No. 483; *Obstet Gynecol* 2011;117(4):1008); women at increased risk (e.g., first-degree relative(s) with breast cancer, BRCA-1 or BRCA-2 mutation) may benefit from earlier initiation of screening or the addition of screening modalities other than mammography, such as ultrasound or MRI. Mammogram should also be performed with the presence of a persistent, palpable mass or other suspicious findings on exam.

Colorectal Cancer Screening

Begin screening at age 50, followed by colonoscopy every 10 years thereafter (preferred). Other screening methods include: 1) annual fecal occult blood testing or fecal immunochemical test (patient-collected; requires 2–3 stool samples collected at home and returned for analysis); 2) flexible sigmoidoscopy every 5 years; 3) double contrast barium enema every 5 years; 4) CT colonography every 5 years; or 5) stool DNA (ACOG Committee Opinion No. 483; *Obstet Gynecol* 2011;117(4):1008).

Begin screening colonoscopy earlier and continue at shorter intervals in women with a family history of colorectal cancer or adenomatous polyps (i.e., in any first-degree relative aged <60 years, or in two or more first-degree relatives at any age), family history of familial polyposis or hereditary nonpolyposis colon cancer, personal history of colorectal cancer, inflammatory bowel disease, or adenomatous polyps. The American College of Gastroenterology recommends that screening in African Americans begin at age 45 with colonoscopy because of increased incidence and earlier age at onset of colorectal cancer (*Am J* Gastroenterol 2005;100:515).

Osteoporosis Prevention

The recommended dietary reference intake for calcium is 1000–2000 mg/day; for vitamin D, 600–800 IU/day (*Dietary Reference Intakes for Calcium and Vitamin D—Consensus Report*. Institute of Medicine. November 2010; http://www.iom.edu/Reports/2010/Dietary-Reference-Intakes-for-Calcium-and-Vitamin-D.aspx. Accessed 7/6/2012). Regular weight-bearing exercise is also recommended. Baseline bone-density screening should be performed at age 65 and periodically thereafter, with the screening interval determined by the presence of bone loss or risk factors for premature bone loss. Earlier screening should be considered in younger postmenopausal women with one or more risk factors for premature bone loss (*Clin Infect Dis* 2009;49(5):651; ACOG Committee Opinion No. 483; *Obstet Gynecol* 2011;117(4):1008).

Risk factors for premature bone loss include
  • caucasian or Asian race/ethnicity,
  • alcohol abuse,
  • smoking,
  • low BMI,
  • sedentary lifestyle,
  • chronic steroid use,
  • phenytoin therapy,
  • hyperparathyroidism,
  • vitamin D deficiency,
  • thyroid disease,
  • history of prior fracture as an adult,
  • dementia,
  • family history of osteoporosis,
  • premature menopause (<45 years),
  • prolonged (>1 year) premenopausal amenorrhea, and
  • history of falls.

Vitamin D deficiency is common and is more severe in darker-skinned women; a baseline 25-OH vitamin D level will detect this. Minimal deficiency and levels near the lower limit of normal can be corrected by an over-the-counter vitamin D supplement of 1000 IU daily; more-severe deficiency requires prescription high-dose (50,000 IU) repletion followed by chronic maintenance dosing of 1000 IU/day.

Lipid Screening

Assess and address risk factors for hyperlipidemia at the initial visit and periodically thereafter. Risk factors include a history of cardiovascular, peripheral vascular, or cerebrovascular disease; age >55 years; family history; smoking; diabetes; hypertension; obesity; and physical inactivity. Perform a fasting lipid profile every 6–12 months in all patients and consider performing it 1–3 months after starting or modifying ART (*Clin Infect Dis* 2009;49(5):651).

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Guidelines for Gynecologic Referral

In general, referral to an obstetric-gynecologic specialist should be considered under the following circumstances:

- Uncertain diagnosis, with a gynecologic condition as part of the differential diagnosis
- Diagnosis of pregnancy
- Inadequate response to standard treatment regimens for gynecologic conditions
- Possible need for surgical intervention
- Suspected premalignant or malignant condition

Color Plates

Plate 1.

Trichomonas vaginalis protozoa in a saline wet mount (high power)
(CDC, 1986)

Plate 2.
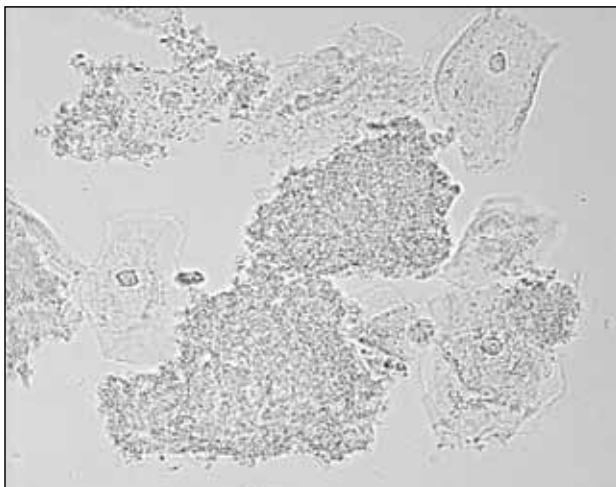
Clue cells of bacterial vaginosis in saline wet mount (high power)
(Seattle STD/HIV Prevention Training Center at the University of Washington)

Plate 3.
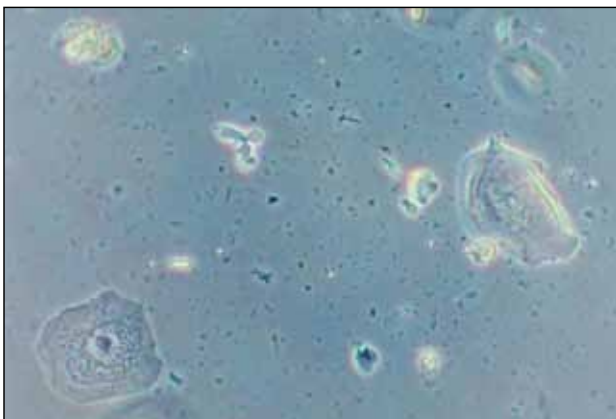
Candida albicans in a saline wet mount (high power) (CDC/
Dr. Stuart Brown, 1976)

Color Plate 4.

Vaginal candidiasis: thrush patches on the vaginal wall of a patient with candidiasis (© courtesy J. Anderson, MD).

Color Plate 5.

Bartholin's abscess (CDC, Division of STD Prevention)

Color Plate 6.

Chancre in a woman with primary syphilis (CDC, Division of STD Prevention)

Color Plate 7.

Secondary syphilis (CDC, Division of STD Prevention)

Color Plate 8.

Extensive vulvar condylomata acuminata (human papillomavirus) (CDC)

Color Plate 9.

Granuloma inguinale (CDC, Division of STD Prevention)

Color Plate 10.

Herpes simplex cervicitis (CDC, Division of STD Prevention)

Color Plate 11.
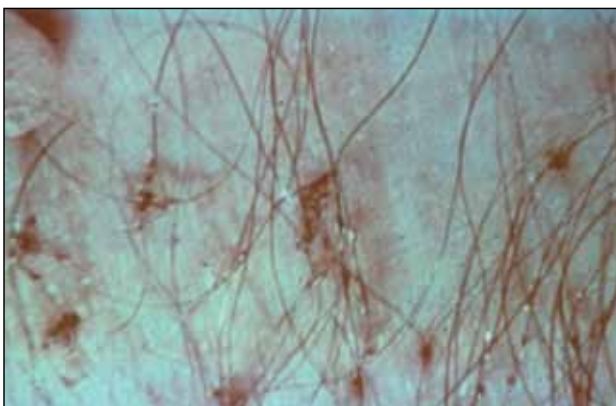
Lice in pubic area (CDC, Division of STD Prevention)

Color Plate 12.
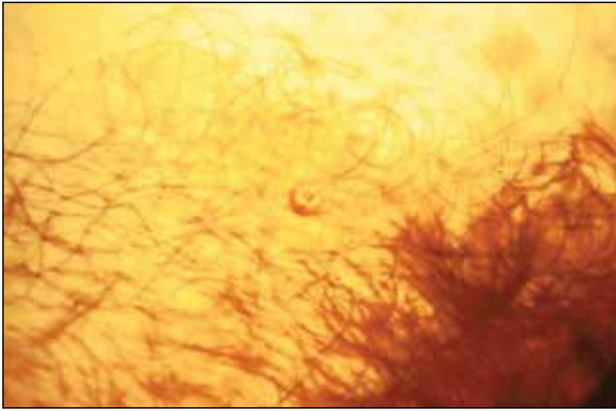
Molluscum contagiosum (CDC, Division of STD Prevention)

Color Plate 13.

Condylomata late in secondary syphilis (CDC, Division of STD Prevention)

Color Plate 14.

Lesion of herpes simplex (© courtesy J. Anderson, MD).

Color Plate 15.

Herpes simplex in woman with AIDS, CD4<50
(© courtesy J. Anderson, MD).

Color Plate 16.

Aphthous genital ulceration (© courtesy J. Anderson, MD).

Color Plate 17.

Aphthous oral ulceration (© courtesy J. Anderson, MD).

Chapter 7:

Preconception Care and Contraception

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Chapter 7: Preconception Care and Contraception

Chapter 7 at a Glance

Preconception Care and Contraception

Studies of pregnancy in the HAART era indicate that pregnancy is common after a diagnosis of HIV and live birth rates are significantly increased when compared with the pre-HAART period; abortion is less common; and HIV infected women often desire more children, influenced by advances in HIV care (*Am J Public Health* 2000;90:1074; *AIDS* 2000;14:2171; *AIDS* 2004;18:281; *Am J Obstet Gynecol* 2007;196:541.e1; *AIDS Care* 2011;23:1093). Many HIV infected women, 80% of whom are of childbearing age, now feel that they can have more normal lives that include bearing children with the realistic hope of raising them to adulthood. Viewed through this lens, pregnancies among women with HIV can be seen as part of the success story of HIV—a chapter in the evolution of HIV infection from a progressive and uniformly fatal condition to a chronic disease that is serious but survivable.

The U.S. Centers for Disease Control and Prevention (CDC), the American Congress of Obstetrics and Gynecology (ACOG), and other national organizations recommend offering all women of childbearing age comprehensive family planning, including effective contraceptive counseling, and the opportunity to receive preconception counseling and care as an integral component of routine primary medical care (*Obstet Gynecol* 2007;110:1473; *Obstet Gynecol* 2009;452:1444; *MMWR Recomm Rep* 2006;55(RR-6):1).

This chapter reviews issues related to reproductive decision-making, including preconception care and counseling and use of contraception to reduce unintended pregnancy.

Preconception Care

The CDC defines preconception care as a series of "interventions that aim to identify and modify biomedical, behavioral, and social risks to a woman's health or pregnancy outcome through prevention and management" (*MMWR Recomm Rep* 2006;55(RR-6):1).

Goals of preconception care include

- prevent unintended pregnancy,

- optimize maternal health prior to pregnancy,

- improve maternal and fetal outcomes in pregnancy,

- prevent mother-to-child transmission of HIV, and

- prevent transmission of HIV to an uninfected sexual partner while trying to conceive.

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When to Discuss Pregnancy

Several studies have documented predictors of the desire to conceive (*AIDS Behav* 2010;14:1106; *PLoS One* 2009;4:e7925; *AIDS Behav* 2009;13:949; *Fam Plann Perspect* 2001;33:144). Commonly, the women who most want to conceive are younger, have no children, and have a husband/partner/other family member who wants them to get pregnant. Nonetheless, the desire to have a child and decisions regarding whether and when to do so are complex, multifaceted, changeable over time, and not necessarily related to health status. Therefore, all women of childbearing capacity should be assessed for childbearing desires or intentions at their initial evaluation with an HIV care provider and at regular intervals throughout the course of care. This is particularly important if a woman

- has expressed an interest in conceiving,

- is not using effective contraception or is not using it regularly or appropriately,

- has changed sexual partners or experienced a change in personal circumstances (e.g., is postpartum),

- is taking medications with potential reproductive toxicity or interactions with hormonal contraception,

- is at risk for unintended pregnancy,

- may benefit from or be otherwise affected by new developments in the field of pregnancy and HIV, and/or

- plans to enroll in clinical trials.

Primary HIV care providers should be proactive in addressing reproductive needs and desires, as many women may not feel comfortable in raising these issues for fear of being judged harshly or discouraged (*AIDS Patient Care STDS* 2010;24:317). Patient-provider tools such as those shown in Figure 7-1 may facilitate this discussion by helping to identify patient needs.

Figure 7-1

HIV and Pregnancy: Decision Aids for the Patient and Provider

1. Patient Decision Aid

With effective HIV treatment, women and men with HIV infection can now enjoy a long and healthy life and can look forward to a future that may include planning a family. When taken during pregnancy, HIV medications can decrease the risk of transmitting HIV to the baby to 1%–2% or less. It is also important to prevent pregnancy when you are not yet ready to become a mother. As a woman with HIV, it is important to plan carefully so that you can get the treatment you need to have a safer pregnancy, prevent transmission of HIV to your baby, and prevent pregnancy until you are ready. This survey is designed to help you and your healthcare provider take the first steps in that planning.

Name: _____ Date: _____

1. Your current age is _____

2. Have you ever been pregnant? ☐ **YES** ☐ **NO**

3. If **YES,** how many times? _____ How many children do you
   have? _____

4. Are you interested in getting pregnant? ☐ **YES** ☐ **NO**

5. If **YES,** when do you wish to conceive?
   ☐ Trying to conceive now   ☐ 6 months – 1 year from now
   ☐ 1 – 2 years from now   ☐ More than 2 years from now

6. Have you had sex with a man in the last 6 months? ☐ **YES** ☐ **NO**

7. Are you currently using condoms? ☐ **YES** ☐ **NO**

8. Are you currently using birth control other than condoms?

   A. What type?
   ☐ None   ☐ Birth control pill   ☐ IUD   ☐ Injection (Depo-Provera)
   ☐ Patch/vaginal ring   ☐ Implant under the skin (Implanon)
   ☐ Sterilization (tubes tied)   ☐ Unsure
   ☐ Other: _____

   B. Are you trying to get pregnant? ☐ **YES** ☐ **NO**

9. Would you or your partner like to talk to someone about planning a
   safer pregnancy that may reduce the risk of HIV transmission to your
   baby? ☐ **YES** ☐ **NO**

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Figure 7-1 continued

HIV and Pregnancy: Decision Aids for the Patient and Provider

2. Provider Decision Aid

This tool is designed to help you, the health care provider, better address fertility issues (desire to conceive and desire to prevent pregnancy) with your patients.

1. Patient is postmenopausal or post-hysterectomy.
   A. Yes – End of tool
   B. No – Go to question 2

2. Does patient wish to have more children?
   A. Yes – Go to question 3
   B. No – Go to question 5

3. Does patient wish to conceive within the next year?
   A. Yes – Go to question 4
   B. No – Go to question 5

4. Patient would like to conceive within the next year.
   A. Review medication list with patient for drugs that are contraindicated in women trying to conceive (e.g., efavirenz, statins, ribavirin, tetracycline/doxycycline). Other drugs should be used unless no alternate agents are available that are both effective and safer in women who are trying to conceive.
   AND
   B. Offer and encourage referral for preconception counseling and evaluation.

5. Patient wishes to prevent pregnancy.
   A. Patient has completed childbearing: Refer to a gynecologist to discuss long-term or permanent options for contraception.
   OR
   B. Patient wants more children, but not within the next year: Review nonpermanent options for contraception and strongly recommend referral for preconception counseling.

Key Considerations:

1. Patient has a problem with irregular menses or amenorrhea: If yes, perform a pregnancy test and refer for a gynecologic evaluation.
2. Menopause: Can be difficult to diagnose
   – If the woman is >50 y with no vaginal bleeding for >1 y, she is postmenopausal.
   – If uncertain, refer for a gynecologic evaluation.
3. Formal preconception counseling and evaluation is strongly recommended if the patient
   A. Is in a serodiscordant relationship
   B. Has significant medical co-morbidities
   C. Has problems with substance abuse
   D. Is taking a medication that is contraindicated in women trying to conceive
   E. Reports a desire to conceive and a history of infertility or difficulty getting pregnant

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While primary HIV care providers may feel comfortable discussing contraception and prevention of mother-to-child-transmission (MTCT) of HIV, they may not feel fully able to address preconception counseling and care needs, in which case consultation and referral are appropriate.

Evaluation

Table 7-1 outlines the comprehensive preconception evaluation designed to identify factors that may affect a woman's ability to get pregnant or may increase the risk of adverse pregnancy outcomes for the mother or her fetus.

Table 7-1

Comprehensive Preconception Evaluation

History	Comments
HIV	• Date of diagnosis • History of OIs or other HIV-related illnesses • ART history, including use in prior pregnancies and/or reasons for change(s) in ART regimens (e.g., adverse effects, resistance, tolerability) • Adherence history and challenges • Results of resistance tests • Nadir and current CD4+ cell count • Current HIV VL
Pregnancy	• Number of previous pregnancies and their outcomes (e.g., miscarriages, abortions, ectopic pregnancy, preterm births) • Number of living children and ages • Number of HIV infected children • Pregnancy complications (e.g., preterm labor, preeclampsia, birth defects) • Modes of delivery
Gynecologic	• Prior and current contraception use • Satisfaction with current contraception method and/or adverse effects • Current condom use and consistency of use (100% vs <100%) • Prior STIs or genital tract infections • Past difficulties in conceiving • Abnormal Pap smears and treatment • Other gynecologic problems and treatment (e.g., fibroids, endometriosis)
General Medical and Surgical	• Other medical conditions (e.g., DM, HTN, renal or cardiac disease, depression or other psychiatric illness) • All prior surgery • Blood type and history of transfusions • Allergies
Immunizations	• HBV, HAV, influenza, pneumococcus, HPV, tetanus
Medications	• All prescribed medications • All OTC medications • All complementary medications
Nutrition	• History of anemia or nutritional deficiencies • Special diet (e.g., vegetarian, vegan, gluten-free) • Use of nutritional supplements and vitamins

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Table 7-1	*continued*

Comprehensive Preconception Evaluation

History	Comments
Social History	• Relationship status • Use of illicit drugs, tobacco, alcohol • Employment status • Social support and disclosure to partner and others • Economic support • History and nature of domestic violence (i.e., physical, sexual, psychological)
Family History of Heritable Diseases	• Birth defects • Chromosomal abnormalities • Muscular dystrophy • Sickle cell disease • Mental retardation • Others

Male Partner	• HIV status and knowledge of partner's status
	• If HIV infected:
	  - Disclosure status
	  - History of OIs and other HIV-related conditions
	  - ART history and history of adverse effects, resistance, adherence problems
	  - Nadir and current CD4+ cell count
	  - Current HIV VL
	• Medical and reproductive history
	• Medications
	• Use of illicit drugs, tobacco, alcohol
	• Employment status

Physical Exam	• Comprehensive, with focus on genital tract
Laboratory (Emphasis is on lab tests that will affect counseling and/or result in changes in care prior to pregnancy)	• Tests • STI screening: GC/chlamydia; syphilis; HSV culture or HSV-2 antibody, if indicated • CBC • Current CD4+ cell count • HIV RNA • Resistance testing, if indicated • Rubella • HBV: HBsAb, HBsAg • HCV antibody and HCV RNA, if indicated • Pap smear • Other, as indicated by medical history and medications

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Preconception Counseling

Preconception counseling of the HIV infected woman should address the following issues:

- Effect of pregnancy on HIV course (see Chapter 8, ***HIV and Pregnancy***)

- Effect of HIV on pregnancy course and outcome (see Chapter 8, ***HIV and Pregnancy***)

- MTCT and prevention, including the role of antiretroviral drugs (ARVs), cesarean section, etc.

- Use of HIV-related medications, including maternal and fetal safety and toxicity

- Long-term care plans, including advance directives, care for children should mother and/or father die or become disabled

- Non-HIV-related factors, including age, drug use, other medical conditions, and their potential effects on pregnancy course or outcome

- Safe conception if the patient is in a serodiscordant relationship

- Safe sexual practices

- Healthy living and health maintenance, including smoking cessation, elimination of alcohol and illicit drug use, etc.

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Preconception Interventions

Preconception interventions for the HIV infected woman may include the following:

- Contraception to reduce unintended pregnancy (see below)

- Initiation or modification of antiretroviral therapy (ART) regimen. ART should be initiated prior to attempts to conceive if the woman meets criteria for starting ART, in which case maximal suppression of HIV viral load (VL) should be achieved prior to pregnancy and the patient's regimen should be well tolerated without significant adverse effects.

- If a woman does not meet current CD4+ cell count criteria, initiation of ART prior to conception may still be considered. Maximal suppression of HIV VL potentially reduces, though it does not eliminate, the risk of perinatal transmission (*AIDS* 2008;22:973; *Clin Infect Dis* 2010;50:585). Also to be considered, however, are the potential adverse effects of ART on certain pregnancy outcomes, the patient's readiness for lifelong therapy, and the risks versus benefits of stopping ART postpartum (see Chapter 8, ***HIV and Pregnancy***).

- If a patient's current ART regimen is not effective (i.e., suboptimal suppression of VL), not well tolerated, associated with significant adverse effects, or contains EFV, it should be modified prior to attempts to conceive.

Optimal treatment of other medical conditions: Also recommended is optimal therapeutic control of hypertension, diabetes, and other medical conditions. Care providers should review all of a woman's current medications (not just HIV-related medications) and, if indicated, substitute medications that may be safer in pregnancy. The risk-benefit profile of any medication is important to consider. A drug classified as U.S. Food and Drug Administration (FDA) category D signifies positive evidence of human fetal risk, but potential maternal benefits may make the risk acceptable. FDA category X is assigned to drugs for which the risk to a pregnant woman clearly outweighs any possible benefit. If a woman is taking an FDA category D or X drug, the feasibility of safely stopping or substituting for the medication must be determined, and expert consultation is advised (see Table 13-1, p. 448). (*Note:* At the time of publication of this guide, the FDA was preparing a revision of drug categories for pregnancy and lactation that will likely do away with the current letter categories.)

Other preconception interventions should include the following when indicated:

- Opportunistic infection (OI) treatment or prophylaxis

- Screening for and treatment of existing genital tract infections in both partners (genital tract inflammation is associated with increased HIV shedding in the genital tract, even when plasma VL is fully suppressed; if untreated, genital tract infections may increase the risk of adverse pregnancy outcomes and potential MTCT)

- Treatment of anemia and/or other nutritional interventions

- Treatment of drug and/or alcohol abuse

- Assistance with smoking cessation

- Treatment of depression and other mental illnesses

- Immunizations

- Provision of prenatal vitamins, including folic acid supplementation for prevention of neural tube defects

- Assistance with advance directives

Safe Conception

If both partners are HIV infected, condom use should be encouraged. Unprotected intercourse should be timed to coincide with the most fertile period of a woman's menstrual cycle. Fertile periods may be determined with ovulation predictors, basal body temperature measurement, or the use of an ovulation calculator (see, for example: http://www.marchofdimes. com/ovulation_calendar.html. Accessed 7/9/2012). Semen analysis should be considered because HIV is associated with a higher prevalence of semen abnormalities (see below).

Serodiscordant Couples

There are an estimated 140,000 HIV-serodiscordant heterosexual couples in the United States, about half of whom want more children (*Am J Obstet Gynecol* 2011;204:488.e1). Expert consultation is recommended to address the individual needs of serodiscordant couples attempting to conceive.

Female HIV infected and male uninfected: The uninfected partner of an HIV infected woman should be encouraged to use condoms with each act of intercourse. Intravaginal insemination for conception using the partner's semen can be performed at home or by the healthcare provider and is effective with normal fertility. Timed insemination during the most fertile period may be considered to maximize the chance of conception. She should be on ART and attain maximal viral suppression prior to attempting conception. PrEp (see below) can also be considered for an uninfected male partner who wants additional protection if the couple opt for timed unprotected intercourse when trying to conceive.

Male HIV infected and female uninfected: The risk of HIV transmission to an uninfected woman with an HIV infected partner can be minimized but not entirely eliminated, unless donor sperm is used. Observational studies and a meta-analysis have demonstrated a decreased rate of HIV transmission among heterosexual serodiscordant couples on ART, particularly when HIV VL is fully suppressed in the infected partner (*AIDS* 2009;23:1397). Recent data from HPTN 052, a randomized clinical trial designed to evaluate ART for the prevention of sexual transmission among serodiscordant couples, indicates that earlier initiation of ART (at CD4+ cell counts 350–550 cells/mm³) reduced HIV transmission to the uninfected partner by 96% (*N Engl J Med* 2011; 365(6):493).

- **ART for the infected male:** He should be on ART and attain maximal viral suppression prior to attempting conception.

- Treatment of an infected partner does not fully protect against HIV transmission, even in the setting of maximal plasma VL suppression. Although effective ART decreases virus in genital secretions, discordance between plasma and genital VLs has been reported, and individuals may have isolated semen HIV shedding even when plasma VL is undetectable (*AIDS* 2008;22:1677; *AIDS* 2010;24(16):2489) and independent of semen drug levels and ART regimen (*AIDS* 2009;23(15):2050). Additionally, ARV penetration of the genital tract varies among agents (*Curr Opin HIV AIDS* 2010;5(4):335).

Screen for and treat genital tract infections: Genital tract infections, both sexually transmitted and nonsexually transmitted (e.g., bacterial vaginosis, yeast), may increase the HIV uninfected woman's vulnerability to HIV acquisition. In the HIV infected man, genital tract infections may increase his infectiousness.

Semen analysis: Semen abnormalities are more common in the setting of HIV. Abnormalities are correlated with lower CD4+ cell counts and may include lower sperm volume, concentration, and motility, and higher rates of abnormal forms (*Hum Reprod* 2004;19:2289; *Arch Gynecol Obstet* 2011; 284(1):229). Some data suggest that ART may have an adverse effect on semen quality. A longitudinal study of 34 men with serial semen analyses prior to ART and

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up to 48 weeks post-ART found that the proportion of progressively motile spermatozoa was low at all time points, but decreased significantly over the course of follow-up (*AIDS* 2008;22:637). Therefore, when there is little or no likelihood of natural conception, an uninfected female partner may be at increased risk for infection through repetitive exposure over time.

Assisted reproductive technology: The method with the lowest risk of transmission is semen washing, with negative PCR testing after preparation, coupled with intrauterine insemination (IUI), in vitro fertilization (IVF), or intracytoplasmic sperm injection (ICSI). The results of studies that, combined, included more than 6500 cycles of sperm washing plus IUI, IVF, or ICSI indicate no female seroconversions (*Reprod Biomed Online* 2005;10:135; *AIDS* 2007;21:1909; *Fertil Steril* 2009;91:2455). A more recent systematic analysis of safety and effectiveness of ART in serodiscordant couples found no seroconversions in 3900 IUI cycles (50% cumulative pregnancy rate) and 738 ICSI/IVF cycles (53% cumulative pregnancy rate (*Fertil Steril* 2011;95:1684).

Most insurance plans, however, (including Medicare/Medicaid) do not cover these services and the cost is usually prohibitive. The National Perinatal HIV Hotline (1-888-448-8765) can provide a list of institutions offering reproductive services for HIV serodiscordant couples.

Timed unprotected intercourse and condom use at all other times: For serodiscordant couples who cannot afford assisted reproduction and who, after comprehensive counseling, still wish to conceive, this is the best approach. The most fertile time in a woman's menstrual cycle can be determined with ovulation predictors (available over the counter at pharmacies), basal body temperature measurement, or ovulation calculators (e.g., http://www.marchofdimes.com/ovulation_calendar.html).

Pre-exposure prophylaxis (PrEP): Providing ARVs topically or orally to an uninfected female partner may offer some additional protection against HIV transmission from an infected male partner during attempts to conceive, but study results to date have been mixed. A Phase IIb randomized placebo-controlled trial (CAPRISA 004) of a 1% intravaginal TDF gel used before and after sex reduced HIV acquisition by 39% and by up to 54% with greater adherence (*Science* 2010;329(5996):1168); however, in the VOICE study, a multi-country, multi-arm Phase IIb study of vaginal and oral PrEP in women at high risk of acquiring HIV, 1% TDF gel used daily was no better than placebo. A Phase III study of daily oral TDF/FTC in uninfected male couples (iPrEX) reported a 44% overall reduction in HIV acquisition compared with placebo; effectiveness was significantly affected by adherence (*N Engl J Med* 2010;363(27):2587; *N Engl J Med* 2010;363(27):2663). In the Partners PrEP study conducted in Kenya and Uganda among more than 1400 HIV-serodiscordant couples, the use of daily TDF or daily TDF/FTC by the uninfected partner was found to have efficacy of 66% and 73%, respectively, compared with placebo, in reducing HIV transmission (reported 97% adherence by returned pill count, but only 81% of those assigned to the active-treatment arm had detectable blood levels of the study drug) (*N Engl J Med* 2012;367(5):399). Within a subgroup of those who received TDF/FTC and whose plasma drug levels were tested, measurable concentrations of TDF

were associated with a 90% reduction in risk compared with placebo. In another trial in Botswana, TDF/FTC given to 1200 HIV uninfected heterosexual men and women reduced transmission by 66% compared with placebo with 84% adherence by returned pill count (Curr *Opin Infect Dis* 2012;25(1):51; *N Engl J Med* 2012;367(5):423). The FEM-PrEP clinical trial and the VOICE study, however, both conducted in high-risk uninfected African women, found no efficacy with either daily oral TDF/FTC or TDF, but adherence was quite low with detectable drug levels found in less than one-third of those tested and randomized to active drug. (Curr *Opin Infect Dis* 2012 Feb;25(1):51; *N Engl J Med* 2012;367(5):411; 20th Conference on Retroviruses and opportunistic Infections, Atlanta, GA, Abstract 26LB, 2013). Therefore, it is likely that adherence is a key factor in the discrepant results of these studies.

In studies of PrEP to date, safety and tolerability were excellent and limited resistance was observed in seroconverters. Twice-weekly and coital dosing of TDF/FTC, as well as longer-acting formulations, intravaginal rings, and new candidate ARVs, are being evaluated for PrEP.

Use of this approach will require individual counseling that addresses a number of considerations: 1) effectiveness of periodic (e.g., use for a certain period of days, currently undefined, around ovulation) versus daily use; 2) effectiveness in the presence of resistance to agents used for prophylaxis in the infected partner; 3) risk of resistance should transmission occur despite the use of prophylaxis; 4) potential risk of adverse effects in pregnancy or to the developing fetus; and 5) potential decrease in other risk-reduction behaviors, such as condom use. Providers should counsel patients that the efficacy of PrEP is highly dependent on adherence. In August 2012 the CDC issued the following interim guidance for clinicians considering the use of PrEP for HIV prevention in heterosexually active adults, particularly those with known HIV-infected partners (*MMWR* 2012; 61(31):586) (see Chapter 3). It is not known if the use of PrEP adds additional benefit when the infected partner has maximal viral suppression.

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HIV and Fertility

HIV appears to have an adverse effect on fertility in both symptomatic and asymptomatic women (*AIDS* 1999;13:517; *J Acquir Immune Defic Syndr* 2000;25(4):345; *Lancet* 1998;351:98; *Am J Epidemiol* 2000;151:1020; *Int J STD AIDS* 2006;17(12):842). This includes increased risk of infertility and pregnancy loss. Recent data from low-resource settings suggest that fertility improves after treatment with ART (*AIDS Res Treat* 2011;2011:519492; *PLoS Med* 2010;7(2):e1000229).

Potential Causes of Infertility

In the setting of HIV infection there are several potential causes of infertility, some of which are confounding factors that may independently reduce fertility.

- HIV infected women frequently have a history of other sexually transmitted infections (STIs), such as gonorrhea, chlamydia, and syphilis, which reduce fertility. In a cross-sectional study of fertility assessment in 130 HIV infected women, 27.8% had tubal occlusion, generally indicative of past tubal damage with gonorrhea or chlamydia (*Reprod Biomed Online* 2007;14:488).

- HIV infected women may be at increased risk for amenorrhea and/or ovulatory dysfunction due to chronic drug use (especially use of opiates) and/or poor nutrition and weight loss.

- Menstrual dysfunction and/or amenorrhea are common in the setting of HIV; however, controlled studies have produced conflicting results regarding a direct effect of HIV or HIV-related immunosuppression on menstrual function.

- Sexual dysfunction is reported in 53%–71% of HIV infected men. It may be associated with the presence and/or treatment of depression or anxiety. Semen abnormalities are also more common in the setting of HIV (see above).

- Higher VLs have been associated with decreased fertility (*Int J STD AIDS* 2006;17:842).

Legal right to care: In a 1998 U.S. Supreme Court decision, *Bragdon v. Abbott*, the Court ruled that a person with HIV is considered to be "disabled" and therefore protected under the Americans with Disabilities Act. "Unless health care workers can show that they lack the skill and facilities to treat HIV infected patients safely or that the patient refused reasonable testing and treatment, they may be legally, as well as ethically, obligated to provide requested reproductive assistance" (*Fertil Steril* 2010;94:11). To date, there have been no reported cases of occupational transmission to personnel providing assisted reproductive care or contamination of gametes or embryos in the provision of this care that would support the denial of services to HIV infected individuals or couples.

Unintended Pregnancy in HIV Infected Women

Many pregnancies among HIV infected women are unintended or unplanned. In the United States, approximately 50% of all pregnancies are unintended, a rate that has not changed in 15 years. Approximately 50% of unintended pregnancies occur in women using contraception, and more than 50% are aborted (*Fam Plan Perspect* 1998;30:24; *Contraception* 2007;75(3):168; *Perspect Sex Reprod Health* 2006;38(2):90). A 2006 study from Italy indicated that the rate of unintended pregnancy among HIV infected women on ART was 57.6% (*Antivir Ther* 2006;11(7):941). A 2007 study of more than 1000 HIV infected pregnant adolescents in the United States found that 83.3% of those pregnancies were unplanned (*Am J Obstet Gynecol* 2007;197(3 Suppl):S123). The majority of pregnancies reported by HIV infected women in the WIHS from 1994 to 2005 occurred in women who were not seeking to conceive

(*AIDS* 2004;18:281). Recent studies have also suggested that ART increases or restores fertility, particularly in those with higher CD4+ cell counts and a good immunologic response to therapy (*AIDS Res Treat* 2011:2011:519492).

Because of advances in HIV treatment, many perinatally infected adolescents are now reaching sexual maturity and may be at particular risk for unplanned or unintended pregnancy. A report on 174 perinatally HIV infected and sexually active girls older than 13 years found that by age 19, 24.2% had been pregnant at least once and some more than once (*Am J Public Health* 2007;97:1047).

Reasons for unintended pregnancy: Women who are not using contraception of any type do not necessarily intend to become pregnant. Other reasons for unintended pregnancy include the following:

- Power imbalance in a sexual relationship

- Pressure from partner and/or family to have children

- Fear of abandonment that results in lack of disclosure and, often, nonuse of condoms or other contraception

- Belief that one cannot become pregnant

- Lack of awareness of contraception options

- Disorganized lifestyle that precludes consistent use of condoms and/or contraception

- Decision to take one's chances

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Increased risk for unintended pregnancy: Women who are in any of the groups listed below are at increased risk for unintended pregnancy (*Fam Plann Perspect* 1998;30:24; *Perspect Sex Reprod Health* 2006;38(2):90):

- Adolescents

- Aged >40 years

- Poor and less educated

- Unmarried but cohabiting

- Mentally ill or mentally retarded

- Victims of domestic violence

- Abusers of drugs or alcohol

- Those with HIV-associated cognitive impairment

Unplanned does not mean unwanted: An unplanned pregnancy is not necessarily an unwanted pregnancy. In the WIHS cohort, abortion was significantly less likely in the era of effective ART than it was in the pre-ART era. Further, abortion rates among HIV infected women were not significantly different from abortion rates among high-risk uninfected women in the ART era (*AIDS* 2004;18(2):281-6). Unintended pregnancy is a predictor, however, for pregnancy termination among women with HIV (*AIDS Care* 2010;22(1):50).

Contraception

The goals of contraception are to prevent unintended pregnancy or to delay pregnancy until it is desired. Women with HIV infection should have access to effective contraception and can use all available methods. Decisions regarding contraceptive options in HIV infected women require thoughtful discussions with the patient and with her partner if appropriate; however, the high proportion of HIV infected women who report unintended pregnancy or who conceive while using contraception suggests that this counseling is not taking place or is not sufficient. A number of barriers to contraceptive counseling have been identified. For example, women may have more immediate and pressing needs that consume the time allocated for clinic visits or preclude an in-depth discussion of contraception. Care providers may not be trained to provide contraceptive counseling.

Additional challenges to contraception use occur when women experience side effects from contraception that they were not prepared for and don't know how to manage or when they do not have enough power to control the use of contraception in an intimate relationship.

Between 1994 and 2005, 2784 women enrolled in WIHS were asked every 6 months about their use of contraception. About one-third of women reported using barrier methods; approximately one-quarter reported using sterilization; and <10% reported using hormonal methods. Use of dual protection—barrier method plus a more effective method of contraception—was low but did increase somewhat over time. Use of no method of contraception was reported in >30% of visits, even though 40% of these women reported sexual activity during the previous 6 months.. Use of all forms of contraception decreased with age and behavior change was minimal over time despite long-term study participation and study participant exposure to a variety of health messages (*J Women's Health* 2007;16(5):657). Other studies have found that condom use among women rises substantially after a diagnosis of HIV (*J Acquir Immune Defic Syndr* 2005;39(4):446)

Considerations in the Choice of a Contraceptive Method

When choosing the most appropriate contraceptive method for themselves and their partners, women should be encouraged to consider several factors, described below. Voluntary informed choice and respectful contraceptive counseling are important to the successful choice and use of contraceptive methods. One effective approach is motivational interviewing (Table 7-2), a client-centered and goal-directed style of counseling that incorporates sensitivity to the patient's current stage of change (*Addict Behav* 1985;10(4):407; *J Consult Clin Psychol* 1988;56(4):520). When appropriate, it is desirable to include the partner in the conversation about contraceptive choice because partner involvement may increase successful and sustainable use of the method.

Table 7-2

Motivational Interviewing for Contraception Counseling

Stage of Change	Counseling and Goal Setting for Condom Use	Counseling and Goal Setting for Prevention of Unwanted Pregnancy
Pre-Contemplation: Patient sees no need to engage in the target behavior ("No way...")	Review information about condom use and consequences of not using condoms.	Review information about contraception and the consequences of not using contraception; prescribe EC.
Contemplation: Patient sees the need to engage in the target behavior, but barriers preclude readiness for action (Yes, but...")	Discuss pros and cons of condom use and ask patient to plan to use them during 3 of the next 5 sexual acts she engages in.	Discuss barriers to contraception use and ways to overcome them and plan initiation of contraception use.\n\nReview contraception choices; plan to review again at next visit; elicit patient's agreement to choose a method at next visit and reinforce use of EC.
Ready for Action: Patient is ready to engage in the target behavior and may already be trying the new behavior ("Let's do it...")	Ask patient to use condoms during 4 of next 5 sexual acts, and help patient practice negotiating use of condoms.	Discuss the importance of consistent use of contraception; prescribe the patient's method of choice and prescribe EC.
Action: Patient has been engaging in the target behavior for 3 to 6 mo ("Doing it...")	Ask patient to plan to use condoms during all 5 of next 5 sexual acts and discuss results of negotiations about condom use.	Discuss patient's experience with contraception use; plan ways to solve future problems, such as the need to obtain refills, how to use EC if doses are missed, and how to handle missed appointments.
Maintenance: Patient has been engaging in the target behavior for more than 6 mo ("Living it...")	Provide positive reinforcement for consistent condom use and discuss relapse prevention.	Provide positive reinforcement for consistent contraception use, and discuss prevention of imperfect use.

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

An ideal strategy for HIV infected women is simultaneous protection against both unintended pregnancy and HIV transmission or STI acquisition or transmission, often called "dual protection." Dual protection can be accomplished through avoidance of penetrative sex, condom use alone, or use of condoms in combination with another more effective method of contraception.

In general, HIV infected women can use all available contraceptive methods. Condom use, while less effective at preventing pregnancy than other contraceptive methods, is the only method that reduces the risk of HIV/STI transmission or acquisition. Dual protection may be optimal, particularly for serodiscordant couples, although this approach does have both pros and cons that should be considered and discussed with a patient during contraceptive counseling.

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Advantages of Dual Protection	Disadvantages of Dual Protection
• Condoms alone have a higher failure rate in prevention of pregnancy than most other methods of birth control.	• Possible reduction in consistent condom use
• Hormonal methods may have significant noncontraceptive benefits, such as a decrease in iron deficiency anemia, decreased risk of PID, and decreased risk of some cancers.	• Potential negative effect on ART adherence (less of a concern with non-oral hormonal delivery systems)
• HIV infected women may be taking medications that have teratogenic potential (e.g., EFV, warfarin, tetracyclines, statins) and need more reliable contraception than is provided by condoms alone.	• Adverse effects and/or safety considerations or contraindications with hormonal methods
• Seroconcordant couples may be less likely to use condoms consistently, while also wishing to prevent pregnancy.	
• Drug interactions between hormonal contraceptives and ART may decrease contraceptive effectiveness, creating a greater need for use of a back-up method.	

Factors to consider when helping a woman choose the best method of contraception for herself and her partner include the following:

• Age

• Childbearing plans (i.e., does she need contraception that is temporary or permanent, short-term or long-term?)

• Cost

• Convenience and ease of use

• Side effects and toxicity

• Efficacy

• Effect on HIV transmission

• Effect on HIV progression

• Noncontraceptive benefits

• Protection against STIs

• Other medical conditions

• Acceptability and accessibility

• Drug interactions

Contraception works best if a woman likes it and if it makes practical sense for her. When choosing the best method, a patient's patterns of adherence to ART and other medications as well as her adherence with clinic visits may serve as predictors of her success with particular contraceptive methods.

Contraceptive decision making should take into consideration current medications, including ART, as well as fetal safety should contraception fail. EFV is the only current ARV agent that is a proven teratogen. Anencephaly,

anophthalmia, microphthalmia, and cleft palate were seen in primates at exposures comparable to those in humans, and there are retrospective case reports and one prospective report of CNS defects in infants of women who received EFV at conception and during the first trimester (Sustiva drug label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020972s03 5,021360s023lbl.pdf. Accessed 4/9/12; Antiretroviral Pregnancy Registry. Interim Report. December 2011. http://www.apregistry.com/forms/interim_ report.pdf. Accessed 4/9/12)

EFV is the only ARV agent labeled as FDA pregnancy category D ("positive evidence of human fetal risk based on adverse reaction data from investigational and marketing experiences, but the potential benefits from the use of the drug among pregnant women might be acceptable despite its potential risks"). The absolute risk after early exposure to EFV may be low, however; a recent meta-analysis found no increased risk of overall birth defects among women exposed to EFV compared with other ARVs during the first trimester (*AIDS* 2011;25(18):2301). Nevertheless, EFV should be avoided in women who are trying to become pregnant or who do not or cannot use effective contraception consistently (*Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States.* September 14, 2011. http://aidsinfo.nih.gov/contentfiles/PerinatalGL.pdf. Accessed 4/4/2012). Long-acting contraceptive methods may be more desirable for women on EFV-containing regimens (*Curr HIV/AIDS Rep* 2007;4:135).

Medications taken for treatment of other medical conditions must be considered as well. In some cases, these medications are FDA category D or category X ("risk for pregnant women clearly outweighs any possible benefit").

In 2010, the CDC released *U.S. Medical Eligibility Criteria for Contraceptive Use* as evidence-based guidelines for the use of different contraceptive methods in the setting of different medical conditions, including HIV. The four categories identified by the CDC are used in the discussion of contraceptive choice in this chapter (*MMWR Recomm Rep* 2010;59(RR-4);1).

- Category 1: a condition for which there is no restriction on the use of the contraceptive method

- Category 2: a condition for which the advantages of using the method generally outweigh the theoretical or proven risks

- Category 3: a condition for which the theoretical or proven risks usually outweigh the advantages of using the method

- Category 4: a condition that represents an unacceptable health risk if the contraceptive method is used

Contraceptive effectiveness depends on both the inherent effectiveness of a method and the need for independent action by the user. Methods that require remembering to take a pill every day will have lower efficacy with typical use than methods with theoretically similar effectiveness that require keeping an appointment for an injection once every 3 months. The relative effectiveness of various contraceptives is outlined in Table 7-3.

Table 7-3

Contraceptive Methods

Method and Convenience	Pregnancies in Year 1 of Typical Use and Perfect Use, %	Contraindications (CDC Category 3 or 4)	Potential Side Effects	Benefits	Disadvantages
COMBINED ORAL CONTRACEPTIVE PILL Use is independent of sexual intercourse	• Typical: 8 • Perfect: 0.3	• History of DVT, stroke, ischemic heart disease • HTN • Hyperlipidemia (depending on type, severity, other risk factors) • Aged >35 y and smoker • Multiple risk factors for arterial cardiovascular disease (e.g., older age, smoking, DM, HTN) • Complicated valvular heart disease • Migraine, especially with aura or in women >35 y • Severe liver cirrhosis, acute hepatitis • Hepatocellular adenoma • DM with nephropathy, retinopathy, neuropathy, or vascular disease • Breast cancer • Major surgery with immobilization • Current gallbladder disease • Postpartum <3 wk	• Nausea • Headache • Weight gain • Dizziness • Breast tenderness • Vaginal spotting • Chloasma • Depression	• Decreased menstrual pain, PMS, and blood loss • May reduce acne • Decreased benign breast disease • Decreased functional ovarian cysts • Decreased ovarian and endometrial cancers • Decreased PID	• No STD protection • May increase susceptibility to some STDs • Must remember to take pill daily • Some ARV agents may decrease or increase bioavailability of ethinyl estradiol and/or progestin component

Table 7-3 *continued*

Contraceptive Methods

Method and Convenience	Pregnancies in Year 1 of Typical Use and Perfect Use, %	Contraindications (CDC Category 3 or 4)	Potential Side Effects	Benefits	Disadvantages
COMBINED ESTROGEN/ PROGESTIN VAGINAL RING (Nuva Ring) Use is independent of sexual intercourse. Vaginal ring is inserted for 3 wk out of every mo. Precise placement is not required.	• Typical: 8 • Perfect: 0.3	• Same as for OCs	• Similar to OCs • Possible increased vaginal discharge	• Same as for OCs	• Confers no STD protection, and may increase susceptibility to some STDs
COMBINED ESTROGEN/ PROGESTIN PATCH (Ortho Evra) Use is independent of sexual intercourse. Patch is applied weekly for 3 of 4 wk.	• Typical: 8 • Perfect: 0.3	• Same as for OCs	• Similar to OCs • Skin irritation	• Same as for OCs • Improved user compliance	• No STD protection • May increase susceptibility to some STDs
DMPA Often causes amenorrhea. Requires only 4 injections per year. Requires no ongoing action by user. Use is independent of sexual intercourse.	• Typical: 3 • Perfect: 0.3	• Breast cancer • Unexplained vaginal bleeding • Multiple risk factors for arterial cardiovascular disease (e.g., older age, smoking, DM, HTN) • Ischemic heart disease, stroke	• Menstrual changes (spotting, irregular bleeding, amenorrhea) • Decreased bone density with long-term use • Weight gain • Breast tenderness • Headache • Adverse effect on lipids • Depression	• May have protective effects against PID, ovarian and endometrial cancer • Decreased blood loss, anemia • Amenorrhea • No interaction with ART established, but data are limited	• No STD protection

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Table 7-3 *continued*					
Contraceptive Methods					
Method and Convenience	**Pregnancies in Year 1 of Typical Use and Perfect Use, %**	**Contraindications (CDC Category 3 or 4)**	**Potential Side Effects**	**Benefits**	**Disadvantages**
ETONOGESTREL IMPLANT (Implanon®) Lasts 3 y. Removal is easier than earlier implant (Norplant). Requires no ongoing action by user. Use is independent of sexual intercourse.	• Typical: 0.5 • Perfect: 0.5	• Unexplained vaginal bleeding • Breast cancer • Severe liver disease, tumors • Ischemic heart disease, stroke	• Tenderness or infection at site • Menstrual changes (spotting, irregular bleeding, amenorrhea • 1/3 of women have amenorrhea after 1 y • Weight gain • Breast tenderness • Depression	• Same as above	• No STD protection • Requires office insertion • Costs $400–$800
PROGESTIN-ONLY PILL Use is independent of sexual intercourse	• Typical: 1.1–13.8 • Perfect: 0.5	• Unexplained vaginal bleeding • Breast cancer • Severe liver disease, tumors • Ischemic heart disease, stroke	• Menstrual changes (spotting, irregular bleeding, amenorrhea) • Breast tenderness • Depression • Weight gain	• Same as above	• No STD protection • Ectopic pregnancy more likely with progestin-only pills than with other forms of hormonal contraception • Must remember to take pill daily • Potential drug interactions with certain seizure medications, rifampin/rifabutin, RTV-boosted PIs
CONDOM, MALE (LATEX, POLYURETHANE, NATURAL MEMBRANE) Inexpensive and readily available. Use does not require a prescription.	• Typical: 15 • Perfect: 2	• Allergy to latex condom material	• Allergy or sensitivity to latex material • Decreased sensitivity	• Protects against STDs, including HIV (except for natural membrane) • Delays premature ejaculation	• Requires partner cooperation • Possible loss of spontaneity during sex

Table 7-3 *continued*

Contraceptive Methods

Method and Convenience	Pregnancies in Year 1 of Typical Use and Perfect Use, %	Contraindications (CDC Category 3 or 4)	Potential Side Effects	Benefits	Disadvantages
CONDOM, FEMALE Woman controlled. Less likelihood of breakage. Can be inserted up to 8 h before intercourse. Use does not require a prescription.	• Typical: 21 • Perfect: 5 • Data are limited	• Polyurethane allergy (rare)	• Allergy or sensitivity to polyurethane • Possible decreased sensitivity	• Protects against STDs, including HIV	• May be awkward to use • Aesthetically unappealing to some
CERVICAL CAP — PAROUS/ NONPAROUS Woman controlled. Can be inserted ahead of time.	• Typical: 36 (parous)/ 18 (nonparous) • Perfect: 26/9	• Latex allergy • Abnormal cervical/ vaginal anatomy • History of TSS or recurrent UTIs • Known or suspected cervical/uterine malignancy • Abnormal Pap smear • Vaginal or cervical infection • Recent delivery or spontaneous or induced abortion	• Pelvic pressure • Vaginal irritation • Allergy or sensitivity to latex • Vaginal or urinary tract infections	• Limited STD protection	• Efficacy based on high motivation • Spermicide re-application required with each act of coitus • Should not be used during menses • Spermicide may increase HIV acquisition and transmission
DIAPHRAGM Woman controlled. Can be inserted up to 6 h before intercourse.	• Typical: 16 • Perfect: 6	• Latex allergy • Abnormal vaginal anatomy • History of TSS or recurrent UTIs	• Same as above	• Limited STD protection • Reduces risk of PID	• No protection against HIV transmission

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Table 7-3 *continued*

Contraceptive Methods

Method and Convenience	Pregnancies in Year 1 of Typical Use and Perfect Use, %	Contraindications (CDC Category 3 or 4)	Potential Side Effects	Benefits	Disadvantages
SPERMICIDES Woman controlled. Use does not require a prescription. Easily available and inexpensive.	• Typical: 29 • Perfect: 18	• Allergy to nonoxynol-9 • HIV/AIDS (CDC category 3)	• Vaginal irritation • Allergy • Vaginal and urinary tract infection	• Protection against some STDs, with significant protection against gonorrhea and chlamydia. • In vitro activity against HIV	• Efficacy reduced when used without a barrier method • Increased susceptibility to HIV with frequent sexual activity • No protection against HIV
IUD (copper-Paragard®) Provides contraception for 10 y. Requires no ongoing user action.	• Typical: 0.8 • Perfect: 0.6	• Unexplained vaginal bleeding • Recent (within 3 mo), recurrent, or active pelvic infection • Postpartum, postabortion endometritis • Active STD • Women at increased risk for STDs • Severely distorted uterine cavity	• Menstrual cramping • Increased bleeding • Risk of PID and uterine perforation following insertion • Anemia	• No increase in pelvic infection with HIV	• No STD protection • Increased risk of PID
LEVONORGESTREL INTRAUTERINE SYSTEM (Mirena) Provides contraception for 5 y. Requires no ongoing user action.	• Typical: 0.2 • Perfect: 0.2	• Unexplained vaginal bleeding • Breast cancer • Active pelvic infection/STDs • Severe liver disease/tumor • Distorted uterine cavity	• Increased incidence of irregular bleeding in first 6 mo compared with copper IUD • Risk of PID and uterine perforation following insertion	• Overall reduction in menstrual blood loss (20% amenorrhea after 1 y) and cramping • Possible decreased rates of anemia, PID • No increase in pelvic infection with HIV	• No STD protection

Table 7-3 *continued*

Contraceptive Methods

Method and Convenience	Pregnancies in Year 1 of Typical Use and Perfect Use, %	Contraindications (CDC Category 3 or 4)	Potential Side Effects	Benefits	Disadvantages
FEMALE SURGICAL STERILIZATION Provides permanent contraception. Requires no ongoing user action.	• Typical: 0.5 • Perfect: 0.5	• Desire for future fertility • Active pelvic infection	• Pain at surgical site • Subsequent regret • Increased risk of ectopic pregnancy if sterilization not achieved	• Possible decreased risk of ovarian cancer • Decreased risk of salpingitis	• Permanent • No STD protection • Requires anesthesia • Surgical procedure in OR
TRANSCERVICAL FEMALE STERILIZATION (Essure®, Adiana®, data more limited for Adiana but suggest somewhat higher failure rate) Provides permanent contraception. Requires no ongoing user action. Lower cost; does not require incision or general anesthesia; may be performed in physician's office. Decreased risk of intra-abdominal injury.	• Typical: 0.2–0.4 • Perfect: 0.2–0.4	• Desire for future fertility • Active pelvic infection	• Subsequent regret • Increased risk of ectopic pregnancy if sterilization not achieved • Cramping, nausea, vomiting with placement • Expulsion or uterine perforation (<3%)	• Probably similar to surgical sterilization (experience limited)	• Permanent • No STD protection • Requires use of alternate contraception for 3 mo • For Adiana, requires confirmation of tubal occlusion by hysterosalpingography (Essure can be visualized radiographically)
MALE STERILIZATION Provides permanent sterilization for the man	• Typical: 0.15 • Perfect: 0.10	• Desire for future fertility	• Pain at surgical site • Subsequent regret	• None	• Same as above, except sterility not immediate

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Table 7-3 *continued*

Contraceptive Methods

Method and Convenience	Pregnancies in Year 1 of Typical Use and Perfect Use, %	Contraindications (CDC Category 3 or 4)	Potential Side Effects	Benefits	Disadvantages
EMERGENCY CONTRACEPTION Levonorgestrel 0.75mg (Plan B); levonorgestrel 0.25mg/ ethinyl estradiol 50 mcg (Preven); ulipristal acetate 30 mg single dose (marketed for EC as Ella®) Can be used after unprotected intercourse or with other contraceptive failure (e.g., condom breakage). Treatment should be initiated as soon as possible to maximize effectiveness and is generally recommended within 72 h after intercourse. Ulipristal given as single dose for EC is effective up to 120 h (5 d) after unprotected intercourse.	• Typical: 3.2 (57% of expected pregnancies prevented) • Perfect: 1.1 (85% of expected pregnancies prevented) • Effectiveness of ulipristal is similar to that of levonorgestrel in first 72 h and superior 72–120 h after unprotected sex	• Established pregnancy	N/A	N/A	• No STD protection • Nausea and vomiting common with levonorgestrel/ethinyl estradiol combination (30–60%); prophylactic antiemetics may be beneficial • Failure rate higher with intercourse during fertile phase of cycle • Ulipristal more expensive than other EC options

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Source: *MMWR Recomm Rep* 2010;59(RR-4);1; *Contraceptive Technology*, 19th ed, 2007

Condoms

The consistent use of male or female condoms protects against HIV and other STD transmission and acquisition and provides contraception. It is the only contraceptive method that provides dual protection against both HIV infection and pregnancy. Therefore, these two issues should be separately discussed when counseling patients. Condom use also should be reinforced for HIV infected women when prevention of pregnancy is not an issue (i.e., postmenopause, during pregnancy, after sterilization, when a woman is infertile, or for use with a more effective contraceptive method).

The female condom is less likely than the male condom to break or leak during sex; however, intrusion of the outer vaginal ring that covers the introitus into the vagina occurs in 2% of cases, allowing potential insertion of the penis between the condom and vaginal wall (*Sex Transm Infect* 2004;80:167). Some couples also complain about noise during sex; however, women who receive instruction about use of the female condom and are given the opportunity to practice its use in the clinical setting have an increased likelihood of using the device correctly and viewing it favorably (*Am J Public Health* 2002;92:109). Counseling during the early adoption phase and an increased sense of power in negotiating for safe sex have been linked to increased acceptability and adoption of the female condom (*AIDS Behav* 2006;10(4 Suppl):S67).

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Spermicides

Standard spermicidal doses of nonoxynol-9 (N-9) have been associated with an increase in irritation, colposcopic and histologic evidence of inflammation, and decreased numbers of vaginal lactobacilli as compared with placebo recipients (*J Acquir Immune Defic Syndr Hum Retrovirol* 1998;17:327). A randomized placebo-controlled clinical trial of an N-9 vaginal gel conducted in four countries among commercial sex workers with high rates of sexual activity did not demonstrate protection against HIV; instead, HIV transmission was increased among those who used the N-9–containing gel more frequently (*Lancet* 2002;360:971). A meta-analysis of randomized controlled trials of N-9 use found no evidence of protection against HIV acquisition (*Cochrane Database Syst Rev* 2002;(4):CD003936). N-9 also appears to offer no protection against STDs such as gonorrhea or chlamydia (*Reprod Health Matters* 2002;10(20):175). Newer spermicides that cause less inflammation are being tested for their potential to decrease the risk of HIV transmission. In the setting of HIV/AIDS, spermicides that may disrupt vaginal or cervical mucosa and potentially increase viral shedding and risk to uninfected partners are assigned to CDC category 3 (risk generally outweighs advantages).

Hormonal Contraception

Combined estrogen/progestin contraceptives: Studies of oral combined estrogen/progestin contraceptives and several ARVs have found drug interactions (primarily through the cytochrome p450 [CYP] 3A4 system) that resulted in an increase or decrease in levels of estrogen and/or progestin (Table 7-4). One study demonstrated a decrease in ARV blood level

(*Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. January 10, 2011. Available at http://www.aidsinfo.nih.gov/ ContentFiles/AdultandAdolescentGL.pdf. Accessed 4/4/12). To date, data on these interactions are primarily pharmacokinetic and the true clinical effect is not clear. The concern is that effectiveness may be decreased, breakthrough bleeding may occur (with decreased hormonal levels), or rates of adverse effects may increase (with increased hormonal levels), although these outcomes have not been confirmed. Only with FPV, which is metabolized to APV, does the drug-drug interaction also reduce the concentration of the ARV. Unboosted FPV should not be co-administered with hormonal contraceptives (HCs). There is minimal information about drug interactions with the use of alternative delivery methods for estrogen/progestin contraceptives (i.e., transdermal patch, intravaginal ring), although a recent study suggests that these delivery methods may also be vulnerable to drug interactions and that different progestins (e.g., norethindrone vs norelgestromin) may be affected differently in interaction with specific ARV agents (*J Acquir Immune Defic Syndr* 2010;55(4):473). Although data are lacking on the safety and efficacy of altering hormonal dosages in an effort to circumvent these interactions, a preparation containing a minimum of 30 mcg ethinyl estradiol is suggested.

Table 7-4

Drug Interactions Between Antiretroviral Therapy and Hormonal Contraception

	Effect on Antiretroviral or Hormonal Drug Concentrations	Dosing Recommendations for Hormonal Contraceptives and Clinical Comments
NRTIs	No effect on hormonal levels	No dosage adjustment is necessary
RTV-Boosted PIs		
ATV/r	Ethinyl estradiol ↓ 19% Norgestimate ↑ 85%	Use alternative or additional method
DRV/r	Ethinyl estradiol AUC ↓ 44% Norethindrone AUC ↓ 14%	Use alternative or additional method
FPV/r	Ethinyl estradiol AUC ↓ 37% Norethindrone AUC ↓ 34%	Use alternative or additional method
LPV/r	Ethinyl estradiol AUC ↓ 42% Norethindrone AUC ↓ 17% Norelgestromin (transdermal patch) AUC ↑ 83%	Use alternative or additional method
SQV/r	↓ Ethinyl estradiol	Use alternative or additional method
TPV/r	Ethinyl estradiol AUC ↓ 48% Norethindrone: no significant change	Use alternative or additional method
Unboosted PIs		
Indinavir (IDV)	Ethinyl estradiol AUC ↑ 25% Norethindrone AUC ↑ 26%	No additional contraceptive protection needed
Nelfinavir (NFV)	Ethinyl estradiol AUC ↓ 47% Norethindrone AUC ↓ 18%	Use alternative or additional method

Table 7-4	*continued*

Drug Interactions Between Antiretroviral Therapy and Hormonal Contraception

	Effect on Antiretroviral or Hormonal Drug Concentrations	Dosing Recommendations for Hormonal Contraceptives and Clinical Comments
ATV	Ethinyl estradiol AUC ↑ 48% Norethindrone AUC ↑ 110%	No additional contraceptive protection needed Oral contraceptive should contain no more than 30 mcg of ethinyl estradiol, or use alternative method. Oral contraceptives containing <25 mcg of ethinyl estradiol or progestins other than norethindrone or norgestimate have not been studied.
FPV	With APV: ↑ ethinyl estradiol and ↑ norethindrone; ↓ APV 20%	Use alternative method
NNRTIs		
EFV	Ethinyl estradiol no change Levonorgestrel AUC ↓ 83% Norelgestromin AUC ↓ 64% With levonorgestrel alone (not as part of combined estrogen/progestin contraceptive, levonorgestrel AUC ↓ 58% Implant: ↓ etonogestrel	Use alternative or additional methods Norelgestromin and levonorgestrel are active metabolites of norgestimate Effectiveness of emergency postcoital contraception may be diminished
ETR	Ethinyl estradiol AUC ↑ 22% Norethindrone: no significant effect	No additional contraceptive protection needed
NVP	Ethinyl estradiol AUC ↓ 20% Norethindrone AUC ↓ 19%	May consider alternative or additional methods
	DMPA: no significant change	No additional contraceptive protection needed
RPV	Ethinyl estradiol AUC ↑ 14% Norethindrone: no significant change	No additional contraceptive protection needed
CCR5 Antagonist		
MVC	No significant effect on ethinyl estradiol or levonorgestrel	No additional contraceptive protection needed
Integrase Inhibitor		
RAL	No clinically significant effect on ethinyl estradiol or levonorgestrel	No additional contraceptive protection needed
Elvitegravir/ Cobicistat	Norgestimate AUC ↑ 2.26 Ethinyl estradiol AUC ↓ 0.75	No additional contraceptive protection needed

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Source: Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.* January 10, 2011; Tables 15a, 15b, and 15d

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Concerns about drug interactions should not cause providers to avoid prescribing combined estrogen/progestin HC, but should prompt close follow-up and thorough counseling about additional or alternative contraceptive methods. The consistent use of condoms is recommended to prevent HIV transmission or other STI acquisition and to compensate for any possible reduction in the effectiveness of the HC.

Other medications are also known to interact with combined estrogen/progestin HCs (and in some cases with progestin-only contraceptives) and may require consideration of alternative and/or additional contraceptive methods and/or dose adjustment for the interacting agent, when appropriate (*Contraceptive Technology,*19th ed, 2007).

Drugs that alter estrogen and/or progestin levels and may reduce the effectiveness of HC:

- Anticonvulsant agents (i.e., phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine) used with combined estrogen/progestin methods or progestin-only pills

- Lamotrigine (if used as single agent) used with combined estrogen/progestin methods

- Rifampin or rifabutin used with combined estrogen/progestin methods, progestin-only pills, or progestin implants

- St. Johns wort used with combined estrogen/progestin methods or progestin-only pills

Recommendation: Use an alternative or additional method. If a combined oral estrogen/progestin method is used, use a formulation containing a minimum of 30 mcg ethinyl estradiol.

Drugs that may require dose adjustment and/or monitoring of drug effect when used with combined estrogen/progestin HC:

- Fluoroquinolones, some anticonvulsants (reduced drug levels)

- Theophylline, diazepam, chlordiazepoxide, tricyclic antidepressants (increased drug levels)

Recommendation: Monitor drug levels when available; dose may need to be increased.

Among HIV infected women, the use of combined estrogen/progestin contraceptives may be contraindicated because of comorbidities such as smoking or hypertension, common in this population. Because chronic viral hepatitis is a frequent comorbidity in the setting of HIV, the concomitant use of combined HCs is of special interest. Data suggest that in women with chronic hepatitis, combined hormone use does not increase the rate or severity of cirrhotic fibrosis, nor does it increase risk for hepatocellular carcinoma. In general, though, these methods should not be used in women with severe liver cirrhosis, acute hepatitis, or liver tumors.

Progestin-only contraceptives: Although data are limited, there is no evidence of significant drug interactions between depot medroxyprogesterone acetate (DMPA) and ARVs. The clinical profile associated with DMPA administration was examined in women on regimens containing NFV, EFV, or NVP and appeared similar to that observed in HIV uninfected women. DMPA prevented ovulation and did not affect CD4+ cell counts or HIV RNA levels in HIV infected women when compared with women on NRTIs only or no ARVs (*Contraception* 2008;77:84). Another study found no DMPA pharmacokinetic differences between 15 women on ZDV, 3TC, and EFV and 15 women on no ART (*Fertil Steril* 2008;90(4):965). The *U.S. Medical Eligibility Criteria* classify DMPA with HIV/AIDS as Category 1 (*MMWR Recomm Rep* 2010;59(RR-4);1). There are few data on drug interactions of progestin implants or progestin-only pills with ARVs and recommendations by experts are generally the same as for combined hormonal contraceptives.

Long-term use of DMPA has been associated with diminished bone mineral density (BMD), although recent studies indicate that the rate of bone loss is greatest in the first 24 months of use and decreases thereafter; furthermore, current evidence suggests that partial or full recovery of bone mass occurs after discontinuation of DMPA (*Fertil Steril* 2006;86:1466; *Contraception* 2006;74:90). There have been no randomized controlled trials of DMPA and fracture risk. Decreased BMD is more common among people with HIV infection and has been associated with the use of a variety of ARVs, in particular d4T and TDF. Although no studies have examined BMD and DMPA use in the setting of HIV infection, the efficacy of DMPA—particularly in adolescents or others who may have difficulty adhering to a contraceptive method—must be balanced against possible adverse effects on bone density. ACOG has stated that "concerns regarding the effect of DMPA on BMD should neither prevent practitioners from prescribing DMPA nor limit its use to 2 consecutive years." (ACOG Committee Opinion #415. September 2008. Available at http://www.acog.org/Resources_And_Publications/Committee_Opinions/Committee_on_Adolescent_Health_Care/Depot_Medroxyprogesterone_Acetate_and_Bone_Effects. Accessed 7/9/12). Daily exercise and appropriate calcium and vitamin D intake should be encouraged.

Hormonal contraception and HIV progression: Data from prospective and cohort studies conflict on the effect of HC (combined estrogen/progestin or DMPA) on HIV progression, defined as progression to AIDS or death (*Clin Infect Dis* 2008;47:945; *J Acquir Immune Defic Syndr* 2011;56(2):125; *AIDS* 2010;24(12):1937; *AIDS* 2009; 23 Suppl 1:S69; *AIDS* 2007;21:749). Members of a cohort of Kenyan women who were taking DMPA at the time of HIV acquisition were found to have higher viral set points and a greater likelihood of multiple viral variants being detected shortly after infection (*Clin Infect Dis* 2006;42(9):1333); however, the use of hormonal contraception prior to seroconversion was not associated with higher viral set points in a Ugandan cohort (*J Acquir Immune Defic Syndr* 2011;56(2):125). Most of these studies did not have VL measurements for comparison. In both a longitudinal U.S. cohort and a prospective cohort in Kenya, however, HC was not associated with a change in VL over time as compared with women who were not using contraception (*AIDS* 2003;17(11):1702; *AIDS* 2007;21(6):749). In general, these studies did not include women on ART, but there is no reason to believe

that women on ART with suppressed HIV RNA levels would be at increased risk for HIV progression related to the use of HC. Given the availability of ARVs and the fact that most studies show no effect of HC on HIV progression, which would be expected to supersede a potential effect on untreated women, the full range of HC methods should continue to be available to women with HIV.

Hormonal contraception and HIV transmission and/or acquisition: Data on the role of HC in HIV susceptibility or infectiousness also conflict. Two large prospective studies have demonstrated a modestly increased risk of HIV acquisition associated with the use of combined oral estrogen/progestin and/or DMPA (*AIDS* 2004;18(16):2179; *AIDS* 2007;21(13):1771; *AIDS* 2010;24(11):1777). A recent secondary analysis of data from a large prevention trial among more than 3700 serodiscordant African couples demonstrated an increased risk of HIV seroconversion (both transmission and acquisition) associated with HC (primarily DMPA). Moreover, HIV infected women who transmitted to their uninfected male sex partners also had higher genital HIV VL, which has the potential to increase transmission (*Lancet Infect Dis* 2012;12(1):19). Other mechanisms with the potential for altering risk of transmission or acquisition include increased cervical ectopy with HC use, possible thinning of vaginal mucosa, alterations in vaginal flora or heightened susceptibility to other STIs, or other changes in local or systemic immunity (*Am J Reprod Immunol* 2011;65(3):302).

There are, however, also significant methodologic issues with most studies, including potential selection bias and confounding factors such as changes in HC use over time, presence of STIs (including HSV-2 serostatus), and dependence on self-report regarding actual use of HC, sexual behavior, and/or condom use (*Am J Reprod Immunol* 2011;65(3):302).

Although some data suggest that HC may increase HIV susceptibility or infectiousness, there is a critical need for safe and effective contraceptive methods for women who are at risk for or infected with HIV. Rather than discouraging the use of effective HC methods, these studies highlight the importance of dual protection with condoms to prevent both acquisition and transmission of HIV in women. Moreover, now that ART has been confirmed to effectively reduce sexual transmission among serodiscordant couples by 96% (*N Engl J Med* 2011;365(6):493), this intervention will be increasingly important to circumvent transmission of HIV, regardless of HC use. A recent update to the CDC's U.S. Medical Eligibility Criteria for Contraceptive Use 2010 reaffirmed the safety of hormonal contraceptives for women at high risk for HIV, but added a clarification for women using progestin-only injectables highlighting the inconclusive nature of the evidence around hormonal contraceptive use and risk for HIV acquisition among women, and strongly encouraging condom use and other measures to prevent HIV (*MMWR* 2012;61(24):449).

Intrauterine Devices

No association between the copper IUD (Cu-IUD) and risk of HIV acquisition or progression has been demonstrated (*Am J Obstet Gynecol* 2007;197(2):144; *Best Pract Res Clin Obstet Gynaecol* 2009; 23(2):263). Although data are

limited, there is also no evidence of higher risk from Cu-IUDs for overall complications or for pelvic infections in HIV infected women in general or when stratified by CD4+ cell count (*BJOG* 2001;108(8):784; *Lancet* 1998;351:1238; *Am J Obstet Gynecol* 2007;197(2):144). Cu-IUD use also was not associated with an increased rate of cervical HIV shedding (*AIDS* 1999;13(15):2091).

In U.S. practice today, the Cu-IUD has largely been eclipsed by the levonorgestrel-releasing intrauterine system (LNG-IUD). The LNG-IUD is both highly effective as a contraceptive method and associated with reduced menstrual blood loss. It is an increasingly popular treatment for menorrhagia, dysmenorrhea, uterine fibroids, endometriosis, and adenomyosis, and also provides endometrial protection in women with or at risk for endometrial hyperplasia. Fewer data are available regarding the use of the LNG-IUD in women with HIV infection; however, a recent study comparing 15 women using the LNG-IUD with 25 age- and CD4+ cell count–matched controls followed for 5 years found no unplanned pregnancies or pelvic infections among the IUD users and no difference in CD4+ cell counts over the follow-up period compared with controls. LNG-IUD use was associated with an increase in hemoglobin levels, which remained higher over time than those of controls (*Am J Obstet Gynecol* 2011;204(2):126.e1). In another study, genital shedding of HIV RNA was not affected by LNG-IUD use and estradiol levels remained in the follicular range in all women (*Hum Reprod* 2006;21(11):2857). Although no data address the issue of drug interactions with ARV agents in the setting of LNG-IUD use, interactions would be expected to be minimal, given the low levels of systemic absorption of LNG.

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Emergency Contraception

Emergency contraception (EC) is the use of a drug or device to prevent pregnancy after unprotected intercourse or contraceptive failure (e.g., condom breakage). EC works by inhibiting or delaying ovulation. It also may interfere with sperm transport, impair corpus luteum function, or inhibit implantation. Since EC does not act after implantation and establishment of pregnancy, it is not considered an abortion method (*NEJM* 1997;337(15):1058). While EC should be initiated as soon as possible after unprotected intercourse to maximize efficacy, it should be made available for up to 5 days after unprotected intercourse to patients who request it. No clinician examination or pregnancy testing is necessary before provision of EC (ACOG Practice Bulletin No. 112; *Obstet Gynecol* 2010;115(5):1100). No data specifically on EC in the context of HIV or ARV treatment are available, but EC does not protect against STI acquisition or HIV transmission.

There are currently four EC options:

- **Progestin only:** Levonorgestrel (marketed for EC as Plan B, Plan B One-Step). The levonorgestrel-only regimens are more effective, with prevention of up to 85% vs 57% of expected pregnancies when compared with combined estrogen/progestin regimens (*Lancet* 1998;352:428). They also are associated with significantly less nausea and vomiting than the combined estrogen/progestin regimens. In the United States, both progestin-only regimens are available over the

counter (OTC) to women aged ≥17 years. Available pharmacokinetic data indicate that, compared with combined estrogen/progestin regimens, progestin-only regimens should cause fewer drug interactions with ARVs.

- Two-dose regimen: levonorgestrel 0.75 mg po, to be repeated 12–24 hours after the first dose

- One-dose regimen: 1.5 mg levonorgestrel

- **Combined estrogen–progestin regimens:** Nineteen combined estrogen/progestin oral contraceptives have been declared safe and effective for use as EC by the FDA (The Emergency Contraception Website. http://ec.princeton.edu/questions/dose.html. Accessed 4/9/12). All of the combined hormonal regimens require two doses taken 12 hours apart. Each dose contains two to six active hormonal (not placebo) pills, depending on the pill formulation, and includes ethinyl estradiol (total of 100–120 mcg) and levonorgestrel (total of 0.50–0.60 mg). As noted above, these regimens are less effective and more likely to cause nausea and vomiting than progestin-only regimens. If given, prophylactic antiemetics may be useful. The EC dose should be repeated if vomiting occurs within 2 hours of ingestion. If severe vomiting occurs, pills may be administered vaginally with effective absorption (*Contraception* 1987;36(4):471).

- **Progesterone agonist/antagonist:** Ulipristal acetate 30 mg single dose (marketed for EC as Ella®) was approved by the FDA in August 2010 for EC up to 120 hours (5 days) after unprotected intercourse (*Obstet Gynecol* 2010;115(2 Pt 1):257).

- **Copper IUD:** Although not currently FDA-approved specifically for EC, the Cu-IUD can be used for EC in women who meet the standard criteria for IUD insertion. It is most effective if inserted within 5 days after unprotected intercourse. The pregnancy rate with this method is 0% to 0.09% (*Hum Reprod* 2012;27:1994). This method has the advantage of providing long-term contraception in addition to EC. The LNG-IUD is not effective as EC (*J Fam Plann Reprod Health Care* 2004;30:99).

EC use should not be encouraged as a regular contraceptive method. Randomized controlled trials have not demonstrated a reduction in unintended pregnancy or abortion associated with access to EC (*Contraception* 2008;78(5):351). Condom use should be encouraged immediately after EC use; other short- or long-term hormonal methods may be initiated following the woman's next menstrual period, when it is clear that she is not pregnant. If menses are delayed by a week or more after the expected time or if lower abdominal pain or persistent irregular bleeding develops, clinical evaluation is indicated to evaluate for intrauterine or ectopic pregnancy.

Conclusions

HIV clinics are experienced in providing systems of care that address the multiplicity of concerns relevant to people with HIV infection. Integration of family planning services within primary HIV care is an additional strategy that can improve the lives of women with HIV. Establishing relationships with local family planning agencies can help to improve linkages to those services and improve access to safe and effective contraception. Integration of HIV services into family planning clinics should be considered as well. "Every woman [at] every visit" should be engaged in discussions concerning her intentions regarding pregnancy and her use of contraception. Integration of preconception counseling and contraceptive options must be an integral part of HIV primary care.

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Chapter 8:

HIV and Pregnancy

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Chapter 8: HIV and Pregnancy

Chapter 8 at a Glance

HIV and Pregnancy

With increasing numbers of HIV infected women, 80% of whom are of childbearing age, and concerns about perinatal transmission of HIV, pregnancy in the setting of HIV infection has been a focus of much interest, research, and, often, discrimination. The number of HIV infected women who become pregnant may grow with therapeutic advances in care and the prevention of vertical transmission and because new diagnoses of HIV are still often made in pregnancy. This chapter reviews issues related to pregnancy and discusses guidelines for care during pregnancy to optimize the health of both the mother and her baby.

Pregnancy Testing

Indications: For currently or recently sexually active women, pregnancy testing is indicated in the following circumstances:

- Missed menses, unless on etonogestrel (ETG)-releasing contraceptive implant, levonorgestrel (LNG) intrauterine device (IUD), or depot medroxyprogesterone acetate (DMPA)

- Irregular bleeding (unless on ETG-releasing implant, LNG-IUD or DMPA)

- New onset of irregular bleeding after prolonged amenorrhea on ETG-releasing implant, LNG-IUD, or DMPA

- New onset of pelvic pain

- Enlarged uterus or adnexal mass on exam

- Before instituting new therapies (consider)

Pregnancy tests are performed on blood or urine and may be qualitative (positive/negative) or quantitative. Quantitative tests are useful in early pregnancy when ectopic pregnancy or abnormal intrauterine pregnancy (e.g., missed abortion) is suspected. Several qualitative urine pregnancy tests are available over the counter. Most pregnancy tests in current use are positive before the first missed menses with normal intrauterine pregnancy. Table 8-1 lists types of available pregnancy tests and their sensitivity.

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Table 8-1			
Pregnancy Tests			
Type	**Source**	**Sensitivity**	**Comments**
Radioimmunoassay	Blood	Positive within 7 d of fertilization	Quantitative or qualitative; used to follow women with possible ectopic pregnancy
Enzyme immunoassay	Blood, urine	Positive approximately 10 d after fertilization	Available for home urine testing; positive results require confirmation
Antibody agglutination inhibition	Urine	Positive approximately 18–21 d after fertilization	False positives may occur with hypothyroidism, renal failure, immunologic disorders, increased luteinizing hormone

Effects of Pregnancy on HIV Infection

CD4+ cell count and HIV RNA levels: The CD4+ cell count response to pregnancy is variable in all women, whether HIV infected or not (*Obstet Gynecol 1997;89:967*). Many studies have suggested that a decline in absolute CD4+ cell count occurs in pregnancy; the count returns to baseline at the end of pregnancy or during the postpartum period. The decline is thought to be secondary to hemodilution because the percentage of CD4+ cells remains relatively stable. Therefore, percentage, rather than absolute number of CD4+ cells, may be a more accurate measure of immune function for HIV infected pregnant women (*AIDS Res Hum Retroviruses* 2007;23:1469; *AIDS* 1997;11:1859; *AIDS* 1995;9:1177).

HIV RNA levels (viral load [VL]) remain relatively stable throughout pregnancy in the absence of treatment (*Am J Obstet Gynecol* 1998;178:355). Recent data suggest, however, that HIV RNA levels increase during the postpartum period regardless of antiretroviral (ARV) treatment (although use of antiretroviral therapy [ART] appears to blunt the effect), possibly as a result of immune activation associated with hormonal changes or labor-induced cytokines (*Clin Vaccine Immunol* 2010;17:2024). The implications of increased VL on the risk of transmission and on treatment recommendations in the early postpartum period are unclear (*Clin Vaccine Immunol* 2010;17:2024). The increase in postpartum VL does not appear to reflect a long-lasting effect of pregnancy on VL (*Am J Obstet Gynecol* 2003;189:552).

Clinical Course of HIV: To date, most studies of the effects of pregnancy on HIV disease have not demonstrated significant differences in HIV progression or survival in HIV infected pregnant women. A meta-analysis of 7 prospective cohort studies found no significant differences between cases and controls in death, HIV disease progression, progression to an AIDS-defining illness, or decline in CD4+ cell count to <200/mm^{3} (*Br J Obstet Gynaecol* 1998;105:827). In a subsequently reported prospective study, 331 women with known dates of seroconversion were followed for a median of 5.5 years, during which time, 69 of the women were pregnant. No differences

in progression were found between those who were and were not pregnant during follow-up (*Arch Intern Med* 1997;157:2585). In addition, a long-term observational study showed no difference in VL, CD4+ cell count, or clinical disease progression in women with repeat pregnancies compared with women with one pregnancy (*Am J Obstet Gynecol* 2003;189:552).

Effect of HIV on Pregnancy Course and Outcome

Adverse outcomes: Adverse pregnancy outcomes may occur secondary to underlying disease processes or their treatment or for reasons that cannot be determined. In the United States, approximately 10% of pregnancies end prematurely and preterm birth is the leading cause of perinatal morbidity and mortality. No evidence supports a significant direct effect of HIV on pregnancy outcome; however, the effects of advanced disease, including anemia, malnutrition, and other HIV-related infections, may increase the risk of some adverse outcomes (*Br J Obstet Gynaecol* 1998;105:836; *AIDS* 1998;12:1087; *J Acquir Immune Defic Syndr* 2003;33:393; *Am J Clin Nutr* 2003;77:1337; *BJOG* 2001;108:1125; *J Acquir Immune Defic Syndr Hum Retrovirol* 1998;18:293; *J Coll Physicians Surg Pak* 2011;21:356; *BJOG* 2008;115:616; *Am J Obstet Gynecol* 2002;186:903; *Lancet* 1998;351:98; *Eur J Obstet Gynecol Reprod Biol* 2010;150:34). Moreover, HIV infected women may be at risk of adverse pregnancy outcomes as a result of an increased likelihood of other risks, such as use of tobacco, alcohol, and illicit drugs; presence of sexually transmitted infections (STIs); and poor perinatal care. If these other risk factors are controlled for, however, HIV infection has no independent effect on adverse outcomes (*AIDS* 2000;14:1389).

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A study of 497 HIV infected pregnant women enrolled in a perinatal clinical trial found that risk factors for adverse pregnancy outcomes (preterm birth, low birthweight, and intrauterine growth retardation) in ARV-treated women were similar to those reported for uninfected women (*AIDS* 2000;14:1389). Although concerns have been raised that ARV use may increase some adverse outcomes in pregnancy (see **Adverse Pregnancy Outcomes**, p. 300), the benefits of this therapy in reducing the risk of perinatal transmission far outweigh the risks. Results of a study comparing hospitalization among HIV infected pregnant women in the United States prior to and during the era of HAART indicate that rates of conditions responsible for increased hospitalization among HIV infected women decreased or remained stable after the introduction of ART (*J Acquir Immune Defic Syndr* 2006;43:186). Those conditions included major puerperal sepsis, genitourinary infections, influenza, bacterial infections, preterm labor/delivery, and liver disorders. Table 8-2 summarizes the relationship between common pregnancy-related complications and untreated HIV.

Table 8-2

Relationship of Adverse Pregnancy Outcomes to Untreated HIV Infection

Adverse Outcome	Relationship to Untreated HIV Infection
• Perinatal/infant mortality • Stillbirth	Evidence of increased risk in developing countries
• Chorioamnionitis	Most studies do not suggest an increased risk in clinical or histologic chorioamnionitis; however, evidence of possible increased risk in developing countries
• Group B strep infection • Intrauterine growth restriction • Spontaneous abortion	Evidence of possible increased risk
• Low birthweight (<2500 g) • Preterm delivery	Evidence of possible increased risk, especially with more advanced disease
• Fetal malformation • Gestational diabetes • Placental abruption • Placenta previa • Preeclampsia • Oligohydramnios	No evidence of increased risk

Effect of HIV and Pregnancy on Other Infections

Both HIV infection and pregnancy may affect the natural history, presentation, treatment, or significance of a number of infections, thereby causing complications in pregnancy or perinatal infection.

Vulvovaginal Candidiasis

Pregnancy is associated with both increased rates of colonization and increased symptomatic infections with species of *Candida*. HIV infection is also associated with increased rates of colonization and may be associated with increased infection rates, especially with declining immune function (*J Infect Dis* 2003;188:118; *Clin Infect Dis* 1997;24:201; *Obstet Gynecol* 1997;90:252; *Clin Infect Dis* 1998;27:1161). Therefore, HIV infected pregnant women may be particularly susceptible to yeast infections.

Treatment: Only topical azole agents should be used during pregnancy, and they should be given for at least 7 days. Prophylactic topical therapy should be considered during courses of systemic antibiotics.

Bacterial Vaginosis

Bacterial vaginosis (BV) has been associated with several adverse pregnancy outcomes, including preterm labor and birth, premature rupture of membranes, low-birthweight infants, chorioamnionitis and amniotic fluid infection, postpartum and postabortal endometritis, and perinatal HIV transmission. HIV infection has been associated with increased prevalence and persistence of BV, the prevalence, persistence, and severity of which increase as CD4+ cell counts decline (*Obstet Gynecol* 2001;98:656).

Screening: Because BV is more common in the setting of HIV, and because both BV and HIV have been linked to an increased risk of preterm birth, pregnant women with HIV should be asked regularly about signs or symptoms of vaginal infection. If such signs or symptoms are present, evaluation for possible BV should follow. Infection should be treated if identified. Currently, data are insufficient to suggest that routine screening for and treatment of BV during pregnancy reduces the rate of preterm birth in the general population (*Am J Prev Med* 2001;20 suppl 3:59); no data are available in the setting of HIV infection. Multiple studies and meta-analyses have found no relationship between birth defects and metronidazole exposure during the first trimester of pregnancy (*Am J Obstet Gynecol* 1995;172:525; *Obstet Gynecol* 1993;82:348; *Br J Clin Pharmacol* 1997;44:179).

Treatment: If BV is diagnosed during pregnancy, preferred therapies are oral metronidazole 500 mg twice daily or 250 mg 3 times daily for 7 days, or oral clindamycin 300 mg twice daily for 7 days.

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Genital Herpes Simplex

Primary herpes simplex virus (HSV) infection during early pregnancy has been associated with prematurity, neonatal chorioretinitis, microcephaly, and, in rare cases, skin lesions (*J Pediatr* 1987;110:97). Although congenital or intrauterine infection is uncommon, maternal HSV shedding at delivery is associated with neonatal HSV infection, which is almost always symptomatic (including skin, eye, and central nervous system [CNS] involvement or disseminated infection involving multiple organ systems). Although the mortality associated with neonatal herpes has declined significantly over the past 2 decades, it remains at 30% for disseminated disease and 4% for CNS disease. Approximately 20% of survivors of neonatal herpes have long-term neurologic sequelae (*Antiviral Res* 2009;83:207)

The risk of neonatal herpes is greatest with primary HSV, especially when acquired close to delivery (30%–60%), whereas only 3% of neonates become infected with recurrent maternal disease at delivery when the mother has recurrent HSV. Because recurrent HSV is more common than primary disease, however, most neonatal infections are associated with recurrent HSV. Two-thirds or more of mothers with HSV infected infants are asymptomatic during pregnancy; in only one-third of cases does either the mother or her sexual partner have a history of HSV infection. Because most neonatal infection occurs during vaginal delivery, if genital lesions or prodromal symptoms are present at the time of labor or membrane rupture, cesarean section (CS)

should be performed. CS is not indicated for recurrent HSV distant from the genital tract, such as on the thighs or buttocks (*ACOG Practice Bulletin* No. 82; *Obstet Gynecol* 2007;109:1489; reaffirmed 2009). HIV infection, particularly with evolving immune compromise and higher plasma HIV VL (*Clin Infect Dis* 2003;36:207), is associated with increased HSV shedding and more frequent, severe, and prolonged episodes of genital or perianal herpes (*Ann Intern Med* 1995;123:845). Approximately 70% of HIV infected individuals are co-infected with HSV-2 (*JAMA* 2006;296:964); co-infection with HSV-2 is common among pregnant HIV infected women, and reactivation of HSV in labor occurs more frequently in the setting of HIV infection (*Am J Obstet Gynecol* 1997;177:450).

Screening: Prevention of neonatal herpes should also emphasize prevention of herpes acquisition in susceptible pregnant women. If a pregnant woman's sexual partner has a history of oral or genital HSV infection or serologic evidence of HSV infection, or if the partner's infection status is unknown, the woman should be counseled to avoid unprotected genital and oral sexual contact during pregnancy. Type-specific HSV serology may be useful to identify the pregnant woman at risk for HSV and to guide counseling, especially if her sexual partner has HSV infection. At the onset of labor, all women should be questioned carefully about HSV symptoms, including prodromal symptoms, and all women should be examined carefully for herpetic lesions, so that judicious decisions can be made about the use of CS.

Treatment: Treatment of symptomatic HSV infections and suppressive therapy for frequent recurrences should be offered to HIV infected women during pregnancy (*Guidelines for Prevention and Treatment of Opportunistic Infections in HIV infected Adults and Adolescents.* 2012 *[in press];*. http://www.aidsinfo.nih.gov) Visceral HSV disease is more likely to occur during pregnancy and can be fatal in rare cases. Either acyclovir or valacyclovir can be used for treatment or suppression (*Guidelines for Prevention and Treatment of Opportunistic Infections in HIV infected Adults and Adolescents.* 2012 [in press]; http://www.aidsinfo.nih.gov); *JAMA* 2010;304:859). During pregnancy, documented HSV infections that do not respond to these agents should be managed with expert consultation.

For pregnant women with recurrences of genital herpes, suppressive therapy with either acyclovir or valacyclovir is recommended starting at 36 weeks' gestation to reduce the need for CS delivery (*ACOG Practice Bulletin* No. 82; *Obstet Gynecol* 2007;109:1489; reaffirmed 2009). No known benefit of suppressive therapy exists for women who are only seropositive for HSV-2 without a history of genital lesions. Maternal genital herpes was a risk factor for perinatal HIV transmission in the pre-HAART era (*Obstet Gynecol* 2005;106:1341); it is not known whether HSV suppression reduces the risk of mother-to-child transmission (MTCT) among women on HAART.

Human Papillomavirus

Correlated with level of immunosuppression, both human papillomavirus (HPV) infection in general and genital warts in particular are more common in HIV infected individuals. Genital warts may be seen more frequently in

pregnancy, when they often enlarge and become friable; in some cases, they cause mechanical obstruction of the vaginal canal during labor. In rare cases perinatal exposure can result in laryngeal papillomatosis in infants and children (*Am J Obstet Gynecol* 1998;178:365).

Screening: Pregnant women with abnormal Pap smears should undergo colposcopy and cervical biopsy if lesions suspicious for high-grade HPV disease or cervical cancer are present. Increased bleeding may occur with biopsy during pregnancy. Endocervical curettage should not be performed during pregnancy. Colposcopy can be deferred until 6 weeks postpartum if Pap results indicate atypical squamous cells of unknown significance (ASCUS). Treatment of cervical intraepithelial neoplasia (CIN) is not recommended during pregnancy unless invasive disease is suspected, in which case diagnostic excision is indicated. Reevaluation with cytology and colposcopy is recommended 6 weeks postpartum. Women with preinvasive cervical lesions can deliver vaginally, if otherwise appropriate. Women with suspected invasive cervical cancer should be referred to a gynecologic oncologist.

Treatment: Podophyllin and podofilox should not be used in pregnancy because of increased risk for fetal death in several animal models and case reports in humans. At present, evidence is insufficient to recommend imiquimod use during pregnancy (*Guidelines for Prevention and Treatment of Opportunistic Infections in HIV infected Adults and Adolescents*. 2012 [in press]; http://www.aidsinfo.nih.gov). Other topical treatments (e.g., bichloroacetic and trichloroacetic acid) and ablative therapies (i.e., laser, cryotherapy, and excision) can be used during pregnancy, although treatment is likely to be less effective in pregnant women than in women who are not pregnant.

CS is not currently recommended to prevent neonatal exposure to HPV, although, in rare instances, CS may be indicated when extensive HPV lesions obstruct the vagina.

Syphilis

HIV may affect clinical manifestations, serologic response, or response to treatment for syphilis. Although pregnancy does not alter the clinical manifestations of syphilis, untreated primary or secondary syphilis during pregnancy affects essentially all fetuses, with a 50% rate of prematurity, stillbirth, or neonatal death (*Sexually Transmitted Diseases*. 3rd ed. New York: McGraw-Hill; 1999). Even with later stages of syphilis, there is a significant increase in adverse pregnancy outcomes, although the frequency and severity of fetal disease decrease with longer duration of untreated maternal infection. Manifestations of congenital syphilis in the newborn include mucocutaneous lesions, hepatosplenomegaly, osteochondritis/periostitis, jaundice, petechiae/purpura, and meningitis.

Screening: Congenital syphilis can generally be prevented by identification and appropriate treatment of syphilis during pregnancy. All pregnant women should have serologic testing for syphilis at the beginning of prenatal care; testing should be repeated at 28 weeks' gestation and at delivery, particularly in women who remain at risk for infection or who live in areas with high syphilis

prevalence. Any woman with stillbirth after 20 weeks' gestation should be tested for syphilis. Development of neurologic symptoms mandates evaluation for possible neurosyphilis. Concurrent syphilis infection in the mother has been associated with increased risk for perinatal transmission of HIV (*AIDS* 2006;20:1869; *BJOG* 2004;111:579).

Treatment: Syphilis during pregnancy should be treated with the penicillin regimen appropriate for the stage of disease. Because of concerns about the effectiveness of standard therapy in pregnant women and in the setting of HIV infection, however, a second injection 1 week after the first should be considered in cases of primary, secondary, or early latent syphilis (*Guidelines for Prevention and Treatment of Opportunistic Infections in HIV infected Adults and Adolescents.* 2012 [in press]; http://www.aidsinfo.nih.gov). Ultrasound evidence of hydrops fetalis or hepatosplenomegaly suggesting fetal syphilis increases risk for treatment failure and should be managed with expert consultation.

Treatment of syphilis during the second half of pregnancy is associated with the Jarisch-Herxheimer reaction in up to 40% of cases, with resulting premature labor and/or fetal distress (*Obstet Gynecol* 1998;92:859). Fetal and contraction monitoring for 24 hours should be considered, especially in the setting of abnormal ultrasound findings; alternatively, patients should be advised to seek immediate medical attention after treatment if contractions or a decrease in fetal movements occur after syphilis treatment (*Guidelines for Prevention and Treatment of Opportunistic Infections in HIV infected Adults and Adolescents.* 2012 (in press); http://www.aidsinfo.nih.gov).

Pregnant women with a history of penicillin allergy should be skin tested and, if necessary, desensitized and treated with penicillin because there are no proven effective alternatives to penicillin for the treatment and prevention of congenital syphilis (*MMWR Recomm Rep* 2010;59 RR-12:1).

Even with appropriate treatment of the pregnant woman with syphilis, fetal infection may still occur; therefore, neonates should be carefully evaluated for evidence of congenital infection. Clinical and serologic follow-up should be performed in the third trimester, at delivery, and at 3, 6, 9, 12, and 24 months following treatment. Treatment failure should be managed with cerebrospinal fluid examination and retreatment. Serologic titers can be checked monthly in women at high risk for reinfection or in geographic areas in which the prevalence of syphilis is high.

Cytomegalovirus

Cytomegalovirus (CMV) is the most common cause of congenital viral infection in the United States: 0.2% to 2.2% of liveborn infants acquire this infection perinatally and it is the leading cause of congenital hearing loss (*Int J Gynaecol Obstet* 2002;76(1):95 [reaffirmed 2011]). Most maternal CMV infections are asymptomatic but may cause a mononucleosis-like illness. Because CMV has been recovered from virtually all body fluids, transmission can occur sexually or with injection drug use. Transmission can also occur with oral contact with infected secretions (e.g., from children). Primary infection, reactivation, and reinfection with different CMV strains during pregnancy all

can lead to in utero transmission and congenital CMV (*Am J Obstet Gynecol* 2010;202:297). Although about one-third of newborns acquire congenital CMV infection after primary infection, only 1%–2% of newborns acquire CMV after a recurrent infection in women who are not HIV infected. Because in most studies >90% of HIV infected pregnant women are CMV antibody positive, the risk for symptomatic infection in the fetus is expected to be low (*JAMA* 1986;256:1904; *JAMA* 1987;257:2617; *J Pediatr* 1998;132:285; *N Engl J Med* 1999;341:77); however, recent studies of HIV-exposed infants suggest that rates of congenital CMV may be increased, ranging from 2%–7%, with higher rates in babies born to mothers with CD4+ cell counts <200/mm³ and in HIV infected infants (*Pediatr Infect Dis J* 2010;29:915; *Clin Infect Dis* 2009;48:1516).

Ninety percent of CMV infected infants are asymptomatic at birth. Symptomatic infection is more likely with maternal infection acquired early in pregnancy. Severe clinical manifestations of congenital CMV include symmetric growth restriction, hepatosplenomegaly, chorioretinitis, microphthalmia, hydrocephaly, microcephaly, and cerebral calcifications. Up to 90% of infected infants who are symptomatic at birth will have serious long-term problems, including hearing loss, visual impairment, mental retardation, and/or cognitive impairment. Among asymptomatic newborns, however, only 5%–15% are at risk for serious long-term impairment, notably late-onset hearing loss in non-HIV infected children (*J Clin Virol* 2006;35:226).

Treatment: Indications for treatment of CMV infection during pregnancy are the same as for treatment of nonpregnant HIV infected adults. Treatment of asymptomatic maternal CMV infection to prevent infant infection is not indicated. For retinal disease, use of intraocular implants or intravitreous injections for local therapy should be considered in the first trimester, if possible, to limit fetal exposure to systemically administered antiviral drugs. Systemic antiviral therapy should then be started after the first trimester. Valganciclovir is recognized as the treatment of choice for CMV during pregnancy (*Guidelines for Prevention and Treatment of Opportunistic Infections in HIV infected Adults and Adolescents.* 2012 (in press); http://www.aidsinfo.nih.gov).

Fetal monitoring: The fetus should be monitored in the third trimester by fetal-movement counting and after 20 weeks' gestation by periodic ultrasound monitoring to look for evidence of hydrops fetalis indicating substantial anemia. Any ultrasound findings suspicious for congenital CMV infection (e.g., cerebral calcifications, abdominal and liver calcifications, hydrops, microcephaly, ventriculomegaly, ascites, echogenic fetal bowel) should prompt consideration of amniocentesis for definitive diagnosis.

Although invasive fetal testing was associated with increased rates of perinatal HIV transmission in early studies (*Am J Obstet Gynecol* 1996;175:661), more recent data suggest that the risk may be minimal in women who are on effective ART and have undetectable HIV RNA levels (*Am J Obstet Gynecol* 2009;200:160.e1; *Eur J Obstet Gynecol Reprod Biol* 2008;140:212; *Eur J Obstet Gynecol Reprod Biol* 2003;108:137).

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Referral to a maternal-fetal medicine specialist for evaluation, counseling, and potential further testing is recommended. Because infants who are co-infected with HIV and CMV have more rapid progression of HIV infection and develop AIDS more frequently (*J Pediatr* 1998; 132:285; *N Engl J Med* 1999;341:77), they should be a priority to receive ART. Methods to reduce the risk of exposure to CMV include safe sexual practices, careful handwashing, and transfusion of only CMV antibody–negative blood products.

Toxoplasmosis

Approximately one-third of women in the United States have toxoplasma antibodies, reflecting prior infection. Primary infection occurs in approximately 0.1%–0.5% of pregnancies and places the fetus at risk for congenital toxoplasmosis. Congenital infection is more common when infection in the mother occurs during the third trimester (>60% in the third trimester vs. 10%–15% in the first trimester) but is generally more severe when occurring in the first trimester. Although the majority of infected infants are asymptomatic at birth, most will develop some sequelae of congenital toxoplasmosis. Two-thirds of infants infected after maternal first-trimester infection have severe manifestations; 5% are stillborn or die in the perinatal period (*ACOG Technical Bulletin* No. 177, February 1993).

Congenital toxoplasmosis may affect all systems, but the most common findings are chorioretinitis, microcephaly, hydrocephaly, and cerebral calcifications. Transmission of toxoplasmosis from a mother with antibody evidence of prior infection can occur in the setting of HIV infection (as opposed to in HIV uninfected women) but seems to be uncommon (0%–3.7% in two studies); there are case reports of transmission with reactivation of chronic infection in HIV infected women with severe immunosuppression (*Eur J Obstet Gynecol Reprod Biol* 1996;68:93; *Am J Obstet Gynecol* 1997;176:555).

Testing for IgG antibodies to toxoplasma is recommended for all HIV infected patients soon after the diagnosis of HIV is made and should be considered as part of prenatal testing in HIV infected pregnant women. Pregnant women with symptoms that may include fever, chills, malaise, lymphadenopathy, myalgias, and headache should be evaluated serologically for possible primary toxoplasmic infection. Primary *Toxoplasma gondii* infection can typically be distinguished from chronic infection with the use of multiple serologic assays, including IgG, IgM, IgA, and IgE antibodies; IgG avidity; and the differential agglutination (AC/HS) tests (*Guidelines for Prevention and Treatment of Opportunistic Infections in HIV infected Adults and Adolescents*. 2012 [in press]; http://www.aidsinfo.nih.gov).

Screening: Detailed ultrasound examination of the fetus to evaluate specifically for hydrocephalus, cerebral calcifications, and growth restriction should be performed in cases of suspected primary or symptomatic reactivation of *T. gondii* during pregnancy (*Clin Infect Dis* 2008;47:554). Polymerase chain reaction (PCR) testing of amniotic fluid may be considered for pregnant women on ART who have serologic evidence of acquired infection during the immediate preconception period or during pregnancy and among those women with ultrasound findings suggestive of fetal *T. gondii* infection

(*Clin Infect Dis* 2008;47:554). Infants born to HIV infected women who are seropositive for toxoplasma also should be evaluated for evidence of congenital toxoplasmosis if suspected by the infant's clinical presentation.

To prevent *T. gondii* exposure, pregnant women should be counseled to avoid raw or undercooked meat, to wash hands after contact with raw meat or with soil, and to thoroughly wash fruits and vegetables before eating them raw. Cats should preferably be kept inside and fed only canned or dried commercial food, and their litter boxes should be changed daily, preferably by someone who is not HIV infected or pregnant.

Treatment: Treatment of the pregnant woman with toxoplasmic encephalitis should be the same as treatment for nonpregnant adults: pyrimethamine plus sulfadiazine plus leucovorin. This regimen is thought to also prevent transmission of *T. gondii* to the fetus and may treat affected fetuses (*Clin Infect Dis* 2008;47:554). Pregnant HIV infected women with suspected or confirmed primary *T. gondii* infection during pregnancy should be managed with expert consultation. (Primary prophylaxis and prophylaxis against recurrent disease in pregnancy are discussed below; see **Opportunistic Infections**, p. 320.)

Hepatitis B

Hepatitis B virus (HBV) is the leading cause of chronic liver disease worldwide (*N Engl J Med* 1997;337:1733). Most patients who become infected with HBV have complete resolution of infection and develop protective levels of antibody (anti-HBs). Of those infected as adults, 6%–10% develop chronic infection (i.e., they are chronically HBsAg+), which puts them at risk for chronic liver disease, including cirrhosis and hepatocellular carcinoma (CDC. *The ABCs of Hepatitis Fact Sheet.* http://www.cdc.gov/hepatitis/HAV/ProfResourcesA.htm. Accessed 6/27/12).

The presence of HBeAg indicates active viral replication and increased infectivity. HBV is transmitted parenterally, sexually, perinatally, and through household or institutional contact. Approximately 25% of regular sexual contacts of infected individuals will become seropositive, and sexual transmission accounts for 30%–60% of new infections. Without preventive measures, perinatal transmission, usually through intrapartum contact with maternal blood and genital secretions, occurs in 10%–20% of women who are HBsAg+. If the mother is also HBeAg+, the perinatal transmission rate increases to approximately 90%. Chronic HBV infection develops in about 90% of infected newborns, putting them at high risk for chronic liver disease (*ACOG Practice Bulletin* No. 86; *Obstet Gynecol* 2007;110:941). Rates of perinatal transmission of HBV are reduced to under 5% when hepatitis B immune globulin (HBIG) and hepatitis B vaccine are provided at birth to infants born to mothers who are HBsAg+.

Approximately 10% of HIV infected individuals have evidence of chronic hepatitis B (*J Acquir Immune Defic Syndr* 1991;4:416; *J Infect Dis* 1991;163:1138). Impaired cellular immunity is associated with higher levels of hepatitis B viremia and lower viral clearance rates following acute HBV infection. HIV patients with chronic HBV infection may be more likely to have

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detectable HBeAg (*Hepatology* 1999;29:1306; *AIDS* 1997;11:597), lower rates of seroconversion, and an increased risk for liver-related mortality and morbidity (*Lancet* 2002;360:1921).

Hepatitis C

Hepatitis C virus (HCV) infection is the most common chronic bloodborne infection in the United States (*Ann Intern Med* 2006;144:705). HCV infection is transmitted primarily through injection drug use, but may also be transmitted sexually. Chronic HCV infection develops in 70%–85% of HCV infected people; 60%–70% of people with chronic HCV infection develop evidence of active liver disease and are at risk for hepatocellular carcinoma (CDC. *The ABCs of Hepatitis Fact Sheet.* www.cdc.gov/hepatitis/HAV/ProfResourcesA.htm. Accessed 6/27/12). Most people remain unaware of their infection because they are not clinically ill.

Among HIV infected pregnant women, the HCV seroprevalence rate ranges from 17%–54% (*Int J Epidemiol* 1998;27(1):108). Co-infection with HIV increases risk for and accelerates the rate of development of progressive liver disease (*Clin Infect Dis* 2001;33:562; *J Hepatol* 1997;26:1). Cofactors influencing disease progression include age, low CD4+ cell count, and history of alcoholism. Evidence suggests that HCV infection may also hasten progression of HIV infection (*J Viral Hepat* 2000;7:302). In most studies, the incidence of HCV transmission from mother to infant increases if the mother is co-infected with HIV, with transmission rates between 10% and 20% (*Clin Infect Dis* 1997;25:1121; *Lancet* 2000;356(9233):904; *J Infect Dis* 2005;192(11):1880; *J Hepatol* 2006;44 suppl 1:S6; *BJOG* 2001;108:371). This is likely related to an increase in HCV viremia and/or other HIV-related effects on HCV disease activity (*Clin Infect Dis* 2007;44(8):1123). Furthermore, maternal co-infection with HIV and HCV may also increase risk for perinatal HIV transmission (*J Infect Dis* 1997;176(2):414). Pregnancy does not appear to influence the course of HCV infection; women with chronic viral hepatitis generally do well during pregnancy unless they have progressed to decompensated cirrhosis (*Ann Hepatol* 2006;5(3):190).

Perinatal Transmission

Rate

The baseline rate of perinatal HIV transmission without prophylactic therapy is approximately 25%; however, with the use of combination ART and suppression of HIV RNA (VL) to undetectable levels, along with avoidance of breast feeding and the use of CS delivery when appropriate, the rate of perinatal transmission may be reduced to 1%–2% or less (*J Acquir Immune Defic Syndr* 2002;29:484; *AIDS* 2008;22:973; *J Public Health Manag Pract*

2010;16:481). Nevertheless, approximately 100–200 infants are infected annually in the United States (*Am J Obstet Gynecol* 2007;197(3 Suppl):S10), most commonly because the mother did not receive HIV testing or other recommended prevention interventions during pregnancy; these infections therefore represent missed opportunities (*Women Health* 2010;50(5):414). Lack of prenatal care and active substance abuse, which frequently coexist, have also been linked to a potentially avoidable increased risk for perinatal transmission (*N J Med* 2001;98:23). Acute HIV infection in pregnancy or during breastfeeding is associated with an increased risk of perinatal HIV transmission and may represent a significant proportion of residual mother-to-child HIV transmission (MTCT) in the United States (*Obstet Gynecol* 2010;115(6):1247).

Timing

The timing of transmission is a critical factor in prevention. Although transmission can occur throughout the course of pregnancy, around the time of labor and delivery, or postpartum through breastfeeding, most transmissions appear to occur during or close to the intrapartum period, particularly in non-breastfeeding populations (*JAMA* 2000;283:1175). Table 8-3 outlines the estimated timing and risk of MTCT; Table 8-4 identifies key clinical and potentially modifiable factors associated with the risk of perinatal transmission.

Risk Factors

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Table 8-3

Estimated Timing and Risk of Mother-to-Child HIV Transmission (Absolute Rate) in the Absence of Antiretroviral Use

	No Breastfeeding	Breastfeeding through 6 mo	Breastfeeding through 18–24 mo
Intrauterine	5–10%	5–10%	5–10%
Intrapartum	10–20%	10–20%	10–20%
Postpartum			
Early (2 mo)		5–10%	5–10%
Late (>2 mo)		1–5%	5–10%
Overall	15–30%	25–35%	30–45%

Source: *JAMA* 2000;283(9):1175

Table 8-4	
Clinical Factors Associated with Risk of Perinatal Transmission	
HIV Related Clinical Factors	
Maternal plasma HIV-1 RNA level	• Risk increases with higher maternal serum HIV-1 RNA levels (*N Engl J Med* 1999;341:394; *J Acquir Immune Defic Syndr* 2002;29:484; *N Engl J Med* 1999;341:385) • No absolute threshold exists below which transmission does not occur or above which transmission always occurs
CD4+ cell count	• Risk of transmission is higher with lower CD4+ counts
Genital tract VL	• Independently associated with perinatal transmission (*J Infect Dis* 2000;181:99), genital tract VL usually correlates with plasma VL, but discordance may occur, especially with genital tract infections
Clinical HIV stage	• Both acute infection and late-stage disease are associated with increased risk of perinatal transmission (*AIDS* 2010;24(4):573; *Obstet Gynecol* 2010; 115(6): 1247)
Maternal Related Clinical Factors	
Co-infection	• Genitally transmitted infections have been shown to increase both genital tract HIV shedding and plasma viremia (*AIDS Res Hum Retroviruses* 1998;14 suppl 1:S5), both of which may increase risk for perinatal transmission • Syphilis, HSV, and vaginal infections (BV, yeast, trichomoniasis) (*AIDS* 2008;22:1169; *Int J Gynaecol Obstet* 1998;63:247; *J Perinatol* 2010;30(11):717) have been associated with increased risk of perinatal transmission • HCV infection, TB, and placental malaria have also been associated with increased risk for vertical transmission (*J Hepatol* 2006; 44 suppl 1:S6; *Int J Epidemiol* 1998;27:296; *J Infect Dis* 2011;203:358)
Substance abuse	• Illicit drug use has been associated with increased risk for perinatal transmission (*AIDS* 1996;10:273)
Cigarette smoking	• Smoking is associated with increased risk for perinatal transmission (*J Acquir Immune Defic Syndr Hum Retrovirol* 1997;14:327)
Sexual behavior	• Unprotected intercourse during pregnancy associated with increased risk for perinatal transmission (*J Acquir Immune Defic Syndr Hum Retrovirol* 1997;15:76)
ARV use	• ARV use is consistently associated with decreased risk for perinatal transmission; the greatest reductions are associated with longer and more complex regimens (*J Acquir Immune Defic Syndr* 2002;29:484; *AIDS* 2008;22:973)

Table 8-4	*continued*

Clinical Factors Associated with Risk of Perinatal Transmission

Obstetrical Related Clinical Factors

Preterm delivery	• Delivery at preterm gestational age has been associated with increased risk for perinatal transmission (*J Infect Dis* 1999;179:52)
Mode of delivery	• CS delivery prior to onset of labor or membrane rupture is associated with decreased risk of perinatal transmission with HIV-1 RNA level >1000 copies/mL near time of delivery or with AZT only (studies done before routine use of VL testing/use of HAART) (*Lancet* 1999;353:1035; *N Engl J Med* 1999;340:977)
	• Data are insufficient to evaluate the potential benefit of CS delivery for prevention of perinatal transmission in pregnant women receiving combination ARV drugs with plasma HIV RNA levels <1000 copies/mL near the time of delivery
Invasive intrapartum monitoring	• Fetal scalp sampling and use of fetal scalp electrodes are associated with increased risk for perinatal transmission in some studies (*Eur J Obstet Gynecol Reprod Biol* 1999;87:63; *JAMA* 1994;271:1925)
Chorioamnionitis/ Placental abruption	• Placental barrier disruption and/or inflammation are associated with increased risk for perinatal transmission (*J Acquir Immune Defic Syndr* 2002;29:262)
Duration of rupture of membranes	• Longer duration of membrane rupture is associated with increased risk for perinatal transmission (*AIDS* 2001;15:357)
Forceps/vacuum/ episiotomy	• A potentially increased risk of transmission exists due to increased exposure to maternal blood/genital secretions with trauma to maternal or neonatal tissue (*Obstet Gynecol* 1999;94:897)

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

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Breastfeeding: Globally, breastfeeding is estimated to have accounted for up to 40%–50% of newly infected children (*JAMA* 1999;282:781). Factors associated with an increased risk of breast-milk transmission are summarized in Table 8-5.

Table 8-5	
Factors Associated with Increased Risk of Transmission of HIV via Breast Milk	
Maternal	• Acute HIV infection (*Lancet* 1992;340:585)
	• Advanced HIV infection with low CD4+ cell counts
	• High VL in plasma or breast milk
	• Breast conditions (e.g., clinical or subclinical mastitis, breast abscess, cracked nipples)
Newborn	• Preterm birth or low birthweight
	• Loss of mucosal integrity resulting from trauma, nutritional deficiency, or infection (e.g., oral thrush)
	• Maternal-infant HLA incompatibility; possible protective effect (*J Infect Dis* 2008;197(8):1156)
Breastfeeding	• Timing and duration; although transmission rates are possibly higher in early breastfeeding, duration is a major determinant of transmission (*PLoS One* 2009;4(10):e7397)
	• Pattern of breastfeeding; mixed feeding (addition of other solids or liquids to breast milk) is associated with increased risk compared with exclusive breastfeeding (*AIDS* 2005;19:699)

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Antiretroviral Drug Use In Pregnancy

The administration of ARV drugs to the mother during pregnancy and labor and to the neonate are the interventions associated with the greatest decreases in perinatal transmission. ARV drugs reduce perinatal transmission by several mechanisms, among them, by lowering maternal VL and by providing pre- and post-exposure prophylaxis for the infant through placental transfer. Therefore, at least 1 nucleoside/nucleotide agent with high placental transfer should be included in ARV regimens in pregnancy (*J Infect Dis* 2004;190(12):2167; *J Clin Pharmacol* 2001;41(7):732; *Clin Pharmacol Ther* 2009;85(2):182; *Antimicrob Agents Chemother* 2009;53(3):1067).

General Principles for Treatment

ARV prophylaxis is recommended for all HIV infected pregnant women, regardless of CD4+ cell count and/or VL. Although rates of perinatal transmission are low in women with undetectable or low HIV RNA levels, no threshold exists below which lack of transmission can be assured.

Decisions regarding use of ART or prophylaxis during pregnancy should be made by the woman after detailed and noncoercive discussion of the benefits and potential risks of therapy.

Regimen: Combination ARV regimens containing at least 3 drugs for prevention of perinatal HIV transmission are associated with the lowest risk of transmission and should be discussed and offered to all pregnant women with HIV infection. Although the initial study (PACTG 076) documenting the

effectiveness of ARVs in reducing perinatal transmission rates involved the use of AZT alone, subsequent studies and clinical experience have shown that the lowest rates of transmission are associated with more complex regimens that lower maternal VL to undetectable levels (*AIDS* 2008;22(8):973).

Choice of ARV regimens in pregnancy should follow the same principles applied when choosing ARV regimens for patients who are not pregnant: 1) optimize efficacy and durability of response; 2) maximize safety and tolerability; 3) simplify regimens to improve the likelihood of adherence and reduce the chance of resistance; and 4) for pregnant women, address special considerations such as maternal and fetal safety. To preserve future maternal options, the durability, tolerability, and simplicity of the ARV regimen is of particular importance. Table 8-6 summarizes maternal and fetal/neonatal factors to be considered when formulating an ARV regimen for a pregnant woman.

Table 8-6

Considerations in Choosing and Individualizing an Antiretroviral Regimen in Pregnancy

Mother:
- Efficacy and durability of response
- Safety and tolerability
- Comorbidities
- Potential for adherence
- Convenience
- Potential adverse drug effects
- Potential interactions with other medications
- Results of genotypic resistance testing
- Pharmacokinetic changes in pregnancy

Fetus/Neonate:
- Potential teratogenic effects
- Potential carcinogenicity or mutagenicity
- Side effects or toxicity from transplacentally transferred drugs

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Potential for adverse effects may be related to several factors: the drug itself, dose, gestational age at exposure, duration of exposure, interactions with other drugs or agents to which the fetus is exposed, and genetic make-up of the mother and fetus. Potential ARV toxicity with perinatal exposure applies both to the infected and uninfected fetus/infant.

Duration: Longer duration and/or earlier initiation of ARVs are associated with lower rates of transmission. In a French study evaluating risk factors for perinatal transmission in women with VL <500 copies/mL at the time of delivery, the overall transmission rate was 0.5%; the highest transmission rates occurred among women who were not taking ARVs at the time of conception and who did not have VL <500 copies/mL at 14, 28, and 32 weeks' gestation (*Clin Infect Dis* 2010;50(4):585). When ARVs were started during pregnancy, gestational age at initiation of therapy did not differ between groups (30 weeks), but VL decreased earlier in the nontransmitters. The ability to reach maximal viral suppression is affected by the VL at the beginning of pregnancy; in a study from the United Kingdom, with initial VL >10,000 copies/mL (c/mL), deferring ARV initiation past 20 weeks' gestation reduced the likelihood of

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VL <50 c/mL at delivery, whereas only 37% of those with initial VL >100,000 c/mL reached maximal VL suppression by the end of pregnancy and this was dependent on the duration of the ARV regimen (*AIDS* 2012;26(9):1095)

Resistance: The development of ARV resistance is a major factor in treatment failure. The most common causes of resistance are the prescription of ineffective regimens and lack of adherence. ARV regimens are ineffective when they include drugs to which there is existing resistance or when they are composed of just one or two drugs or drugs from just one ARV class. Viral replication of HIV is inherently mutation-prone and resistant viral variants emerge under selective pressure, especially with incompletely suppressive regimens. Resistant viral variants are believed to be archived permanently in latent HIV reservoirs, and resistance to one drug may be associated with resistance to other drugs within the same class; therefore, if ineffective regimens are used or if ARV regimens are taken incorrectly, patients' future treatment options may be significantly limited.

When developed during pregnancy, drug resistance may compromise the prevention of perinatal transmission or may result in transmission of a resistant virus to the fetus, which would limit the infant's future treatment options. It could also limit the mother's future treatment options or decrease the effectiveness of prophylactic regimens in future pregnancies. Although perinatal transmission of resistant virus has been reported, it appears to be unusual, and little evidence exists that the presence of resistance mutations increases the risk of transmission when current recommendations for ARV management in pregnancy are followed.

Several factors unique to pregnancy may increase risk for the development of resistance:

- If prophylactic regimens include drugs with significant half-life differences, such as NVP or EFV combined with two nucleoside analogue drugs, then postpartum discontinuation of all regimen components simultaneously may result in persistent subtherapeutic drug levels and increase risk for the development of NNRTI resistance.

- Problems such as nausea and vomiting in early pregnancy may compromise adherence or absorption.

- Pharmacokinetic changes during pregnancy, such as increased plasma volume and renal clearance, may lead to subtherapeutic drug levels that increase risk for resistance.

Current recommendations for HIV drug-resistance testing in pregnant women are as follows (resistance testing requires VL >500–1000 copies/mL for accurate detection of resistance mutations):

- Before starting treatment or prophylaxis, test for resistance in all pregnant women not currently taking ARVs (unless previously tested and patient ARV-naïve).

- Test for resistance in all pregnant women entering pregnancy on ART with detectable VL.

- Test for resistance in all pregnant women who have suboptimal viral suppression after initiation of ARV drugs in pregnancy (*Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*. 2013. http://www.aidsinfo.nih.gov).

For optimal prevention of perinatal transmission, empiric initiation of ARV drugs before obtaining the results of resistance testing is warranted for women who present late in pregnancy, with adjustment as needed after the test results are available.

Women who have documented ZDV resistance should still receive intravenous ZDV during labor **if VL >400 c/mL near delivery**, along with their established ARV regimens, and their infants should receive oral ZDV.

Recommendations for preventing ARV resistance include the following:

- Use of an effective combination ARV regimen

- Emphasis on and reinforcement of the importance of good adherence at each patient visit

- **Not recommended:** Addition of single-dose NVP (sdNVP) to a combination ARV regimen; sdNVP does not increase efficacy of MTCT prevention and may lead to maternal or infant NVP resistance (*J Infect Dis* 2002;186:181)

- For pregnant women receiving an NNRTI-based combination regimen that is discontinued after delivery:
  - Continue the NRTI components after stopping the NNRTI (*J Infect Dis* 2006;193(4):482; *PLoS Med* 2009;6(10):e1000172)

  - An alternative strategy is to substitute a PI for the NNRTI prior to the interruption and continue the PI with dual NRTIs (*AIDS* 2008;22(17):2279)

The optimal interval between stopping an NNRTI and discontinuing the other ARVs is not known, but current recommendations suggest an interval of 7–30 days. Because NNRTI concentrations may remain detectable for more than 3 weeks in patients receiving EFV-based therapy, some experts recommend continuing other ARV agents or substituting a PI plus two other agents for up to 30 days (*J Acquir Immune Defic Syndr* 2005;38(3):283; *AIDS* 2005;19(15):1716). A recent study of 412 women who received single-dose nevirapine and were randomized to receive zidovudine/lamivudine, tenofovir/emtricitabine, or lopinavir/ritonavir for either 7 or 21 days found an overall new nevirapine resistance mutation rate of 1.2% when assessed by population genotype at 2 and 6 weeks following completion of treatment, with no difference by length of treatment. However, low-frequency nevirapine-resistant mutations at codons 103, 181, and 184 detected using allele-specific PCR emerged significantly more often in the 7-day arms (13/74 [18%]) than in the 21-day arms (3/66 [5%], P = .019). (*Clin Infect Dis* 2013;56(7):1044).

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All cases of ARV drug exposure during pregnancy should be reported to the Antiretroviral Pregnancy Registry (see details at http://www.APRegistry.com. Accessed 6/26/12). The registry is a collaborative project of pharmaceutical manufacturers, with an advisory committee of obstetric and pediatric practitioners, that collects observational data regarding ARV exposure during pregnancy for the purpose of assessing the potential teratogenicity of these drugs. The registry does not use patient names; registry staff members obtain birth outcome follow-up information from the reporting provider.

Limited data are available on both the long-term maternal consequences of ARV drug use during pregnancy solely for transmission prophylaxis and on the long-term consequences for the infant of in utero ARV exposure.

Expert consultations: Expert consultation on care of the HIV infected pregnant woman is recommended and/or should be considered in the following situations:

- When use of ZDV alone is being considered

- If maximal virologic suppression is not achieved with the prescribed ARV regimen

- When choosing an ARV regimen for a woman with extensive ART experience and/or multiple resistance mutations

- Prior to discontinuation of ARVs when they were being taken only for prophylaxis

- If a patient has significant toxicity that is related to, or potentially related to, use of ARVs

- If a patient has significant medical comorbidities that may affect drug choice (e.g., HBV)

- If premature membrane rupture occurs

- When maternal ARV resistance is known or suspected, with high maternal VL at or near delivery, or when the mother has received no ARVs prior to and/or during labor (to determine potential for use of additional drugs in the infant; consult with a pediatric HIV specialist)

Recommendations for Use of Specific ARV Agents In Pregnancy

Table 8-7 provides information about all currently Food and Drug Administration (FDA)-approved ARV agents, with information and recommendations specific to pregnancy. These recommendations specifically relate to agents used to construct initial ARV regimens in antiretroviral naïve pregnant women and are predicated on ARV sensitivity by resistance testing. If a woman enters pregnancy on a stable ARV regimen with viral suppression, the regimen should be continued. Antiretroviral drugs or drug combinations are divided into several categories for use in pregnancy, based on efficacy and durability; safety for mother, fetus and newborn; ease of use; available pregnancy-specific pharmacokinetic data; medical comorbidities limiting drug choice; and experience in pregnancy.

Table 8-7

Antiretroviral Drugs in Pregnancy and Recommendations for Antiretroviral Naïve Women

NRTIs/NRTIs: Nucleoside/nucleotide reverse transcriptase inhibitors are recommended for use as part of combination regimens that usually include 2 NRTIs plus either an NNRTI or 1 or more PIs. Use of single or dual NRTIs/NRTIs alone is not recommended for treatment of HIV infection. Long-term use is associated with potential maternal and infant mitochondrial toxicity.

Drug Name	Dosing and Available Formulations	Adverse Effects	Placental Transfer and PK in Pregnancy	Notes Regarding Use in Pregnancy
PREFERRED				
LAMIVUDINE (Epivir®, 3TC)	**Dose:** 150 mg po bid or 300 mg po qd **Food requirements:** Take without regard to meals. **Available as:** • Tabs: 150 mg; 300 mg • Oral sol: 10 mg/mL • Combivir: ZDV 300 mg/3TC 150 mg (1 tab po bid) • Trizivir: ZDV 300 mg/3TC 150 mg/ABC 300 mg (1 tab po bid) • Epzicom: 3TC 300 mg/ABC 600 mg (1 tab po qd)	Generally very well tolerated Occasional headache, nausea, diarrhea, abdominal pain, and insomnia Lactic acidosis/hepatic steatosis not generally associated with 3TC Severe acute exacerbation of hepatitis may occur in HBV-co-infected patients who d/c 3TC	**Placental transfer:** High **PK:** Not significantly altered in pregnancy; use standard doses	Because of extensive experience with 3TC in pregnancy in combination with ZDV, 3TC + ZDV is a recommended dual NRTI/NRTI backbone for pregnant women Active against HBV Resistance profile is identical to FTC No evidence of human teratogenicity
ZIDOVUDINE (Retrovir®, AZT, ZDV)	**Dose:** 300 mg po bid or 200 mg po tid **Food requirements:** Take without regard to meals. **Intrapartum:** 2 mg/kg IV for first hour then 1 mg/kg IV until birth **Available as:** • Caps: 100 mg • Tabs: 300 mg • IV sol: 10 mg/mL • Oral sol: 10 mg/mL • Combivir: ZDV 300 mg/3TC 150 mg (1 tab po bid) • Trizivir: ZDV 300 mg/3TC 150 mg/ABC 300 mg (1 tab po bid)	GI intolerance, malaise; headache (in 5%–10%); bone marrow suppression (anemia and neutropenia), myopathy/myalgia; transaminase elevation; fingernail discoloration Rare cases of lactic acidosis and severe hepatomegaly with steatosis have been reported	**Placental transfer:** High **PK:** Not significantly altered in pregnancy; use standard doses	Because of extensive experience with ZDV in pregnancy in combination with 3TC, ZDV + 3TC is a recommended dual NRTI/NRTI backbone for pregnant women ZDV should not be included in prenatal regimen if there is severe toxicity, d4T use, documented resistance, or if already on effective and well-tolerated regimen that does not include ZDV No evidence of human teratogenicity Short-term safety for mother and infant has been demonstrated

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Table 8-7 continued

Antiretroviral Drugs in Pregnancy and Recommendations for Antiretroviral Naïve Women

Drug Name	Dosing and Available Formulations	Adverse Effects	Placental Transfer and PK in Pregnancy	Notes Regarding Use in Pregnancy
PREFERRED				
ABACAVIR (Ziagen®, ABC)	**Dose:** 300 mg po bid or 600 mg po qd **Food requirements:** Take without regard to meals **Available as:** • Tabs: 300 mg • Oral sol: 20 mg/mL • Trizivir: ZDV 300 mg/3TC 150 mg/ ABC 300 mg (1 tab po bid) • Epzicom: 3TC 300 mg/ABC 600 mg (1 tab po qd)	Hypersensitivity reaction: fever, rash, fatigue, malaise, GI symptoms, and arthralgias~4% before HLA B5701 testing in nonpregnant patients (rate in pregnancy unknown) Deaths reported upon rechallenge	**Placental transfer:** High **PK:** Not significantly altered in pregnancy; use standard dose	Must screen for HLA-B5701 before starting ABC and results documented as negative before initiating ABC. Mandatory and permanent d/c with hypersensitivity reaction Patients should be educated regarding symptoms of hypersensitivity reaction No evidence of human teratogenicity
EMTRICITABINE (Emtriva®, FTC)	**Dose:** 200 mg po qd or 240 mg (24 mL) oral solution once daily **Food requirements:** Take without regard to meals **Available as:** • Caps: 200 mg hard gel • Oral sol: 10mg/mL • Truvada: FTC 200 mg/ TDF 300 mg (1 tab po qd) • Atripla: FTC 200 mg/EFV 600 mg/TDF 300 mg (1 tab po hs; take on empty stomach to reduce side effects)	Generally well tolerated Occasional headache, diarrhea, nausea, rash, hyper-pigmentation/skin discoloration Lactic acidosis/hepatic steatosis not generally associated with FTC Severe acute exacerbation of hepatitis may occur in HBV-co-infected patients who d/c FTC	**Placental transfer:** High **PK:** Slightly lower concentrations in 3rd trimester compared with postpartum; no clear need to increase dose	Active against HBV Resistance profile is identical to 3TC No evidence of human teratogenicity

Table 8-7 *continued*

Antiretroviral Drugs in Pregnancy and Recommendations for Antiretroviral Naïve Women

Drug Name	Dosing and Available Formulations	Adverse Effects	Placental Transfer and PK in Pregnancy	Notes Regarding Use in Pregnancy
TENOFOVIR DF (Viread®, TDF)	**Dose:** 300 mg po qd **Food requirements:** Take without regard to meals **Available as:** • Tabs: 300 mg • Truvada: TDF 300 mg/FTC 200 mg (1 tab po qd) • Atripla: FTC 200 mg/EFV 600 mg/TDF 300 mg (1 tab po hs); take on empty stomach to reduce side effects)	Generally well tolerated Headache, diarrhea, nausea and vomiting reported; renal insufficiency, Fanconi's syndrome; potential decrease in bone mineral density Lactic acidosis with hepatic steatosis not generally associated with TDF Severe acute exacerbation of hepatitis may occur in HBV–co-infected patients who d/c TDF	**Placental transfer:** High **PK:** Lower AUC in the 3rd trimester compared with postpartum, but adequate trough levels	Considered a preferred NtRTI in combination with 3TC or FTC in women with chronic HBV infection; monitor renal function. Possible HBV flare if drug is d/c'ed postpartum. No evidence of human teratogenicity Clinical studies in humans (particularly children) show bone demineralization with chronic use. Recent study found no difference in growth patterns, bone health or markers of bone metabolism in infants with and without in utero TDF exposure (Antivir Ther 2011;16:1259).
NOT RECOMMENDED				
DIDANOSINE (Videx® EC, generic didanosine enteric coated (EC), ddI)	**Dose:** Wt ≥ 60 kg: 400 mg po qd; with TDF, 250 mg po qd Wt <60 kg: 250 mg po qd; with TDF, 200 mg po qd Preferred dosing with oral solution is bid (i.e., total daily dose divided into 2 doses) **Food requirements:** Take 1/2 h before or 2 h after meals **Available as:** • Caps (enteric coated): 125 mg, 200 mg, 250 mg, or 400 mg • Oral sol: 10 mg/mL	GI intolerance (diarrhea, mouth sores); peripheral neuropathy (in 5%–12% of patients); pancreatitis (in 1%–9% of patients with 6% of cases fatal); transaminase elevation; rare cases of lactic acidosis and severe hepatomegaly with steatosis; noncirrhotic portal hypertension resulting in esophageal variceal bleed, liver failure, and death have been reported; optic neuritis	**Placental transfer:** Moderate **PK:** Not significantly altered in pregnancy; use standard dose	Not recommended due to toxicity Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving ddI and d4T together. In the Antiretroviral Pregnancy Registry, an increased rate of birth defects with ddI compared with general population was noted after both 1st trimester (4.6%) and later exposure (4.3%). No specific pattern of defects was noted and clinical relevance is uncertain.

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Table 8-7 continued

Antiretroviral Drugs in Pregnancy and Recommendations for Antiretroviral Naïve Women

Drug Name	Dosing and Available Formulations	Adverse Effects	Placental Transfer and PK in Pregnancy	Notes Regarding Use in Pregnancy
STAVUDINE (Zerit®, d4T)	**Dose:** Wt ≥ 60 kg: 40 mg po bid; Wt <60 kg: 30 mg po bid; WHO recommends 30 mg po bid for all patients. **Food requirements:** Take without regard to meals. **Available as:** • Caps: 15 mg, 20 mg, 30 mg, 40 mg • Oral sol: 1mg/mL	Peripheral neuropathy (in 5%–15% of patients); transaminase elevation (in 8% of patients); rare cases of lactic acidosis and severe hepatomegaly with steatosis; lipoatrophy; pancreatitis; rare cases of rapidly progressive ascending neuromuscular weakness	**Placental transfer:** High **PK:** Not significantly altered in pregnancy; use standard doses	Not recommended due to toxicity. Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving combination of d4T and ddI as component of ARV therapy. Due to antagonism, ZDV and d4T should never be used together as a part of a combination ARV regimen. No evidence of human teratogenicity

NNRTIs: *Non-nucleoside reverse transcriptase inhibitors are recommended for use in combination regimens that include 2 NRTI/NRTI drugs. Hypersensitivity reactions, including hepatic toxicity and rash, are more common in women; unclear if risk is increased in pregnancy.*

PREFERRED

EFAVIRENZ (Sustiva®, EFV) May be initiated after first 8 wks of pregnancy.	**Dose:** 600 mg po qhs **Food requirements:** Take on empty stomach to decrease side effects **Available as:** • Caps: 50 mg, 200 mg • Tabs: 600 mg • Atripla: EFV 600 mg/FTC 200 mg/TDF 300 mg (1 tab po hs; take on empty stomach to reduce side effects)	Morbilliform rash in 15%–27% of patients, with 1%–2% requiring d/c; 1 case of Stevens-Johnson syndrome reported; CNS effects (confusion, depersonalization, abnormal dreams) seen in up to 52% of patients (generally resolves in 2–4 wk); transaminase elevation in 2%–3% of patients, hyperlipidemia	**Placental transfer:** Moderate **PK:** AUC decreased during the 3rd trimester compared with postpartum, but generally exceeded target exposure; no change in dose needed	Significant malformations (anencephaly, anophthalmia, cleft palate) observed in 3 (15%) of 20 infants born to cynomolgus monkeys receiving EFV during 1st trimester at a dose that produced plasma levels comparable to systemic human therapeutic exposure. Human retrospective reports and 1 prospective case report of NTDs with 1st-trimester exposure and 1 prospective case of anophthalmia with facial defts. However, meta-analysis of >1300 1st-trimester EFV exposures found no increased risk of birth defects and only 1 NTD (incidence 0.07%) (AIDS 2011;25:2301). More data are needed to conclusively determine association (or lack of) between EFV and NTDs. EFV should be avoided during 1st trimester whenever possible. However, EFV should be continued in women presenting in 1st-trimester on EFV-containing regimen and with maximal VL suppression. After 1st-trimester, EFV may be considered if best choice compared with alternatives. Women of childbearing age trying to conceive or not using effective contraception should not use EFV unless other effective and acceptable regimens are not available. Recommend effective contraception if EFV is to be continued or initiated postpartum. Because EFV may decrease hormonal contraceptive efficacy, a reliable method of contraception (e.g., barrier) should be used in addition to hormonal contraceptives.

Table 8-7 continued

Antiretroviral Drugs in Pregnancy and Recommendations for Antiretroviral Naïve Women

Drug Name	Dosing and Available Formulations	Adverse Effects	Placental Transfer and PK in Pregnancy	Notes Regarding Use in Pregnancy
ALTERNATIVE				
NEVIRAPINE (Viramune®, NVP)	**Dose:** 200 mg po qd for 14 d, then 200 mg po bid **Note:** If mild to moderate rash develops without constitutional symptoms, continue lead-in dosing until rash resolves, but no longer than 28 d total **Food requirements:** Take without regard to meals **Available as:** • Tabs: 200 mg • Oral suspension: 50 mg/5mL	Rash in 17% of patients (7% d/c'ed due to rash; many patients require hospitalization) Stevens-Johnson syndrome reported; transaminase elevation; severe hepatitis; fever; nausea; headache Women may be at increased risk of rash and liver toxicity, especially with CD4+ cell count >250/mm³ (AIDS 2002;16(1):1566; Clin Infect Dis 2001;32(1):124; J Acquir Immune Defic Syndr 2003;34 suppl 1:S21) or with baseline elevated liver enzymes (HIV Med 2010;11(10):650); unclear if pregnancy increases risk. This toxicity not reported in women receiving single-dose NVP for prophylaxis of perinatal transmission.	**Placental transfer:** High **PK:** Not significantly altered in pregnancy; use standard doses.	Initiate NVP in pregnant women with CD4+ cell counts >250/mm³ only if benefit clearly outweighs risk, because of increased risk of potentially life-threatening hepatotoxicity in women with high CD4+ cell counts. Elevated transaminase levels at baseline also may increase the risk of NVP toxicity. Women who enter pregnancy on NVP regimens and are tolerating them well may continue therapy, regardless of CD4+ cell count Monitor LFTs q 2 wk x 1 mo, then q 1 mo x 4 mo, then q 1–3 mo Repeat lead-in dosing period if therapy d/c'ed for >7 d No evidence of human teratogenicity

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Table 8-7 continued

Antiretroviral Drugs in Pregnancy and Recommendations for Antiretroviral Naïve Women

Drug Name	Dosing and Available Formulations	Adverse Effects	Placental Transfer and PK in Pregnancy	Notes Regarding Use in Pregnancy
INSUFFICIENT DATA TO RECOMMEND USE				
RILPIVIRINE (Endurant, RPV)	**Dose:** 25 mg po qd **Food requirements:** Take with a meal **Available as:** • Tabs: 25 mg • Complera (RPV 25 mg/TDF 300 mg/FTC 200 mg) 1 tab po qd with meal	Rash; depression, insomnia, headache	**Placental transfer:** Unknown **PK:** No pharmacokinetic studies in human pregnancy	Limited experience in human pregnancy. Safety and pharmacokinetic data in pregnancy are insufficient to recommend use during pregnancy. RPV not recommended with pretreatment HIV RNA >100,000 c/ml or CD4+ cell count <200 cells/microliter. Do not use with proton pump inhibitor.
NOT RECOMMENDED				
ETRAVIRINE (Intelence, ETR)	**Dose:** 200 mg po bid **Food requirements:** Take with food **Available as:** • Tabs: 100 mg, 200 mg	Rash in up to 17%, severe in 1.3% of patients; generally occurs in first 2 wk and resolves within 1–2 wk on continued therapy, but 2% required ETR d/c Stevens-Johnson syndrome reported Hypersensitivity reactions have been reported (rash; constitutional symptoms; and organ dysfunction, including liver failure)	**Placental transfer:** Unknown **PK:** Limited data in pregnancy suggests no change in dose needed (HIV Med 2011;12(4):257)	Not recommended in naïve adults as limited data. Limited experience in pregnancy

Table 8-7 continued

Antiretroviral Drugs in Pregnancy and Recommendations for Antiretroviral Naïve Women

Drug Name	Dosing and Available Formulations	Adverse Effects	Placental Transfer and PK in Pregnancy	Notes Regarding Use in Pregnancy
PIs: Protease inhibitors are recommended for use in combination regimens with 2 NRTI/NtRTI drugs. Hyperglycemia, new onset or exacerbation of diabetes mellitus, and diabetic ketoacidosis have been reported with PI use; unclear if pregnancy increases risk. Conflicting data regarding preterm delivery in women receiving PIs.				
PREFERRED				
ATAZANAVIR (Reyataz®, ATV)	**Dose:** (ATV 300 mg po + RTV 100 mg po) qd **2nd and 3rd trimesters:** Some experts recommend increased dose (ATV 400 mg + RTV 100 mg po qd) in all pregnant women in the 2nd and 3rd trimesters **Note:** Increased dose (ATV 400 mg po) qd is recommended in the following situations: • With TDF or H2-receptor antagonist in ARV-experienced pregnant patients • With EFV in ARV-naïve patients Concurrent use of ATV with EFV in ARV-experienced patients is not recommended due to decreased ATV levels **Food requirements:** Take with food **Available as:** • Caps: 100 mg, 150 mg, 200 mg, 300 mg	Reversible benign hyperbilirubinemia (grade 3–4 occurring in 35%–47% of patients), jaundice, scleral icterus PR interval prolongation, 1st-degree AV block reported Nausea, vomiting, abdominal pain (generally better tolerated compared with LPV/r); skin rash (20%); headache; serum transaminase elevation Class adverse events such as hyperlipidemia, fat redistribution and hyperglycemia ATV alone has less impact on serum lipids, but elevated lipids can be a problem with RTV boosting	**Placental transfer:** Low **PK:** With standard ATV/r dosing, lower ATV concentrations during pregnancy as compared to nonpregnant adults (*J Acquir Immune Defic Syndr* 2011;56(5):412; AIDS 2007;21(18):2409). Use of an increased dose during 2nd and 3rd trimesters resulted in plasma concentrations equivalent to those in nonpregnant adults on standard dosing. ATV concentrations further reduced ~25% with concomitant TDF use (*J Acquir Immune Defic Syndr* 2011;56(5):412; AIDS 2007;21(18):2409)	Must be combined with low-dose RTV boosting Theoretical concern of increased indirect bilirubin exacerbating physiologic hyperbilirubinemia in neonates not observed in clinical trials to date (*J Acquir Immune Defic Syndr* 2011;56(5):412; AIDS 2007;21(18):2409) No evidence of human teratogenicity

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Table 8-7 *continued*

Antiretroviral Drugs in Pregnancy and Recommendations for Antiretroviral Naïve Women

Drug Name	Dosing and Available Formulations	Adverse Effects	Placental Transfer and PK in Pregnancy	Notes Regarding Use in Pregnancy
LOPINAVIR/ RITONAVIR (Kaletra®, LPV/r)	**Dose:** LPV 400 mg /r 100 mg /r (2 tabs or 5 mL) po bid **2nd and 3rd trimesters:** PK studies suggest dose should be increased to LPV 600 mg/ r 150 mg po bid, especially in PI-experienced patients If standard dosing is used, monitor virologic response and LPV drug levels, if available **Note:** Once-daily dosing (LPV 800 mg/r 200 mg) is not recommended during pregnancy because no data address whether drug levels are adequate with such administration Dose adjustment required if co-administered with NVP or EFV: LPV500 mg/r 125 mg po bid **Food requirements:** Tabs: Take without regard to food Oral sol: Take with food **Available as:** • Tabs: (LPV 200 mg + RTV 50 mg) or (LPV 100 mg + RTV 25 mg) • Oral solution: Each 5 mL contains (LPV 400 mg + RTV 100 mg) Oral solution contains 42% alcohol and therefore may not be optimal for use in pregnancy	Generally well tolerated, good short-term safety profile Diarrhea in 13.8%–23.8% of patients; nausea, vomiting, abdominal pain, asthenia, headache, and rash reported Serum transaminase elevation Class adverse events such as hyperlipidemia, fat redistribution, and hyperglycemia	**Placental transfer:** Low **PK:** AUC decreased in 2nd and 3rd trimesters with standard dosing (*AIDS* 2010;24(14):2193; *AIDS* 2006;20(15):1931; *HIV Med* 2011;12(3):166). AUC with dose of LPV/r 600 mg/150 mg bid in 3rd trimester resulted in AUC similar to nonpregnant adults taking LPV/r 400 mg/100 mg bid (*J Acquir Immune Defic Syndr* 2010;54(4):381).	No evidence of human teratogenicity. Short-term safety demonstrated in Phase I/II studies.

Table 8-7 *continued*

Antiretroviral Drugs in Pregnancy and Recommendations for Antiretroviral Naïve Women

Drug Name	Dosing and Available Formulations	Adverse Effects	Placental Transfer and PK in Pregnancy	Notes Regarding Use in Pregnancy
ALTERNATIVE				
DARUNAVIR (Prezista®, DRV)	**Dose:** Must be combined with low-dose RTV boosting: • ARV naïve: DRV 800 mg po + RTV 100 mg po qd • ARV experienced with no DRV resistance mutations: (DRV 800 mg po + RTV 100 mg po) qd • ARV experienced and any DRV resistance mutations: (DRV 600 mg po + RTV 100 mg po) bid Some experts recommend use of only bid dosing (DRV 600 mg po + RTV 100 mg po) during pregnancy **Food requirements:** Take with food **Available as:** • Tabs: 75 mg, 150 mg, 400 mg, 600 mg	GI intolerance (20%); diarrhea, but less common than with LPV/r; headache (15%); rash (7%); contains a sulfa moiety Stevens-Johnson syndrome and erythema multiforme have been reported; serum transaminase elevation and hepatitis Class adverse events such as hyperlipidemia, fat redistribution, and hyperglycemia	**Placental transfer:** Minimal to low **PK:** In the 3rd trimester and postpartum, decreased DRV levels, especially with qd dosing	Must be combined with low-dose RTV boosting Use with caution or avoid in patients with sulfa allergy Limited experience in human pregnancy
SAQUINAVIR (Invirase®, SQV)	**Dose:** (SQV 1000 mg po + RTV 100 mg po) bid Unboosted SQV is not recommended in pregnancy **Food requirements:** Take with meals or within 2 h after a meal **Available as:** • Caps (hard gel): 200 mg • Tabs: 500 mg	GI intolerance: nausea, diarrhea, abdominal pain; transaminase elevation; PR interval prolongation; QT interval prolongation Class adverse events such as hyperlipidemia, fat redistribution, and hyperglycemia	**Placental transfer:** Minimal **PK:** Limited data on SQV-HGC and 500 mg tablet suggest that (SQV 1000 mg + RTV 100 mg) bid achieves adequate drug levels in pregnancy	Must be combined with low-dose RTV boosting Well tolerated; short-term safety demonstrated for mother and infant for SQV in combination with low-dose RTV Baseline EKG recommended before starting because of potential PR and/or QT interval prolongations. Drug is contraindicated in patients with pre-existing conduction-system disease. Insufficient data to assess for teratogenicity in humans

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Table 8-7 continued

Antiretroviral Drugs in Pregnancy and Recommendations for Antiretroviral Naïve Women

Drug Name	Dosing and Available Formulations	Adverse Effects	Placental Transfer and PK in Pregnancy	Notes Regarding Use in Pregnancy
NOT RECOMMENDED				
INDINAVIR (Crixivan®, IDV)	**Dose:** (IDV 800 mg po + RTV 100 mg po) bid Unboosted IDV is not recommended in pregnancy **Meals:** Take without regard to meals **Available as:** • Caps: 100 mg, 200 mg, 400 mg	Nephrolithiasis +/- hematuria in 5%–15% of patients; indirect hyperbilirubinemia (≥2.5 mg/dL in 10–15% of patients); transaminase elevation Class adverse events such as hyperlipidemia, fat redistribution, and hyperglycemia	**Placental transfer:** Minimal **PK:** Significantly lower levels with standard dosing of IDV alone during pregnancy compared with postpartum. (Antimicrob Agents Chemother 2007;51(2):783; AIDS 2000;14(8):1061) With (IDV 400 mg + RTV 100 mg po) bid, 82% of women met target trough level (Antimicrob Agents Chemother 2008;52(4):1542)	Because of 2x daily dosing, pill burden, and potential for renal stones and hyperbilirubinemia, IDV is not recommended in pregnancy. No evidence of human teratogenicity
NELFINAVIR (Viracept®, NFV)	**Dose:** 1250 mg po bid (750 mg po tid not recommended in pregnancy) **Food requirements:** Take with fatty meal **Available as:** • Tabs: 250 mg, 625 mg • Oral powder: 50 mg/g	Generally well tolerated Diarrhea; serum transaminase elevation Class adverse events such as hyperlipidemia, fat redistribution, and hyperglycemia	**Placental transfer:** Minimal to low **PK:** Adequate drug levels with 1250 mg po bid during 1st and 2nd trimester, but higher variability and lower concentrations observed during 3rd trimester compared with postpartum. NFV 1250 mg po bid was associated with lower blood levels in the 3rd trimester than in the 2nd trimester (Br J Clin Pharmacol 2006;62(3):309; HIV Med 2008;9(10):875).	Not recommended due to lower rate of viral suppression with NFV. In Antiretroviral Pregnancy Registry, a small increase in overall birth defect rates was noted. No specific pattern of defects was noted and clinical relevance is uncertain. Good short-term safety profile for mothers and infants.

Table 8-7 *continued*

Antiretroviral Drugs in Pregnancy and Recommendations for Antiretroviral Naïve Women

Drug Name	Dosing and Available Formulations	Adverse Effects	Placental Transfer and PK in Pregnancy	Notes Regarding Use in Pregnancy
NOT RECOMMENDED				
RITONAVIR (Norvir®, RTV) When used as low-dose booster with other PIs	**Dose:** RTV is used at low doses (i.e., 100–200 mg qd or bid) with other PIs as a pharmacologic enhancer or booster (refer to other PIs for specific dosing recommendations) **Food requirements:** Tabs: Take with food Caps: Take with food if possible (may improve tolerability) **Available as:** • Caps: 100 mg • Tabs: 100 mg • Oral sol: 80 mg/mL (contains 43% alcohol and therefore may not be optimal for use in pregnancy)	GI intolerance: nausea, vomiting, diarrhea; abdominal pain Dose-dependent taste perversion; asthenia; circumoral and peripheral paresthesias; pancreatitis; transaminase elevation Class adverse events such as hyperlipidemia, fat redistribution, and hyperglycemia	**Placental transfer:** Minimal **PK:** Lower drug concentrations during pregnancy compared with postpartum	Should be used only in combination with second PI as low-dose RTV "boost" because of low drug levels in pregnant women when used as a sole PI and poor tolerance when given at full dose RTV as a single PI is not recommended because of inferior efficacy and increased toxicity Limited experience at full dose in human pregnancy No evidence of human teratogenicity
TIPRANAVIR (Aptivus®, TPV)	**Dose:** Must be combined with low-dose RTV boosting: (TPV 500 mg po + RTV 200 mg po) bid **Food requirements:** When taken with RTV tablets, take with meals; with RTV caps or sol, take without regard to meals **Available as:** • Caps: 250 mg • Oral sol: 100 mg/mL	GI intolerance LFTs elevation (17.5%) more common with TPV; severe hepatitis Rash (8-14%); contains a sulfa moiety Rare cases of intracranial hemorrhage Class adverse events such as hyperlipidemia, fat redistribution and hyperglycemia	**Placental transfer:** Moderate, based on very limited data **PK:** Limited studies in human pregnancy	Not recommended in naïve adults and increased toxicity with higher ritonavir dose Limited experience in human pregnancy Must be combined with low-dose RTV boosting Use with caution or avoid in patients with sulfa allergy Insufficient data to assess for teratogenicity in humans

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Table 8-7 *continued*

Antiretroviral Drugs in Pregnancy and Recommendations for Antiretroviral Naïve Women

Drug Name	Dosing and Available Formulations	Adverse Effects	Placental Transfer and PK in Pregnancy	Notes Regarding Use in Pregnancy
INSUFFICIENT DATA TO RECOMMEND USE				
FOSAMPRENAVIR (Lexiva®, FPV)	**Dose:** • ARV naïve: (FPV 1400 mg po + RTV 100–200 mg po) qd • or (FPV 700 mg po + RTV 100 mg po) bid • or FPV 1400 mg po bid ARV experienced: (once daily dosing NOT recommended): • (FPV 700 mg po + RTV 100 mg po) bid • With EFV: (FPV 700 mg po + RTV 100 mg po) bid • or (FPV 1400 mg po + RTV 300 mg po) qd **Food requirements:** Tabs: Take with meals when RTV-boosted Oral suspension: Take without food **Available as:** • Tabs: 700 mg • Oral suspension: 50 mg/mL	GI intolerance most common: nausea, vomiting, diarrhea; headache; rash (in 19% of patients) (contains a sulfa moiety), usually mild-moderate but Stevens-Johnson syndrome reported; serum transaminase elevation Class adverse events such as hyperlipidemia, fat redistribution, and hyperglycemia	**Placental transfer:** Low **PK:** With RTV boosting, AUC reduced in 3rd trimester; however, exposure is greater in 3rd trimester with boosting than in nonpregnant adults without boosting, and trough concentrations in 3rd trimester are adequate for patients without PI resistance mutations	Limited experience in human pregnancy Recommended to be given with low-dose RTV boosting Use with caution or avoid in patients with sulfa allergy Insufficient data to assess for teratogenicity in humans
Integrase Inhibitor				
ALTERNATIVE				
RALTEGRAVIR (Isentress®, RAL)	**Dose:** RAL 400 mg po bid (with rifampin: 800 mg po bid) **Food requirements:** Take without regard to meals **Available as:** • Tabs: 400 mg	Generally well tolerated with adverse effect rates comparable to placebo Nausea, headache, diarrhea, pyrexia Reports of myopathy and rhabdomyolysis Reports of CNS side effects (dizziness, ataxia, depression)	**Placental transfer:** Variable but high **PK:** Extensive variability in 3rd trimester, but RAL exposure not consistently altered compared with postpartum/historical data. Standard dosing recommended.	May be used when drug interactions with PI regimens a concern Limited experience in human pregnancy Insufficient data to assess for teratogenicity in humans

Table 8-7 *continued*

Antiretroviral Drugs in Pregnancy and Recommendations for Antiretroviral Naïve Women

Drug Name	Dosing and Available Formulations	Adverse Effects	Placental Transfer and PK in Pregnancy	Notes Regarding Use in Pregnancy
INSUFFICIENT DATA TO RECOMMEND USE				
ELVITEGRAVIR (EVG)—currently only available as a co-formulation with Cobicistat (COBI/ TDF/FTC) Stribild	**Dose:** (EVG 150 mg + COBI 150 mg + TDF 300 mg + FTC 200 mg) po qd with food	GI intolerance (nausea, diarrhea) New onset or worsening renal impairment Potential decrease in bone mineral density Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue FTC and TDF	**Placental transfer:** No information **PK:** No data in human pregnancy	No experience in human pregnancy
Entry Inhibitors				
NOT RECOMMENDED				
ENFUVIRTIDE (Fuzeon®, T-20)	**Dose:** T-20 90 mg (1 mL) subcut bid into upper arm, anterior thigh, or abdomen, with each injection given at a site different from the preceding injection **Available form:** Single-use vial containing 108 mg of T-20 (as powder) to be reconstituted with 1.1 mL of sterile water for injection, with delivery of approx. 90 mg/mL	Local site reaction (grade 3 or 4) including pain (9%), erythema (32%), pruritus (4%), induration (57%), and nodules or cysts (26%) (with 3% requiring d/c) Bacterial pneumonia (reported in 4.68 events vs. 0.61 events per 100 pt-y) Hypersensitivity reaction (<1%); symptoms may include rash, fever, nausea, vomiting, chills, hypotension, elevated transaminases; may recur on rechallenge	**Placental transfer:** None, but limited data **PK:** Limited data in human pregnancy	Not recommended due to lack of data in ART-naïve adults Minimal data in human pregnancy Insufficient data to assess for teratogenicity in humans Requires twice daily injections

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Table 8-7 *continued*

Antiretroviral Drugs in Pregnancy and Recommendations for Antiretroviral Naïve Women

Drug Name	Dosing and Available Formulations	Adverse Effects	Placental Transfer and PK in Pregnancy	Notes Regarding Use in Pregnancy
INSUFFICIENT DATA TO RECOMMEND USE				
MARAVIROC (Selzentry®, MVC)	**Dose:** • MVC 150 mg po bid when given with strong CYP3A inhibitors, with or without CYP3A inducers, including PIs (except TPV/r) • MVC 300 mg po bid when given with NRTIs, NVP, RAL, T-20, TPV/r, and other drugs that are not strong CYP3A inhibitors or inducers • MVC 600 mg po bid when given with CYP3A inducers, including EFV, ETR (without a CYP3A inhibitor) **Food requirements:** Take without regard to meals **Available formulation:** • Tabs: 150 mg, 300 mg	Generally well tolerated Abdominal pain; cough; upper respiratory tract infections; musculoskeletal symptoms; pyrexia; rash; dizziness, orthostatic hypotension (especially with chronic renal insufficiency) Rare cases of hepatotoxicity	**Placental transfer:** Unknown **PK:** No data in human pregnancy	Limited experience in human pregnancy Insufficient data to assess for teratogenicity in humans

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

For ARV-naïve pregnant women, preferred or alternative regimens include one of the preferred or alternative PIs, NNRTIs or integrase inhibitors, as noted in Table 8-7, combined with a 2 NRTI backbone. This backbone may be ZDV/3TC, ABC/3TC or TDF/FTC. 3TC and FTC can substitute for each other. TDF/FTC and ABC/3TC may be preferred because of once daily co-formulations and less frequent toxicity than ZDV-containing regimens, but there is less experience with use of these regimens in pregnancy. ABC should NOT be used in patients who test positive for HLA-B*5701. Drugs listed in the Do Not Recommend category are placed in that category either because of toxicity or lower rate or viral suppression, or because they are not currently recommended in naïve adults and adolescents due to limited data. The latter group may eventually move to a different category as more data becomes available.

Special Considerations

Pharmacokinetics: Physiologic changes that occur during pregnancy may affect the kinetics of drug absorption, distribution, biotransformation, and elimination, thereby also affecting requirements for drug dosing and potentially altering a pregnant woman's susceptibility to drug toxicity (*Clin Pharmacokinet* 2004;43(15):1071; *Br J Clin Pharmacol* 2008;66(2):179). In general, the pharmacokinetics of NRTI and NNRTI drugs are similar in women who are and are not pregnant; protease inhibitor (PI) pharmacokinetics are more variable, particularly in later pregnancy. The need for a dose adjustment depends on the PI, the patient's treatment experience, and the use of interacting concomitant medications (Reyataz [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2011. http//www packageinserts.bms.com/pi/pi_reyataz.pdf. Accessed 7/11/2012; *AIDS* 2006;20(15):1931; *Br J Clin Pharmacol* 2006;62(3):309; *Br J Clin Pharmacol* 2006;62(3):309; *J Acquir Immune Defic Syndr* 2008;49(5):485; *J Antimicrob Chemother* 2009;63(6):1223; *J Acquir Immune Defic Syndr* 2010;54(4):381).

Gastrointestinal upset and/or hyperemesis: ARV drugs that cause gastrointestinal upset may not be well tolerated in early pregnancy, when morning sickness is common, and may increase risk for nonadherence or inadequate absorption. Some pregnant women also develop hyperemesis in early pregnancy, though there is no evidence this is increased in the setting of HIV. If antiemetics are not effective, consideration should be given to temporary discontinuation of all ARVs, in which case, all drugs should be stopped simultaneously and restarted simultaneously when nausea and vomiting have resolved or been effectively treated.

Teratogenicity: The potential harm to the fetus from maternal intake of a specific drug depends on a number of factors: the drug itself, dose, gestational age at exposure, duration of exposure, interaction with other agents to which the fetus is exposed, and, to an unknown extent, the genetic makeup of the mother and fetus. Of the currently FDA-approved ARV drugs available in the United States, only EFV is considered to have significant teratogenic potential. Primate studies have demonstrated an increase in significant malformations (anencephaly, anoophthalmia/microophthalmia, cleft palate) at doses similar to human therapeutic exposures, and both retrospective and prospective studies have reported CNS defects in human infants exposed to

EFV in utero. The magnitude of the risk is not known, however, and may be low. A recent systematic review and meta-analysis of data from 21 studies reporting on first-trimester exposures did not indicate an increased risk of birth defects among infants born to women taking EFV during the first trimester compared with those taking other ARVs during the first trimester (*AIDS* 2011;25(18):2301); one neural tube defect occurred among 1,437 live births (incidence 0.07%). No visible anomalies were found among 147 infants in a West African cohort born after first-trimester use of EFV, whereas an analysis of the PACTG219 database found a significantly increased risk of birth defects (including one neural tube defect) among 5 of 32 infants exposed to EFV in the first trimester (*Pediatr Infect Dis J* 2010;29(8):721; *J Acquir Immune Defic Syndr* 2011;56(2):183).

EFV has been classified as an FDA Pregnancy Category D drug. Because of the potential for teratogenicity, women who are taking EFV should avoid pregnancy and use of EFV should whenever possible be avoided during the first trimester, which is the primary period of fetal organogenesis; however, EFV can be continued in women who present for care in the first trimester on EFV-containing regimens that are effective in suppressing VL. This is because the risk of neural tube defects is restricted to the first 5-6 weeks of pregnancy (and pregnancy is rarely recognized prior to this) and unnecessary ARV drug changes during pregnancy may be associated with a loss of virologic control and may thus increase the risk of transmission to the infant (*HIV Clin Trials* 2010; 11:303). Initiation after the first trimester can be considered if, after considering other alternatives, EFV is the best choice for an individual woman. If EFV is to be continued postpartum, adequate contraception should be assured.

Adverse Pregnancy Outcomes

Preterm birth: Although currently published data show conflicting results, there may be a small increased risk of preterm birth in pregnant women who are taking PI-based combination ART or prophylaxis (*AIDS* 2007;21(5):607; *AIDS* 2006;20(18):2345; *AIDS* 2004;18(17):2337; *N Engl J Med* 2002;346(24):1863; *J Acquir Immune Defic Syndr* 2005;38(4):449). A variable that may confound published observational studies is the increased rate of preterm birth if combination ART is started before conception, as compared with later in pregnancy, which itself may reflect confounding by severity or indication (*Sex Transm Infect* 2009;85(2):82). When data from the IMPAACT P1025 observational cohort were examined by multivariable analysis to correct for HIV disease stage, excluding delivery initiated at preterm gestation due to medical or obstetrical factors, PI-based combination ART was no more likely than non-PI-based combination ART to be associated with spontaneous preterm birth (odds ratio [OR] 1.22; 95% confidence interval [CI], 0.70–2.12) (*J Infect Dis* 2010;201(7):1035). A recent combined analysis of three large studies, two from Europe and one from the United States, found that injection drug use and more advanced HIV disease were associated with preterm birth in all three cohorts (*BJOG* 2010;117(11):1399). Given the clear benefits of such therapy for both a woman's health and prevention of MTCT, PIs should not be withheld for fear of altering pregnancy outcome.

Hyperglycemia and/or diabetes: Although hyperglycemia and diabetes have been reported in individuals on PIs and pregnancy is a risk factor for hyperglycemia (*Ann Intern Med* 1997;127(10):948; *AIDS Clin Care* 1998;10(6):41), the majority of studies to date have not shown an increased risk of glucose intolerance associated with PI-based regimens in pregnancy (*Infect Dis Obstet Gynecol* 2002;10(4):187; *Obstet Gynecol* 2006;107(50):1115; *Am J Obstet Gynecol* 2007;196(4):331).

Secondary analyses of two large cohorts did not find an association with type of ART and gestational diabetes, except for an association of PI initiation before pregnancy or during the first trimester with gestational diabetes in the PACTG 316 cohort (*Am J Obstet Gynecol* 2004;190(2):506; *J Acquir Immune Defic Syndr* 2005;38(4):449). Standard glucose screening at 24–28 weeks of gestation should be performed in HIV infected women who are taking ART during pregnancy. Some experts recommend earlier glucose screening in women who continue PI-based therapy that was initiated prior to pregnancy (particularly in women of minority race/ethnicity); this approach is similar to the recommendations for women with risk factors for glucose intolerance, such as maternal obesity, advanced maternal age, and family history of type II diabetes mellitus (*Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*. 2012. http://www.aidsinfo.nih.gov).

Mitochondrial toxicity (maternal risk): NRTI drugs are known to induce mitochondrial dysfunction; risk varies by specific drug and is associated with long-term use. In one study, ddI and ddI-containing regimens were associated with the greatest degree of mitochondrial suppression (*Antimicrob Agents Chemother* 2008;52(8):2825). Clinical disorders linked to mitochondrial toxicity include neuropathy, myopathy, cardiomyopathy, pancreatitis, hepatic steatosis, and lactic acidosis. Among these disorders, symptomatic lactic acidosis and hepatic steatosis may occur more frequently in women (*Clin Infect Dis* 2007;45(2):254; *Clin Infect Dis* 2007;45(2):261). Typical initial symptoms are relatively nonspecific and include nausea, vomiting, abdominal pain, dyspnea, and weakness. Metabolic acidosis with elevated serum lactate and liver enzymes is common. Bristol-Myers Squibb has reported several maternal deaths due to lactic acidosis/hepatic steatosis, all in women who were taking a combination of d4T/ddI as part of their ARV regimen at the time of conception and for the duration of pregnancy (the d4T/ddI combination is no longer recommended for HIV infected adults, pregnant or not). Other nonfatal cases of lactic acidosis have been reported in pregnant women taking this combination (*Sex Transm Infect* 2002;78(1):58; *AIDS* 2003;17(2):272). Cases of lactic acidosis have also been described with exposure to other NRTIs (*Lancet* 1999;353(9156):901). It is not known if pregnancy increases the incidence of this syndrome; however, pregnancy itself can mimic some of the early symptoms of lactic acidosis/hepatic steatosis and is also associated with several rare but life-threatening disorders of liver metabolism (acute fatty liver of pregnancy, hemolysis, elevated liver enzymes and low platelets—the HELLP syndrome). Data suggest that a disorder of mitochondrial fatty acid oxidation in the mother or her fetus during late pregnancy may play a role in the development of these disorders, as well as ARV-related mitochondrial toxicity (*Proc Natl Acad Sci USA* 1995;92(3):841; *N Engl J Med* 1999;340(22):1723;

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Semin Perinatol 1999;23(2):100; *Mol Genet Metab* 2000;71(1-2):182). Therefore, obstetric providers should be aware of lactic acidosis/hepatic steatosis syndrome, be alert to and educate patients about suggestive signs and symptoms, and consider it in their differential diagnosis when appropriate. If the diagnosis is suspected, then serum lactate, liver enzymes, and electrolyte levels should be obtained, expert consultation engaged, and all ARV drugs should be discontinued.

Mitochondrial toxicity (infant risk): Some studies suggest that mitochondrial dysfunction might develop in infants with in utero exposure to NRTI drugs (*AIDS* 2003;17(12):1769; *Lancet* 2002;359(9306):583; *AIDS* 2003;17(14):2053), generally presenting as neurologic disease, and in some cases resulting in death; however, results from large clinical studies from the United States and Europe have been reassuring (*J Acquir Immune Defic Syndr* 2000;25(3):261; *J Acquir Immune Defic Syndr* 2003;32(4):380). Several studies, often small, have reported laboratory abnormalities without clinical symptoms (differences in mtDNA, lactate levels, echocardiographic abnormalities, and hematologic parameters) among infants with perinatal ARV exposure compared with unexposed infants (*Pediatrics* 2009;124(6):e1189; *J Infect Dis* 2008;198(6):851; *Environ Mol Mutagen* 2007;48(3-4):201; *Environ Mol Mutagen* 2007;48(3-4):173; *AIDS* 2005;19(10):1071; *J Infect Dis* 2006;194(8):1089; *J Am Coll Cardiol* 2011;57:76). The clinical significance of these laboratory findings is unclear. Even if an association is more clearly demonstrated, the development of severe or fatal mitochondrial disease appears to be extremely rare and the benefit of reduced perinatal transmission is thought to clearly outweigh the risk. Mitochondrial dysfunction should be considered in uninfected children with perinatal ARV exposure who present with severe clinical findings of unknown etiology, particularly neurologic findings. Current recommendations call for long-term clinical follow-up for any child with in utero exposure to ARVs.

Hepatotoxicity and/or skin rash: Although all ARV drugs may cause liver toxicity, special concerns have been raised regarding the use of NVP. Several studies have demonstrated an increased risk of developing symptomatic, often rash-associated, NVP-related hepatotoxicity among women, particularly those with CD4+ cell counts >250/mm^3 (*J Acquir Immune Defic Syndr* 2004;35:538; *Clin Infect Dis* 2001;32:124; *J Acquir Immune Defic Syndr* 2003;34:S21). Deaths from hepatic failure have been reported in pregnant women taking ARV regimens that include NVP (*J Acquir Immune Defic Syndr* 2004;36:772; *HIV Med* 2006;7:255). In general, in controlled clinical trials, hepatic events, regardless of severity, have occurred in 4.0% (range 0%–11.0%) of patients on NVP and severe or life-threatening rash has occurred in approximately 2% of patients taking NVP (Viramune package insert. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.; 2011. http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing+Information/PIs/Viramune/Viramune.pdf. Accessed 7/11/2012).

In a recent analysis of two multi-center prospective cohorts, pregnancy itself was a risk factor for liver enzyme elevations (RR 4.7; 95% CI; 3.4–6.5) but NVP use was not, regardless of pregnancy status (*AIDS* 2010;24(1):109). Nevertheless, because some of the early symptoms of hepatotoxicity are relatively nonspecific and can be confused with common symptoms during

pregnancy, care providers should be aware of potential liver toxicity with or without rash if NVP is used in pregnancy and should conduct frequent and careful monitoring of clinical symptoms and liver enzymes (i.e., ALT and AST), particularly during the first 18 weeks of therapy. NVP should be used only as a component of a combination regimen when ART is being initiated in women with CD4+ cell counts >250 cells/mm³ if the benefit clearly outweighs the risk. In patients with pre-existing liver disease, monitoring should be performed more frequently when initiating therapy and monthly thereafter (*Semin Liver Dis* 2003;23(2):173). Liver enzyme levels should be checked in all women who develop a rash while taking NVP. Patients who develop suggestive clinical symptoms accompanied by elevation in serum transaminase levels (ALT and/or AST) or who have asymptomatic but severe liver enzyme elevations (i.e., more than 5X the upper limit of normal) should stop NVP and should not take NVP in the future. Hepatic toxicity has not been seen in women receiving single-dose NVP during labor for prevention of perinatal transmission of HIV (*Drug Saf* 2009;32(2):147). Women who enter pregnancy on NVP-containing regimens and are tolerating them well may continue therapy, regardless of CD4+ cell count.

Anemia: Several ARVs, and ZDV in particular, may cause bone marrow suppression and result in anemia. Pregnant women are at increased risk for anemia because of increased demands on nutritional stores, including iron and folic acid; the addition of ARV regimens that include ZDV may exacerbate anemia. Nutritional counseling, along with iron and folate supplementation, should be provided to ensure adequate intake of other nutrients. Administration of ZDV is usually associated with macrocytosis. When evaluating anemia in a pregnant woman who is taking ZDV, the presence of macrocytosis should not exclude consideration and evaluation of causes of anemia usually resulting in microcytic or normocytic red blood cell indices; nor should the presence of macrocytosis result in an assumption of more typical causes of macrocytic anemia, such as folate or B12 deficiency. Depending on severity, anemia should be treated and a non-ZDV-containing regimen may be considered.

8

Guidelines for Antepartum Care

History and Physical Examination

The following is the key information that should be obtained from the initial and follow-up history and physical evaluation for the HIV infected pregnant woman. Certain symptoms of HIV disease, ARV toxicity, and normal or abnormal pregnancy may overlap, resulting in possible delays in appropriate diagnosis and management. (See also Chapter 4, *Primary Medical Care*.)

HIV History

- Date of diagnosis
- History of HIV-related symptoms, OIs, or malignancies
- CD4+ cell count nadir and current value
- Current and highest VL

- Results of any prior drug resistance testing
- Complete ARV history, including specific drugs, side effects or toxicity, length of treatment, adherence, response to treatment, and reasons for any changes
- Partner's HIV status
- Disclosure of HIV status: to whom

Pregnancy History

- Previous pregnancies and outcomes
- Pregnancy complications
- Mode(s) of delivery
- Use of ARV prophylaxis or ART in previous pregnancy(ies)
- HIV status of other children

Family History

- Relevant family history of possible heritable diseases

Signs and Symptoms of HIV/AIDS (initial and follow-up visits)

- Generalized lymphadenopathy
- Thrush
- Constitutional symptoms, such as fever (38.5°C) or diarrhea >1 mo
- Herpes zoster involving 2 episodes or >1 dermatome
- Peripheral neuropathy
- Wasting
- Dysphagia
- Dyspnea
- Persistent mucocutaneous herpetic ulcerations
- Cognitive dysfunction

Signs and Symptoms of Pregnancy-Related Complications

- Elevated blood pressure
- Significant edema
- Severe headache
- Vaginal bleeding or fluid leakage
- Intractable nausea and vomiting
- Dysuria
- Abnormal vaginal discharge
- Persistent abdominal or back pain or cramping
- Decreased fetal movement

Signs or Symptoms of ARV Toxicity

- Nausea/vomiting
- Abdominal pain
- Jaundice
- Extreme fatigue
- Skin rash

Laboratory Examination

Recommended laboratory evaluations for HIV infected pregnant women are listed in Table 8-8.

Table 8-8

Recommended Laboratory Evaluations for the HIV Infected Pregnant Woman

Upon Entry into Prenatal Care and Ongoing

Test	Frequency and Comments
HIV serology	• Test at initial visit if HIV infection not previously confirmed • Test if there is positive rapid or screening test without confirmatory assay
CD4+ cell count and/or CD4+%	• At baseline and every 3 mo during pregnancy • Consider repeat test if significant change in clinical status or near milestones for therapeutic decisions (e.g., OI prophylaxis) • Consider extending test interval to every 6 mo for patients who are adherent to therapy, with sustained viral suppression and stable clinical status >2–3 y
HIV RNA	• At baseline • 2–4 wk after initiating or changing ART (should see decrease by minimum of 1 log 10 copies/mL by 1 mo after start of potent regimen) • Monthly until RNA levels are undetectable • At least every 3 mo during pregnancy • At 36 wk to determine mode of delivery • More frequently if adherence is a concern
ARV resistance assay	• At baseline with VL >500–1000 c/mL, whether ARV naïve or currently on therapy • Repeat with virologic failure • Genotypic testing preferred over phenotypic
CBC	• At baseline • Repeat (at least) every trimester in women on stable ARV regimen • Consider more frequent testing if marrow-toxic drugs (e.g., ZDV) are used or with anemia
Liver enzymes	• At baseline • Repeat at least every trimester in women on stable ARV regimen • More frequent monitoring with initiation of NVP or with clinical signs/symptoms of hepatotoxicity • Repeat as indicated with abnormal results or use of other hepatotoxic drugs
Electrolytes, BUN, creatinine	• At baseline • Repeat as indicated with abnormal results or use of potentially nephrotoxic drugs
Urinalysis, calculated creatinine clearance	• At baseline in newly diagnosed patients and those not previously evaluated, in Black patients and in those with advanced HIV or comorbid conditions • Consider prior to initiating regimens containing TDF or IDV
Syphilis serology	• At baseline • Repeat, as noted below, on the basis of gestational age

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Table 8-8	*continued*

Recommended Laboratory Evaluations for the HIV Infected Pregnant Woman

Upon Entry into Prenatal Care and Ongoing

Test	Frequency and Comments
Hepatitis serology: • HBsAg • HBcAb • HBsAb • HCV Ab • HAV Ab	• Initiate HBV vaccine series if negative for HBsAg, HBcAb, and HBsAb • Initiate HAV vaccination if negative HAV Ab, particularly in the setting of HBV or HCV Infection • If anti-HCV+, order HCV RNA • Consider HCV RNA with negative HCV Ab with risk factors for HCV or unexplained liver enzyme abnormalities, especially with CD4+ cell count <200/mm^3
Rubella, blood type and Rh, antibody screen, urine culture, GC/chlamydia, Pap smear	• At baseline • Repeat antibody screen, as noted below, on the basis of gestational age • Repeat urine culture as needed with symptoms • Repeat GC/chlamydia, as noted below, on the basis of gestational age; as needed with signs/symptoms of infection; or on the basis of risk factors • Cytobrush can be used for Pap smear during pregnancy
PPD or interferon-gamma release assay	• Positive skin test = ≥5 mm induration • Anergy testing not indicated and prior BCG vaccination not contraindication to skin testing • Positive results: obtain CXR and other evaluation to rule out active TB • Consider repeat testing if recent TB exposure
Hemoglobin electrophoresis, red blood cell indices	• Perform in women at increased risk for hemoglobinopathies
G6PD	• Consider screening women with predisposing racial/ethnic background (e.g., Black, Middle Eastern) before receiving oxidant drugs (e.g., dapsone, sulfonamides)
CMV IgG	• Consider baseline serology in patients at low risk for CMV (non-IDU)*
Toxoplasmosis IgG	• Screen all patients with initial HIV diagnosis • Repeat with CD4+ cell count <100/mm^3 if not on TMP-SMZ, or with symptoms suggestive of toxoplasmic encephalitis
Varicella zoster virus IgG	• Consider if no history of chicken pox or shingles • Consider for post-exposure prophylaxis considerations
Urine toxicology screen	• As indicated on the basis of patient history, signs/symptoms, and local protocols
Serum screening for Tay-Sachs disease	• Consider screening both partners if at increased risk (i.e., Ashkenazi Jewish, French-Canadian, or Cajun descent)
Bacterial vaginosis screening	• Perform if signs/symptoms of vaginitis
Ultrasound	• Perform in first trimester for confirmation of gestational age

Table 8-8	*continued*

Recommended Laboratory Evaluations for the HIV Infected Pregnant Woman

Upon Entry into Prenatal Care and Ongoing

Test	Frequency and Comments
Nuchal translucency, PAPP-A, free or total beta-hCG	• Voluntary; requires counseling • Screening for Down syndrome; abnormal result requires further evaluation

At 16–20 Weeks

Ultrasound	• Anomaly screen • Repeat as indicated to monitor fetal growth
Maternal serum alpha-fetoprotein	• Voluntary; requires counseling • Screening test for neural tube and abdominal wall defects • Abnormal result (usually >2.5 multiple of the median) requires further evaluation
Quadruple screen (hCG, unconjugated estriol, MSAFP, Inhibin A)†	• Voluntary; requires counseling • Noninvasive test to determine risk of neural tube and abdominal wall defects, Down syndrome, and trisomy 18 • Abnormal result requires further evaluation

At 24–28 weeks

CBC, syphilis serology, antibody screen	
Diabetes screen	• Glucose 1 h after 50 g Glucola ; 3 h oral GTT if abnormal (an alternative screen is a "one-step" 75 g oral GTT, recently endorsed for non-HIV-infected pregnant women by the American Diabetes Association and the International Association of Pregnancy Study Groups [*Am J Obstet Gynecol* 2010; 202(6):654.e1; *Diabetes Care* 2010; 33(3):676]). • Consider earlier screening in women with ongoing PI-based therapy initiated prior to pregnancy or other high-risk factors for glucose intolerance.

At 32–36 weeks

GC/chlamydia testing	
Group B streptococcus culture – 35–37 wk; vaginal and rectal	• Recommend intrapartum chemoprophylaxis with IV PCN G (2.5 million units q 4 h) if positive (or if GBS bacteriuria during current pregnancy or with previous infant with invasive GBS disease • If unknown GBS status, IP prophylaxis: with delivery <37 wk gestation, membrane rupture ≥18 h, or IP temperature ≥100.4°F/38.0°C or positive intrapartum GBS nucleic acid amplification test (ACOG *Practice Bulletin* No. 485, April 2011. Available at http://www.acog.org/Resources_And_Publications/Committee_Opinions/Committee_on_Obstetric_Practice/Prevention_of_Early-Onset_Group_B_Streptococcal_Disease_in_Newborns. Accessed 6/26/2012)
HIV RNA	• Results may influence decisions about mode of delivery
Syphilis serology	• Consider in high-risk patients or populations

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Table 8-8	*continued*

Recommended Laboratory Evaluations for the HIV Infected Pregnant Woman

Upon Entry into Prenatal Care and Ongoing

Test	Frequency and Comments
Other Considerations	
HLA B*5701	• Obtain prior to starting ABC
Coreceptor tropism assay	• Obtain prior to prescribing CCR5 entry inhibitor
Serum lactate, electrolytes, liver enzymes; consider anion gap, CPK, amylase, lipase	• Signs or symptoms suggest possible lactic acidosis in setting of NRTI therapy, especially if long term
Fasting lipid profile	• May delay until postpartum, unless baseline history of hyperlipidemia +/- treatment • If obtained, subsequent measurements on the basis of history and initial results
Liver enzymes (ALT, AST)	• With initiation of NVP (does not apply to single-dose prophylactic therapy in labor); q 2 wk during mo 1; monthly through mo 4; every 1–3 mo thereafter. More frequently in patients with pre-existing liver disease.
Type-specific HSV serology	• May be useful to identify women at risk for HSV and to guide counseling, especially if sexual partner has HSV infection

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

* Seroprevalence CMV IgG in US adults is 50–60%; IDU patients ≥90%

† Accurate gestational age is essential for interpretation

Antepartum Fetal Surveillance and Testing

The general purpose of antepartum fetal surveillance and testing is to identify fetal abnormalities or compromise so that appropriate interventions can be undertaken to optimize fetal health and prevent fetal damage or death. In some instances, the purpose is to aid in decisions regarding continuation of the pregnancy versus early delivery (*ACOG Practice Bulletin* No. 9; *Int J Gynaecol Obstet* 2000;68(2):175; reaffirmed 2009).

Indications for antepartum fetal surveillance and testing:

- **Maternal conditions that increase risk of fetal death:** include but are not limited to the following conditions: hemoglobinopathies, chronic renal disease, systemic lupus erythematosus, hypertension, and diabetes

- **Pregnancy-related conditions that increase risk of fetal death:** include pregnancy-induced hypertension, decreased fetal movement, oligohydramnios, polyhydramnios, intrauterine growth retardation, post-term pregnancy, mild to moderate isoimmunization, previous fetal death, and multiple gestation

- **HIV considerations:** Data are lacking specifically on the need for and use of fetal surveillance techniques in HIV infected women during pregnancy. HIV infection per se is not an indication for fetal testing; however, fetal surveillance should be performed in HIV infected women with comorbidities that may increase fetal risk. Furthermore, HIV infection, especially when more advanced or associated with substance abuse, may be associated with increased risk for poor fetal growth, which places the fetus at increased risk. Fetal surveillance may be considered for pregnant women on ART, particularly when the mother's regimen contains newer agents with which there is little experience in pregnancy. Ultimately, the need for fetal surveillance should be determined case by case.

Fetal surveillance techniques include the following:

- **Fetal movement assessment:** Also known as kick counts; the perception of 10 distinct movements in a period of up to 2 hours is reassuring.

- **Nonstress test (NST):** A reactive or reassuring result is defined as two or more fetal heart rate accelerations (at least 15 beats/minute above baseline and lasting at least 15 seconds on a fetal monitor) within a 20-minute period.

- **Contraction stress test (CST):** A negative or reassuring result is the absence of late or significant variable fetal heart rate decelerations with at least three contractions (lasting at least 40 seconds) within 10 minutes.

- **Biophysical profile:** Consists of an NST combined with observations of fetal breathing, fetal movements, fetal tone, and amniotic fluid volume by real-time ultrasonography. Each component is assigned a score of 2 (normal or present) or 0 (abnormal or absent); a composite score of 8 or 10 is normal.

- **Modified biophysical profile:** Combines NST and amniotic fluid index (AFI), which is the sum of measurements of the deepest amniotic fluid pocket in each abdominal quadrant; normal AFI is >5 cm. This test combines a short-term indicator of fetal acid-base status (NST) and an indicator of long-term placental function (AFI); placental dysfunction often leads to poor fetal growth and oligohydramnios.

- **Umbilical artery Doppler velocimetry:** Evaluation of flow velocity wave forms in the umbilical artery, which is characterized by high-velocity diastolic flow in a normally developing fetus. This technique is beneficial only in pregnancies complicated by intrauterine growth restriction.

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Although data from randomized clinical trials are lacking, antepartum fetal surveillance has been consistently associated with lower rates of fetal death when compared with rates among untested pregnancies from the same institution or among historic controls with similar complicating factors. Testing should be initiated at 32–34 weeks' gestation, but may be started as early as 26–28 weeks' gestation in very high-risk pregnancies. When the condition prompting testing persists, testing should be repeated periodically (weekly or, in some cases, twice weekly) until delivery. Fetal reevaluation should also be repeated if the mother's medical condition deteriorates significantly or if there is an acute decrease in fetal movement, regardless of the amount of time elapsed since the previous test.

NST, CST, biophysical profile, and modified biophysical profile are the most commonly used forms of testing; they have a negative predictive value >99%. They are not predictive of acute events, however, such as placental abruption or umbilical cord accidents. On the other hand, the positive predictive value of an abnormal test can be quite low and the response to an abnormal result should be dictated by the individual clinical situation. Any abnormal test result requires further evaluation or action. Management should be based on test results, gestational age, degree of oligohydramnios (if assessed), and maternal condition. Oligohydramnios should prompt evaluation for membrane rupture. Depending on the degree of oligohydramnios, gestational age, and maternal medical condition, oligohydramnios warrants either delivery or close maternal/fetal surveillance.

Ultrasound: There are many indications for obstetric ultrasound; some of the more common include the following (*Obstet Gynecol* 2009;113(2 Pt 1):451):

- Pregnancy dating
- Evaluation of fetal growth
- Evaluation of vaginal bleeding during pregnancy
- Determination of fetal presentation
- Suspected multiple gestation
- Significant uterine size/clinical dates discrepancy
- Pelvic mass
- Suspected ectopic pregnancy
- Documentation of fetal viability and/or to rule out fetal death
- Biophysical profile for antepartum fetal surveillance
- Suspected polyhydramnios and/or oligohydramnios
- Placental localization
- Abnormal serum alpha-fetoprotein or quadruple screen
- Evaluation for fetal anomalies
- Evaluation of fetal condition in late registrants for prenatal care

With transvaginal ultrasound, an intrauterine gestational sac can be seen as early as 5 weeks after the woman's last menstrual period and fetal heart activity can be detected by 6 weeks. First-trimester bleeding is the most common indication for early ultrasound, when the major differential diagnoses are threatened abortion (miscarriage) and ectopic pregnancy. Accurate pregnancy dating is best accomplished late in the first trimester or in the second trimester; screening for anomalies is best performed at 16–20 weeks' gestation. A third-trimester (or other follow-up) ultrasound(s) should be considered, particularly in women with more advanced disease and/or other maternal pregnancy-related factors that could affect fetal growth.

Amniocentesis, chorionic villus sampling, cordocentesis: Though data are still somewhat limited, risk of MTCT does not appear to increase during amniocentesis or other invasive diagnostic procedures among women who are on effective combination ART. HIV infected women who have indications for invasive testing in pregnancy, such as abnormal ultrasound or aneuploidy screening, should be counseled about the potential risk of HIV transmission along with other risks of the procedure so they can make an informed decision about testing. Ideally, a woman should have an undetectable VL at the time of any procedure. Procedures should be performed under continuous ultrasound guidance and, if possible, the placenta should be avoided. Some experts consider chorionic villus sampling and cordocentesis too risky to offer to HIV infected women and recommend limiting procedures to amniocentesis (*Am J Obstet Gynecol* 2006;194(1):192).

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Prevention for Positives

All HIV infected pregnant women should be encouraged to disclose their HIV status to their sexual partners, with assistance if needed, and HIV testing should be encouraged for partners. Condom use during pregnancy is recommended, particularly if partners are serodiscordant; recent data suggest that pregnancy may increase risk of female-to-male HIV transmission (*AIDS* 2011;25 (15):1887). However, even when both partners are HIV infected, condom use is encouraged to prevent both acquisition of other STIs and potential reinfection with another HIV strain. Women who have active substance abuse problems should be encouraged and assisted in accessing treatment, including opioid-assisted therapy if indicated. Harm reduction practices, such as needle exchange and not sharing injection equipment, should be discussed and encouraged in IDUs who are not able or not willing to stop using altogether.

Antepartum Scenarios for Antiretroviral Drug Use

(Source: *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States.* 2012. http://www.aidsinfo.nih.gov)

ARV naïve (no prior experience with ARVs): Current adult treatment guidelines are updated regularly and can be accessed online at http://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0/.

- HIV infected pregnant women should be prescribed standard potent combination ART, taking into account current information about use in pregnancy, including safety and risk of teratogenicity. (See Table 8-7.)

- **Current adult treatment guidelines recommend ART for all HIV-infected individuals. The strength of this recommendation varies on the basis of the pretreatment CD4+ cell count (see Chapter 4 *Primary Medical Care*).**

  - **CD4+ cell count ≤500 cells/mm³ (strong recommendation)**

  - CD4+ cell count >500/mm³ (moderate recommendation)

  - ART also is recommended for HIV-infected individuals for the prevention of transmission of HIV (strong recommendation) and therefore should be recommended for women with partners who are HIV-negative or of unknown status, without regard to CD4+ cell count.

  - Patients starting ART should be willing and able to commit to lifelong treatment and should understand the benefits and risks of therapy and the importance of adherence. The potential benefits of early therapy must be weighed against possible drug toxicity, cost, and the patient's risk of developing viral resistance with suboptimal adherence, which may be more likely during the postpartum period (*AIDS Care* 2008;20(8):958; *J Acquir Immune Defic Syndr* 2008;48(4):408; *Curr Opin Infect Dis* 2012;25(1):58; *J Womens Health* 2010;19(10):1863; *AIDS* 2012:26:2039).

- In women who require immediate initiation of therapy for their own health, ART can begin in the first trimester, but use of EFV should be avoided in the first trimester.

- Pregnant women with CD4+ cell counts >500/mm³ should be counseled about current treatment recommendations, the potential risks and benefits of stopping and continuing with an ART regimen following delivery, and the need for strict adherence if the regimen is continued postpartum.

- The use of raltegravir in late pregnancy for women who are diagnosed late in pregnancy and have high viral loads has been suggested because of its ability to rapidly suppress viral load (approximately 2-log copies/mL decrease by Week 2 of therapy). (*AIDS Patient Care STDS* 2012; 26(12):717; *J Antimicrob Chemother* 2010;65(9):2050;. *AIDS* 2010; 24(15):2416). However, this approach has only been described in anecdotal reports and efficacy and safety of this approach is unclear; it is not routinely recommended and should only be used in consultation with an expert.

- While it is considered suboptimal to use a non-HAART regimen (i.e., triple NRTIs, ZDV only) for prophylaxis alone during pregnancy, with ARV discontinuation after delivery, that approach may be considered in some limited circumstances.

- The decision to start the ARV regimen in the first trimester or delay until 12 weeks of gestation will depend on CD4+ cell count, VL, and maternal conditions such as nausea and vomiting. Earlier initiation of a combination

ARV regimen may be more effective in reducing in utero transmission, but the benefit must be weighed against the potential long-term effects of first-trimester drug exposure.

- If possible, one or more NRTIs with high levels of placental transfer to the fetus should be included to provide pre-exposure prophylaxis (ZDV, 3TC, FTC, d4T, TDF, ABC).

- If VL is above the threshold for resistance testing (e.g., >500–1000 c/mL), ARV drug resistance studies should be performed before therapy is initiated. If HIV is diagnosed late in pregnancy, the ARV regimen should be initiated promptly without waiting for the results of resistance testing.

- NVP may be used as a component of initial therapy for pregnant women with CD4+ cell counts <250/mm³; however, due to an increased risk of hepatic toxicity, NVP should be used as a component of ART in pregnant women with CD4+ cell counts >250 cells/mm³ only if the benefit clearly outweighs the risk.

ARV experienced (currently on ART):

- In general, a pregnant woman who is taking and tolerating an ART regimen that is effective in suppressing her VL should continue on the regimen. Discontinuation or interruption of therapy may lead to an increase in VL, with possible disease progression and a decline in immune status, and has been associated with increased risk of perinatal transmission (*Clin Infect Dis* 2009;48(9):1310).

- ARV drug resistance testing is recommended if a pregnant woman has detectable viremia (e.g., >500–1000 copies/mL) on therapy. Results of this testing can be used to select a regimen that may be more effective in suppressing VL to an undetectable level.

- If a woman is taking EFV and her pregnancy is recognized during the first trimester, EFV should be continued if there is maximal VL suppression and the regimen is well tolerated.

  - Treatment changes during pregnancy increase the risk of incomplete viral suppression at the end of pregnancy (*HIV Clin Trials* 2010;11(6):303).

  - The risk of neural tube defects is restricted to the first 5–6 weeks of pregnancy and pregnancy is rarely recognized prior to 4–6 weeks of pregnancy.

- If a pregnant woman has an undetectable VL and is taking and tolerating NVP, she should continue with that ARV regimen regardless of CD4+ cell count. Increased risk of hepatic toxicity has not been seen in pregnant women who are taking and have achieved immune reconstitution with NVP-based therapy.

Prior ART for treatment or prophylaxis:

- If a patient has taken ARVs in the past for treatment or prophylaxis, the care provider should obtain an accurate history of all prior ARV use, including tolerance; clinical, virologic, and immunologic efficacy; the indication for stopping therapy; and results of prior resistance testing.

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- Perform HIV ARV resistance testing prior to initiating repeat ARV prophylaxis or therapy if VL >500-1000 c/mL. In women who present late in pregnancy, treatment or prophylaxis should be initiated promptly, based on available history, without waiting for the results of resistance testing. Limited data regarding rates of resistance after pregnancy-limited use of combination ARV regimens for prophylaxis, particularly with documented virologic suppression at the time of labor, suggest that PI-based regimens may be less likely than NNRTI-based regimens to be associated with detection of resistance mutations (*Clin Infect Dis* 2010;50(6):890; *AIDS* 2010;24(1):45; *J Acquir Immune Defic Syndr* 2009;51(5):522; *AIDS Res Hum Retroviruses* 2010;26(3):293). This may be related to the longer half-life of NNRTIs, resulting in functional monotherapy if the regimen is stopped abruptly (see **Guidelines for Postpartum Care**, p. 333, for discussion of strategies to prevent resistance with NNRTI regimens). No data exist to guide the choice of ARV regimens for women with prior experience taking ARVs as pregnancy-limited prophylaxis solely for prevention of MTCT.

- Data are limited on ART efficacy following the use of ARV solely for prevention of MTCT. Most experience is with NVP-based ART regimens initiated after peripartum single-dose NVP. Data suggest decreased virologic and clinical efficacy when regimens are started within 12–24 months after delivery (*N Engl J Med* 2010;363(16):1499; *PLoS Med* 2010;7(2):e1000233; *AIDS* 2007;21(8):957; *N Engl J Med* 2007;356(2):135). Investigators recently assessed data from the French Perinatal Cohort on virologic suppression with PI-based ART administered for prevention of MTCT to women who had received ARV prophylaxis during a previous pregnancy; no differences were seen in rates of VL suppression at delivery among ARV-naïve women compared with those who had received previous prophylaxis or according to previous prophylaxis regimens (*J Acquir Immune Defic Syndr* 2011;57(2):126).

- If a woman is ARV-experienced and requires ART for her own health, her care provider should perform a thorough clinical evaluation (including assessment of liver, renal, and cardiovascular function) prior to reinitiating ART.

- Initiate a combination ARV drug regimen, with the regimen chosen on the basis of resistance testing and prior ART history (including efficacy and toxicity), avoiding EFV in the first trimester or drugs with known risk for the pregnant woman (e.g., combination ddI/d4T). Virologic response should be monitored carefully; if virologic response is inadequate, resistance testing should be repeated.

- Expert consultation is recommended when choosing ARVs for pregnant women with prior ARV experience.

Stopping ART During Pregnancy

HIV infected women taking ART who present for care during the first trimester should generally not discontinue or interrupt treatment during pregnancy. Women who present in the first trimester and are taking an EFV-containing regimen should not interrupt therapy but can continue on treatment if VL is suppressed. A recent analysis from a prospective cohort of 937 HIV infected mother-child pairs found that interruption of ART during pregnancy, including interruption in the first and third trimesters, was independently associated

with perinatal transmission (*Clin Infect Dis* 2009;48(9):1310). Furthermore, unnecessary ARV drug changes during pregnancy may be associated with a loss of virologic control and thus may increase the risk of MTCT (*HIV Clin Trials* 2010;11(6):303).

If an ARV regimen for therapy and/or prophylaxis is stopped abruptly for severe or life-threatening toxicity, severe pregnancy-induced hyperemesis unresponsive to anti-emetics, or other acute illnesses precluding oral intake, all ARVs should be stopped at the same time and reinitiated at the same time.

If an ARV regimen is being stopped electively and the patient is receiving an NNRTI, then one of the following options should be considered: (1) stop the NNRTI first and continue other ARVs for a period of time; or (2) switch from an NNRTI to a PI prior to interruption and continue the PI with the other ARVs for a period of time before electively stopping. The optimal interval between stopping an NNRTI and stopping other ARVs is not known, but a period of at least 7 days is recommended. Given the potential for prolonged (i.e., >3 weeks) detectable EFV concentrations, some experts recommend continuing the other ARVs or substituting a PI plus two other agents for up to 30 days. A recent study of 412 women who received single-dose nevirapine and were randomized to receive zidovudine/lamivudine, tenofovir/emtricitabine, or lopinavir/ritonavir for either 7 or 21 days found an overall new nevirapine resistance mutation rate of 1.2% when assessed by population genotype at 2 and 6 weeks following completion of treatment, with no difference by length of treatment. However, low-frequency nevirapine-resistant mutations at codons 103, 181, and 184 detected using allele-specific PCR emerged significantly more often in the 7-day arms (13/74 [18%]) than in the 21-day arms (3/66 [5%], P = .019). (*Clin Infect Dis* 2013;56(7):1044).

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If NVP is stopped and more than 2 weeks have passed prior to restarting therapy, then NVP should be restarted with the 2-week dose escalation period.

Failure of Viral Suppression in Pregnancy

Women on antiretroviral (ARV) regimens who have detectable virus at any time during pregnancy using ultrasensitive assays should

- be evaluated for resistant virus (if plasma HIV RNA is >500–1,000 copies/mL);

- be assessed for adherence, tolerability, incorrect dosing, or potential problems with absorption (such as with nausea/vomiting or lack of attention to food requirements);

- be considered for ARV regimen modification.

Treatment modification during pregnancy has been independently associated with an HIV-1 RNA level >400 copies/mL in late pregnancy highlighting the importance of using potent and well-tolerated regimens during pregnancy to maximize effectiveness and minimize need to modify treatment. (*HIV Clin Trials* 2010;11(6):303–311.)

Baseline HIV RNA levels have been shown to affect the time to response; most patients with an adequate viral response at 24 weeks have had at least a 1-log copies/mL HIV RNA decrease within 1–4 weeks after starting therapy. In a retrospective multicenter cohort of 378 pregnant women, 77.2% achieved HIV RNA <50 c/ml by delivery, with success of viral suppression varying by baseline HIV RNA level: with baseline <10,000 c/ml, gestational age at initiation did not affect success up to 26.3 weeks but with baseline >10,000 c/ml, delaying initiation past 20.4 weeks significantly reduced ability for maximal suppression at deliver. (*AIDS* 2012;26(9):1095)

A recent systematic review and meta-analysis of adherence to antiretroviral regimens during and after pregnancy in low-, middle- and high-income countries (27% of studies were from the US) found a pooled estimate of 73.5% adherence during pregnancy (threshold defining good adherence to ART varied across studies from >80–100%) (*AIDS* 2012;26(16):2039) Therefore, evaluation of and support for adherence during pregnancy is critical to achievement and maintenance of maximal viral suppression.

The addition of raltegravir in late pregnancy has been suggested for women who have high viral loads and/or in whom multiple drug-resistant mutations have resulted in incomplete suppression of viremia because of the ability of raltegravir to rapidly suppress viral load. In the setting of a failing regimen related to nonadherence and/or resistance, there are concerns that the addition of a single agent may further increase risk of resistance and potential loss of future effectiveness with raltegravir. A recent report found 10–23-fold increase in transaminase levels following introduction of a raltegravir-containing regimen in late pregnancy, with return to normal levels after raltegravir discontinuation. (*J Obstet Gynaecol Can* 2013;35(1):68). Therefore, at the current time, this approach cannot be recommended.

Scheduled cesarean delivery is recommended for HIV-infected pregnant women who have HIV RNA levels >400 copies/mL near the time of delivery.

Special Situations

Acute infection: Preventing HIV acquisition is a subject that should be addressed with all pregnant and breastfeeding women. Several studies suggest that pregnancy may be a time of increased risk for HIV transmission (*Lancet* 2005;366(9492):1182; *AIDS* 2009;23(10):1255; *J Clin Virol* 2010;48(3):180), even when controlling for sexual risk behaviors (*Lancet* 2005;366(9492):1182). Primary or acute HIV infection in pregnancy or while a woman is breastfeeding is associated with an increased risk of perinatal HIV transmission and may represent a significant proportion of residual MTCT in the United States. This high rate of transmission is likely related to two factors: 1) the high VL of plasma, breast milk, and the genital tract associated with acute infection; and 2) the difficulty of diagnosis. Because acute infection is easily missed, opportunities for prevention are missed as well (*AIDS* 2002;16(8):1119; *AIDS* 2010;24(4):573).

All pregnant women with acute or recent HIV infection should start combination ART as soon as possible to prevent MTCT, with the goal of suppressing plasma HIV RNA levels to below detectable levels.

Data from the United States and Europe indicate that transmitted virus may be resistant to at least one ARV in 6%–16% of patients (*J Infect Dis* 2005;192(6):958; *AIDS* 2010;24(8):1203). Genotypic resistance testing should be performed at baseline, simultaneously with initiation of ART or prophylaxis, with a subsequent adjustment in ARV regimen if needed to optimize virologic response. Because clinically significant PI resistance is less common than NNRTI resistance in ARV-naïve patients, an RTV-boosted PI-based regimen should generally be initiated.

Healthcare providers should maintain a high level of suspicion of acute HIV infection in pregnant or breastfeeding women who have a compatible clinical syndrome (e.g., fever, lymphadenopathy, pharyngitis, skin rash, myalgias/arthralgias) even in the absence of reported high-risk behaviors.

When acute retroviral syndrome is suspected in pregnancy or during breastfeeding, a plasma HIV RNA test should be obtained in conjunction with an HIV antibody test. A low-positive HIV RNA level (<10,000 copies/mL) may represent a false-positive test because values in acute infection are generally very high (i.e., >100,000 copies/mL) (*Ann Intern Med* 2001;134(1):25; *AIDS* 2002;16(8):1119); however, non-B HIV-1 subtypes may not amplify as well as subtype B, which may result in a lower HIV RNA level, even with acute infection.

If seroconversion is suspected in nursing mothers, breastfeeding should be interrupted until definitive confirmation of infection is obtained; if seroconversion is confirmed, breastfeeding should not be resumed.

Hepatitis B infection: Women with chronic HBV infection (persistent hepatitis B surface antigenemia for at least 6 months) and who are hepatitis A virus (HAV) IgG negative should receive the HAV vaccine series because of the added risk of acute HAV in people with chronic viral hepatitis. This vaccine can be given safely during pregnancy (*ACOG Practice Bulletin* No. 86; *Obstet Gynecol* 2007;110(4):94; reaffirmed 2009).

An ART regimen that includes drugs active against both HIV and HBV (i.e., TDF + 3TC or FTC) is recommended for pregnant women with HIV/HBV co-infection to avoid reactivation of HBV and development of immune reconstitution inflammatory syndrome (IRIS). An IRIS-related flare of HBV activity during pregnancy can occur even among women with relatively high CD4+ cell counts. Use of ARVs that have anti-HBV activity will also reduce HBV viremia and may decrease the risk of failure of neonatal HBV immune globulin (HBIG) and HBV vaccine for prevention of perinatal transmission of HBV.

Elevation of hepatic enzymes after ART initiation may be related to HBV flare due to immune reconstitution with effective ARV regimens; HBV infection also increases hepatotoxic risk of PIs and NVP. Liver enzymes should be assessed 2–4 weeks after initiation of ARVs and then at least every 3 months. If hepatic toxicity occurs, consultation with an expert in HIV and HBV co-infection is strongly recommended. Pregnant women with HBV/HIV co-infection should be counseled about signs and symptoms of liver toxicity and advised to avoid alcohol. If ARVs are discontinued postpartum in women with HIV/HBV co-infection, frequent monitoring of liver function tests for potential HBV flare is recommended, with prompt re-initiation of treatment for both HIV and HBV if a flare is suspected.

Interferon (IFN) and peg-IFN are not recommended for use in pregnancy because of direct antigrowth and antiproliferative effects and should be used only if the potential benefit outweighs the risk (*Neurology* 2005;65(6):807).

All infants born to mothers who are HBsAg+ should receive hepatitis B immune globulin (HBIG) and should receive an initial dose of HBV vaccine within 12 hours after birth. The second and third doses of vaccine should be administered at 1 and 6 months of age, respectively. This regimen is >95% effective in preventing HBV infection in these infants.

Hepatitis C infection: Because of an increased risk for fulminant HAV or HBV in patients infected with HCV, HAV vaccination is recommended for HCV infected women who are anti-HAV-negative; HBV vaccination is recommended for women who are HBV uninfected. These vaccinations may be given safely during pregnancy (*ACOG Practice Bulletin* No. 86; *Obstet Gynecol* 2007;110(4):94; reaffirmed 2009).

Treatment of HCV aims to eradicate infection and prevent the long-term complications of progressive liver disease. It generally includes combination therapy with pegylated interferon plus ribavirin; however, treatment with these agents is not recommended during pregnancy (*Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States.* Updated Sept. 14, 2011; http://www.aidsinfo.nih.gov/Guidelines/HTML/3/perinatal-guidelines/188/initial-postnatal-management-of-the-hiv-exposed-neonate). Ribavirin is teratogenic at low doses in multiple animal species. Both women and men of childbearing potential who are receiving ribavirin should be counseled about the need to use effective contraception during therapy and for 6 months after completion. Interferons are not recommended for use in pregnancy because of direct antigrowth and antiproliferative effects. The recently FDA-approved drugs boceprevir and telaprevir should be used only in combination with interferon and ribavirin and therefore should not be used in pregnancy. Evaluation for treatment, including liver biopsy, can be delayed until 3 months or more after delivery to allow pregnancy-related changes in disease activity to resolve.

A European study of perinatal HCV transmission found that the use of effective combination ART was associated with a strong trend for reduction in HCV transmission [OR 0.26, 95% CI, 0.07–1.01] (*J Infect Dis* 2005;192(11):1872).Therefore, standard recommendations for ARV drug use during pregnancy for treatment of HIV and/or prevention of MTCT HIV transmission should be followed.

As with HBV infection, elevation in hepatic enzymes may occur after starting ARVs; this may be related to HCV flare due to immune reconstitution with effective ARV regimens or to greater vulnerability to hepatotoxicity with ARVs drugs.

Liver enzymes should be assessed 2–4 weeks following initiation of ARVs and then at least every 3 months. (*Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*). If hepatic toxicity

occurs, consultation with an expert in HIV and HCV co-infection is strongly recommended. Pregnant women with HCV/HIV co-infection should be counseled about signs and symptoms of liver toxicity and advised to avoid alcohol.

Internal fetal monitoring, amniocentesis, and duration of membrane rupture greater than 6 hours may increase risk of HCV transmission (*J Infect Dis* 2005;192(11):1880; *Ann Hepatol* 2010;9 suppl:92). Most studies that have included both HIV infected and uninfected pregnant women with HCV have found that elective CS delivery does not reduce the risk of perinatal HCV transmission (*AIDS* 2007;21(13):1811; *Am J Obstet Gynecol* 2008;199(3):315; *Arch Gynecol Obstet* 2011;283:255).

HIV-2 infection: HIV-2 infection is endemic in some West African countries and in parts of India (*JAMA* 1993;270(17):2083; *AIDS* 1989;3 suppl 1:S89). It also occurs in countries with large numbers of immigrants from these regions (*Bull Epidemiol Hebd* 2007;46-47:386). HIV-2 is less infectious than HIV-1, with a 5-fold lower rate of sexual transmission and a 20–30-fold lower rate of vertical transmission (*Lancet* 1990;335(8697):1103; *Lancet* 1994;343(8903):943).

HIV-2 infection should be suspected if a pregnant women or her partner is from an endemic country and presents with the following pattern of HIV testing: a positive test on HIV screening assay with a repeatedly indeterminate HIV-1 western blot and HIV-1 RNA VL at or below the limit of detection. Although most commercially available HIV screening tests can detect both HIV-1 and HIV-2, the Bio-Rad Laboratories Multispot HIV1/2 test is the only FDA-approved antibody test that can distinguish between HIV-1 and HIV-2; in some laboratories HIV-2 supplemental tests such as HIV-2 immunoblot or HIV-2-specific western blot are available, but these tests do not have FDA approval for diagnosis. One HIV-2 VL assay is now commercially available in the United States; it can be ordered through the University of Washington (1-800-713-5198 or commserv@u.washington.edu).

For HIV-2+ pregnant women who require treatment for their own health (e.g., significant clinical disease or CD4+ cell count <500/mm^3), two NRTIs and a boosted PI are currently recommended for treatment. On the basis of available safety data in pregnancy, ZDV/3TC + LPV/r, or, alternatively, TDF/FTC + LPV/r or TDF + 3TC + LPV/r is recommended for treatment during pregnancy.

Optimal prophylaxis regimens for HIV-2+ pregnant women (without HIV-1 co-infection) who do not require treatment for their own health (e.g., CD4+ cell count >500/mm^3 and no significant clinical disease) have not been defined. Some experts would use a boosted PI-based regimen for prophylaxis and stop the drugs postpartum. Other experts would use ZDV prophylaxis alone during pregnancy and intrapartum (*Clin Infect Dis* 2010;51(7):833). Some experts would not provide any drug prophylaxis because the risk of transmission from such women is very low (*HIV Med* 2008;9(7):452). The infant should receive the standard 6-week ZDV prophylactic regimen. Expert consultation is advised.

NNRTIs and ENF are not active against HIV-2 and should not be used for treatment or prophylaxis.

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Infants born to HIV-2+ mothers should be tested with HIV-2-specific virologic assays at similar time points as HIV-1 testing would be conducted. Because these tests are not commercially available, testing must be referred to academic or research laboratories. Determining loss of HIV-2 antibodies by age 18 months is also recommended (*HIV Med* 2008;9(7):452). Breastfeeding is not recommended for infants of HIV-2+ mothers.

Opportunistic Infections

Prophylaxis indications and recommendations for primary prophylaxis of OIs in pregnancy are noted in Table 8-9. Once an individual has had the listed infections, prophylaxis to prevent recurrence is recommended as standard of care. Criteria for discontinuation of secondary prophylaxis vary by infection. See the USPHS *Guidelines for Prevention and Treatment of Opportunistic Infections in Adults and Adolescents* (http://aidsinfo.nih.gov/Guidelines/) for current recommendations for treatment and secondary prophylaxis of each OI In pregnancy.

Table 8-9

Primary Prophylaxis for Opportunistic Infections in Pregnant Women*

Pathogen	Indication	Regimen	Alternatives[1]	Comment
Pneumocystis pneumonia	Strong recommendation: CD4+ cell count <200 c/mm^3 or oral thrush Moderate recommendation: CD4+% <14% or history of AIDS-defining illness	TMP-SMZ DS or SS 1 po qd	Dapsone Atovaquone	Test for G6PD deficiency before administration of dapsone Criterion for stopping primary prophylaxis: CD4+ cell count >200 c/mm^3 for >3 mo in response to ART
Toxoplasma gondii	Strong recommendation: Toxoplasma IgG+ with CD4+ cell count <100 c/mm^3 or if toxoplasma seroconversion occurs	TMP-SMZ DS 1 po qd	TMP-SMZ (alternate dosing) Dapsone + pyrimethamine + leucovorin	Test for G6PD deficiency before administration of dapsone Criterion for stopping primary prophylaxis: CD4+ cell count >200 c/mm^3 for >3 mo in response to ART

| Table 8-9 | *continued* |

Primary Prophylaxis for Opportunistic Infections in Pregnant Women*

Pathogen	Indication	Regimen	Alternatives[1]	Comment
Mycobacterium tuberculosis	Strong recommendation: Positive diagnostic test for latent TB (e.g., TST reaction ≥ 5 mm or (+) interferon gamma release assay), no prior treatment for active or latent TB and no evidence of active TB, **or** Negative diagnostic test for latent TB but contact with active TB and no evidence of active TB	INH 300 mg qd or 900 mg twice weekly plus pyridoxine 25 mg qd for 9 mo	Rifampin Rifabutin	Must rule out active TB prior to beginning prophylaxis; for persons exposed to drug-resistant TB, select drugs with consultation
Mycobacterium avium complex	Strong recommendation: CD4+ cell count <50 c/mm^3	Azithromycin 1200 mg po once weekly or 600 mg po twice weekly	Rifabutin (must rule out active TB)	Must rule out active MAC infection Criterion for stopping primary prophylaxis: CD4+ cell count >100 c/mm^3 for >3 mo in response to ART

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

* See OI Guidelines for Dosing (http://aidsinfo.nih.gov/Guidelines) (accessed 5/20/13)

Immunizations

See the USPHS *Guidelines for Prevention and Treatment of Opportunistic Infections in Adults and Adolescents* (http://aidsinfo.nih.gov/Guidelines/) for current recommendations for immunizations in pregnancy.

Immunization should be considered in pregnancy when the risk for exposure or maternal and/or fetal infection is high and the vaccine is thought unlikely to cause harm. Immune-suppressed HIV infected patients and pregnant women should avoid live-virus or live-bacteria vaccines. HIV-infected patients who are symptomatic or have low CD4+ cell counts may have suboptimal responses to vaccination. Some, but not all, studies have shown a transient (<4 weeks) increase in VL after immunization. This increase in viremia may be prevented with appropriate ART (*Medical Management of HIV Infection*, 2009–2010. Johns Hopkins University School of Medicine). For this reason, clinicians may consider deferring routine vaccination until after the patient is on an effective ARV regimen and avoiding administration late in pregnancy (i.e., close to delivery), when most transmission is thought to occur. Table 8-10 presents current immunization recommendations for HIV-infected pregnant women.

Table 8-10

Immunizations Recommended for HIV Infected Pregnant Women

Vaccines	Recommendation	Comments
Pneumococcal (see Table 4-9)	Recommended if patient has not received the vaccine during the previous 5 y	
Influenza	Recommended	Administer annually before flu season begins Use of live attenuated influenza vaccine is contraindicated
Tetanus-diphtheria-pertussis (Tdap)	Recommended with each pregnancy • optimal timing is 27–36 weeks gestation • if tetanus booster indicated for wound management, administer at any time • if unknown or incomplete tetanus vaccination, administer 3 vaccinations containing tetanus and diphtheria (Td) toxoids with recommended schedule 0, 4 weeks, 6–12 mo. Tdap should replace 1 dose of Td, preferably between 27–36 wks gestation	Pregnant women who have not already received Tdap should receive a dose as soon as possible after delivery to ensure pertussis immunity and reduce the risk for transmission of Td to the newborn
HBV	Recommended for all susceptible patients	3 doses: at 0, 1 mo, 6 mo of pregnancy

Table 8-10 *continued*

Immunizations Recommended for HIV Infected Pregnant Women

Vaccines	Recommendation	Comments
HAV	Recommended for all susceptible (HAV Ab-negative) patients with chronic HCV or HBV; also indicated before travel to endemic areas, in IDUs, and with community outbreaks	2 doses: at 0, 6 mo of pregnancy
Enhanced-potency inactivated polio vaccine	Use if not previously immunized and traveling to areas where risk for exposure is high	Oral polio vaccine is a live virus vaccine and is contraindicated in HIV infected people
Immune Globulins		
	Recommended for measles exposure in persons with symptomatic HIV	
	Recommended for HAV, with exposure to HAV in close contact/sex partner, or with travel to underdeveloped country (especially in patients with advanced HIV, who may have poor antibody response to vaccine)	
	Recommended for rubella, within 72 h of exposure	
Hyperimmune Globulins		
Varicella-zoster virus (VZV) immune globulin	Recommended for susceptible adults (i.e., undetectable antibodies to VZV or no history of either chickenpox or shingles) after significant exposure to chickenpox or VZV (significant exposure = household, hospital room, close indoor contact >1 h, prolonged face-to-face contact)	Give within 96 h of exposure
Hepatitis B immune globulin	Recommended for needlestick or sexual contact with HBsAg+ person in susceptible individuals	Give HBIG; start HBV vaccine series within 14 d of exposure

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

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Frequency of Visits

The frequency of prenatal care visits depends on several factors specific to each patient, including the health of the mother, gestational age, presence of pregnancy-related complications, ARV regimen and response, and psychosocial needs. In uncomplicated pregnancies, visits generally are scheduled monthly in early pregnancy and every 1–2 weeks from 28–30 weeks of gestation until delivery; when possible, they should be coordinated with other healthcare visits.

Consultations to Consider During Pregnancy

HIV infected women may need certain specialty consultations during pregnancy. Ideally, many of these consultations can be handled within the same clinic or center where the patient is seen for obstetrical or primary medical care. When possible, referral of the HIV infected pregnant woman to an obstetrician with HIV expertise and experience is advised, in which case the obstetrician may manage many of the patient's HIV-specific treatment issues.

In general, consultative needs may include the following:

- **Perinatology** to address special obstetrical concerns, including use of HIV-related or other medications in pregnancy, discussions about fetal monitoring/evaluation, other appropriate antepartum/intrapartum evaluation and management. When indicated, consultation should ideally be with a perinatologist who has HIV experience/expertise.

- **Infectious disease/HIV specialist** to address HIV-related treatment issues, including choice of ARV regimen and need for OI prophylaxis or treatment. This consultation is particularly important if the patient is newly diagnosed with HIV infection during pregnancy.

- **Pediatrics** to address care of the infant after birth, including testing for HIV, use of ZDV, and *Pneumocystis jirovecii* pneumonia (PCP) prophylaxis in exposed infants

- **Nutrition** to address proper diet, the need for nutritional or vitamin/mineral supplementation, and food safety issues when needed

- Substance abuse management when indicated

- **Psychiatry/psychology** to address signs/symptoms of depression and other psychiatric disorders and their management, if needed

- **Social services** to address needs related to housing, transportation, domestic violence, access to medications and medical care, etc.

Counseling and Support

Support systems: At the initial visit, the healthcare provider should assess a patient's support systems (i.e., determine who knows the patient's HIV status, what problems she has encountered with disclosure, which family members and/or friends provide ongoing support, and what barriers exist to disclosing her HIV status to sexual or needle-sharing partners). These issues should be readdressed at intervals throughout pregnancy as needed. The use of peer counselors may be especially helpful.

Contraception use postpartum: Discussion about postpartum contraceptive plans should be initiated in early to mid-pregnancy to allow time for comprehensive education and counseling about available options and adequate time for informed decision making. Women who receive family planning counseling during prenatal care are more likely to use effective contraception postpartum (*Thromb Res* 2011;127 Suppl 3:s35).

Condom use during pregnancy: Sexual activity should be reviewed at each visit and condom use reinforced.

Drug use/treatment: History of and/or ongoing substance abuse, including use of tobacco and alcohol as well as illicit drugs, should be assessed at the initial visit and at intervals during prenatal care, if indicated. Type of substance(s), amount of use, route of administration, and prior drug or alcohol treatment should be documented. The patient should be counseled about specific risks associated with substance abuse in pregnancy (see Chapter 9, **Psychosocial Issues**) and drug or alcohol treatment during pregnancy should be encouraged and facilitated for active problems.

Adherence: Before initiating an ARV regimen, each patient should be educated and counseled about the importance of adherence to prescribed medications, and medication adherence should be assessed and reinforced at each visit (see Chapter 5, **Adherence**).

Clinical trials: Pregnant HIV infected women should be informed about the availability of and offered participation in clinical trials for which they are eligible.

Advance directives: The issue of advance directives for care in the event of sudden deterioration in the woman's health, as well as guardianship plans for children in the event of the mother's incapacitation or death, should be discussed, and legal assistance should be facilitated, if needed.

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Guidelines For Intrapartum Care

The goals of intrapartum management are to further reduce the risk of perinatal transmission and minimize the risk of maternal and neonatal complications.

Universal Precautions

Gowns, gloves, and eye protection should be used in all deliveries and in examinations or procedures likely to generate splashing blood or amniotic fluid. (See Chapter 12, **Occupational Exposure.**) When used, this should provide adequate protection for healthcare workers. Medical care should not be altered because of considerations of potential occupational exposure.

Intrapartum ART and Prophylaxis (http://aidsinfo.nih.gov)

Intravenous (IV) ZDV is recommended during the intrapartum period for HIV infected pregnant women with VL ≥ 400 c/mL (or unknown VL), regardless of their antepartum regimen or mode of delivery, to reduce perinatal HIV transmission.

- Administer a loading dose of 2 mg/kg IV over 1 hour, followed by continuous infusion of 1 mg/kg/hour until delivery.

- For a scheduled CS delivery, IV ZDV should begin 3 hours before surgery; with unscheduled CS, consideration may be given to shortening this interval, depending on the indications for CS.

- IV ZDV should be given even with documented or suspected ZDV resistance.

However, IV ZDV is not required for HIV infected women receiving combination ARV regimens who have HIV RNA <400 copies/mL near delivery. In a study from the French Perinatal Cohort, intrapartum prophylaxis was not associated with transmission in women with VL <400 c/mL at delivery (*AIDS* 2008;22(2):289).

Women who are taking an antepartum combination ARV regimen should continue it on schedule, to the degree possible, during labor and prior to scheduled CS delivery to maximize virologic efficacy and minimize the development of resistance. If oral ZDV is a part of the antepartum regimen and IV ZDV is indicated, the oral ZDV component of the regimen can be stopped while the patient receives IV ZDV. For women who are receiving a d4T-containing antepartum regimen, d4T should be discontinued during labor if IV ZDV is being administered. If maternal ART must be interrupted temporarily (e.g., for less than 24 hours) in the peripartum period, all drugs (except for intrapartum IV ZDV, when indicated) should be stopped and reinstituted simultaneously to minimize the chance of developing resistance.

When CS delivery is planned, oral medications may be continued preoperatively with sips of water. Medications requiring food ingestion for absorption can be taken with liquid dietary supplements, contingent on consultation with the attending anesthesiologist during the preoperative period.

HIV infected women in labor who have not received antepartum ARV drugs should receive IV ZDV during labor, with subsequent infant combined ARV prophylaxis for 6 weeks. Women of unknown HIV status who present in labor should have a rapid HIV test performed. If the test is positive, a confirmatory HIV test should be sent as soon as possible and maternal/infant ARVs should be initiated without waiting for results of the confirmatory test. Rapid HIV testing (see http://www.cdc.gov/hiv/topics/testing/rapid/index.htm. Accessed 4/10/12) should be available on a 24-hour basis at all facilities with a maternity service and/or neonatal intensive care unit. The National HIV/AIDS Clinicians' Consultation Center website provides information on state HIV testing laws (http://www.nccc.ucsf.edu/consultation_library/state_hiv_testing_laws. Accessed 4/10/12).

Mode of Delivery

(Current recommendations: *Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*, http://www.aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf. Accessed 4/9/12)

Planned vaginal delivery: Vaginal delivery can generally be safely planned in women who are taking combination ARV regimens and who have plasma HIV RNA levels <1000 copies/mL near the time of delivery because of the low rate of transmission among this group and the lack of data that establish the additional benefit of CS in this situation. Recent studies indicate that the use of combination ARV regimens and attainment of a very low or undetectable HIV VL are associated with very low rates of perinatal HIV transmission. These include a recent report from a comprehensive national surveillance system in the United Kingdom and Ireland, where HIV transmission occurred in three (0.1%) of 2,309 and 12 (1.2%) of 1,023 infants born to women with HIV RNA of <50 copies/mL and 50–999 copies/mL, respectively. The transmission rate among all women who received at least 14 days of ART was 40 (0.8%) of 4,864, regardless of mode of delivery (*AIDS* 2008;22(8):973). In this and another large cohort (*Clin Infect Dis* 2005;40(3):458), there were no significant differences in transmission rates by mode of delivery when VL and the use of combination ARV regimens were taken into account.

Scheduled cesarean section: Scheduled CS at 38 weeks' gestation is recommended for women with HIV RNA levels >1000 copies/mL near the time of delivery (whether on ARVs or not) and for women with unknown HIV RNA levels near the time of delivery. Early studies, performed before VL testing and the use of optimal combination ARV regimens became the standard of care, found that scheduled CS, when performed before the onset of labor and/or membrane rupture, reduced MTCT by 55% to 80% in the absence of ARV prophylaxis and with ZDV alone (*Lancet* 1999;353:1035; *N Engl J Med* 1999;340:977).

When CS is performed to prevent HIV transmission, it should be scheduled at 38 weeks' gestation to decrease the likelihood of labor onset or membrane rupture before delivery. In a study of 1,194 infants born to HIV infected mothers, no statistically significant association was observed between mode of delivery and infant respiratory distress syndrome when adjusted for gestational age and birthweight (*Obstet Gynecol* 2010;116 2 Pt 1:335).

For women who are not HIV infected, ACOG recommends that planned CS not be performed before 39 weeks' gestation due to the risk of iatrogenic prematurity (*Obstet Gynecol* 2008;112(3):717; *N Engl J Med* 2009;360(2):111). When CS is performed for standard obstetrical indications (e.g., malpresentation), it should be scheduled at 39 weeks, with timing based on menstrual dating and ultrasound.

For HIV infected women presenting in late pregnancy and not taking ARVs, scheduled CS is likely to provide additional benefit in reducing risk of perinatal transmission of HIV unless viral suppression can be documented

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prior to 38 weeks. Depending on the baseline RNA level, reduction in plasma HIV RNA to undetectable levels usually takes several weeks (*Clin Infect Dis* 2007;44(12):1647).

It is not clear whether CS after membrane rupture or labor onset provides benefit in preventing perinatal transmission. Management of women originally scheduled for CS who present with ruptured membranes or in labor must be individualized on the basis of the duration of rupture, progress of labor, plasma HIV RNA level, current ARV therapy or prophylaxis, and other clinical factors.

When preterm membrane rupture occurs (<37 weeks' gestation), decisions about delivery should be made on the basis of gestational age, HIV VL level, current ARV regimen, and evidence of acute infection (e.g., chorioamnionitis). Expert consultation is recommended. The ARV regimen should be continued and initiation of IV ZDV, if indicated, considered if imminent delivery seems possible.

Maternal morbidity and mortality are increased with CS compared with vaginal delivery (*Obstet Gynecol* 1999;94:942). Most studies have demonstrated that HIV infected women have increased rates of postoperative complications, mostly infectious, compared with women who do not have HIV infection, and that the risk of complications is related to the degree of immunosuppression (*Acta Obstet Gynecol Scand* 1999;78(9):789; *Eur J Obstet Gynecol Reprod Biol* 2000;90(1):73; *Int J Gynaecol Obstet* 2001;74(1):9; *Am J Obstet Gynecol* 2001;184(6):1108).

A Cochrane review of six studies of HIV infected women concluded that urgent CS delivery was associated with the highest risk of postpartum morbidity, that scheduled CS was intermediate in risk, and that vaginal delivery had the lowest risk of morbidity (*Cochrane Database Syst Rev* 2005;(4):CD005479).

Complication rates in most studies (*Am J Obstet Gynecol* 2000;183(1):100; *J Acquir Immune Defic Syndr* 2001;26(3):236; *Am J Obstet Gynecol* 2002;186(4):784; *AIDS* 2004;18(6):933) were within the range reported in populations of women who were not HIV infected but had similar risk factors, and were not of sufficient frequency or severity to outweigh the potential benefit of reduced transmission.

Most complications relate to postpartum infections (e.g., endometritis, wound infection, urinary tract infection, pneumonia) but also include complications related to hemorrhage, since blood loss is generally greater with CS. Factors that increase the risk of complications include low socioeconomic status, genital infections, malnutrition, smoking, and prolonged labor or membrane rupture, some of which may be more common in the setting of HIV infection.

Prophylactic antibiotics should be given when CS is performed for prevention of HIV transmission.

Women should be counseled about the risks and potential benefits of CS for the purpose of reducing perinatal HIV transmission; decisions should be individualized on the basis of this discussion and the specific situation. The woman's autonomy to make an informed decision regarding route of delivery should be respected and honored.

Other Intrapartum Considerations

If spontaneous membrane rupture occurs before or early in the course of labor, interventions to decrease the interval to delivery, such as administration of oxytocin, may be considered in women without indications for CS.

Absent clear obstetric indications , the following procedures should generally be avoided because of potential increased risk of transmission: artificial rupture of membranes, routine use of fetal scalp electrodes, operative delivery with forceps or vacuum extractor, or episiotomy.

Delayed cord clamping has been associated with improved iron status and additional benefits (e.g., decreased risk of intraventricular hemorrhage) in both term and preterm births to HIV uninfected mothers (*Pediatrics* 2006;117(4):1235; *Neonatology* 2007;93(2):138; *J Perinatol* 2011;31 suppl 1:S68). Although HIV-specific data are lacking, there is no reason to modify this practice when the mother is HIV infected.

Treatment for postpartum hemorrhage due to uterine atony: If a woman is receiving a CYP3A4 enzyme inhibitor (e.g., PI), methergine should not be used unless alternative treatments for postpartum hemorrhage (e.g., prostaglandin F2-alpha, misoprostol, oxytocin) are not available and if the need for pharmacologic treatment outweighs the risks. If used, methergine should be administered in the lowest effective dose for the shortest duration possible. If she is receiving a CYP3A4 enzyme inducer (e.g., NVP, EFV, etravirine), the potential exists for decreased methergine levels and inadequate treatment effect; therefore, additional uterotonic agents may be needed.

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Postnatal Care for the HIV-Exposed Infant

Antiretroviral prophylaxis

The 6-week neonatal component of the ZDV prophylaxis regimen is recommended for all HIV exposed neonates. Short-term toxicity of infant ZDV prophylaxis has been minimal, consisting primarily of transient hematologic toxicity, mainly anemia, which generally resolves by age 12 weeks.

A 4-week neonatal ZDV prophylaxis regimen is recommended in the United Kingdom and several European countries when the mother has taken ARVs prenatally (*HIV Med* 2008;9(7):452; *Pediatr Infect Dis J* 2011;30(5):408). This approach may be considered if there are concerns about adherence or toxicity with the 6-week regimen. The 4-week ZDV regimen may allow earlier recovery of anemia in otherwise healthy infants compared with the 6-week ZDV course (*Pediatr Infect Dis J* 2010;29(4):376). Consult with a pediatric HIV specialist if early discontinuation of infant prophylaxis is considered.

Table 8-11 presents recommendations for neonatal ZDV dosing to prevent MTCT; Table 8-12 presents recommended neonatal combination antiretroviral regimens for use in special circumstances.

Table 8-11		
Recommendations for Neonatal Zidovudine Dosing to Prevent Mother-to-Child Transmission of HIV		
Age	**Dosing**	**Duration**
>35 wk gestation	• 4 mg/kg body weight per dose, po bid • Start as close to the time of birth as possible and within 12 h of delivery • If unable to tolerate oral agents: 3 mg/kg body weight per dose given IV, started within 6–12 h of delivery, then q 12 h	Birth through 6 wk
<35–>30 wk gestation	• 2 mg/kg body weight per dose po **or** • 1.5 mg/kg body weight per dose IV • Start within 6–12 h of delivery, then q 12 h • Advance to 3 mg/kg per dose po (or 2.3 mg/kg per dose IV) q 12 h at 15 days of age	Birth through 6 wk
<30 wk gestation	• 2 mg/kg body weight per dose po **or** • 1.5 mg/kg body weight per dose IV • Start within 6–12 h of delivery, then q 12 h • Advance to 3 mg/kg per dose po (or 2.3 mg/kg per dose IV) q 12 h at 4 wk of age	Birth through 6 wk

Source: *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States.* Sept 14, 2011. http://aidsinfo.nih.gov/content files/PerinatalGL.pdf

Table 8-12		
Recommended Neonatal Combination Antiretroviral Regimens for Use in Special Circumstances		
Regimen	**Administration**	**Notes**
ZDV 4 mg/kg bid + NVP • 12 mg po if birth weight >2 kg • 8 mg po if birth weight 1.5–2.0 kg	• Give birth through 6 wk • Administer 3 doses in first week of life: - Dose 1: Give within 48 h of birth (birth–48 h) - Dose 2: Give 48 h after Dose 1 - Dose 3: Give 96 h after Dose 2	• ZDV dosing regimen is for infants >35 weeks' gestation. See Table 8-11 for recommended doses for premature infants. • NICHD HPTN 040/ PACTG 1043 used NVP 12 mg po bid if birth weight >2 kg and 8 mg po bid if birth weight 1.5-2.0 kg

Source: NICHD HPTN 040/PACTG 1043. 18th Conference on Retroviruses and Opportunistic Infections. Boston, MA, 2011.

ZDV should be initiated as close to the time of birth as possible, preferably within 6–12 hours. The 6-week ZDV prophylaxis regimen is recommended at gestational age-appropriate doses (see Table 8-11). Use of ARVs other than ZDV and nevirapine is not recommended in premature infants because of a lack of dosing and safety data. The use of neonatal ZDV is recommended regardless of maternal ZDV resistance history.

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Infants born to HIV infected women who have not received antepartum or intrapartum ARVs or who have received only intrapartum ZDV should receive prophylaxis with a combination ARV regimen started as close to the time of birth as possible. This recommendation is based on a phase III randomized trial conducted in 4 countries (see Table 8-12) (*N Engl J Med* 2012 Jun 21;366(25):2368), which enrolled 1,746 infants born to HIV infected women who did not receive any ARVs during pregnancy prior to labor. The study compared the standard 6-week ZDV regimen alone with two different combination regimens: 6 weeks of ZDV plus three doses of NVP; or 6 weeks of ZDV plus 2 weeks of 3TC and NFV. In this trial, 41% of women received ZDV during labor and transmission rates did not vary by whether intrapartum ZDV was given. The overall HIV transmission rate was significantly lower in the two- and three-drug arms compared with the ZDV-alone arm; however, the two-drug regimen (ZDV plus NVP) was less toxic than the three-drug regimen (ZDV plus 3TC plus NFV). Although transmission rates with the two combination regimens were similar, neutropenia was significantly more common with the three-drug regimen compared with the two-drug regimen (27.5% vs. 15%, p < .0001). Furthermore, NFV powder is no longer commercially available in the United States.

No specific data address whether a more intensive combination infant prophylaxis regimen provides further protection against transmission when the mother receives antepartum/intrapartum prophylaxis but has suboptimal viral suppression near delivery, particularly in the absence of scheduled CS, or when the mother has ARV drug-resistant virus. On the basis of extrapolated findings

from the NICHD HPTN 040/PACTG 1043 study, the use of a combination infant prophylaxis regimen should be considered, depending on risk assessment (e.g., maternal VL and mode of delivery). Expert consultation is advised. The decision to use other drugs with 6 weeks of ZDV in other scenarios should be made only after expert consultation and a discussion of risks and benefits with the mother, preferably before delivery.

Appropriate drug formulations and dosing regimens for neonates are incompletely defined and minimal data are available concerning the safety of combination drugs in the neonate. Neonatal dosing information is not available for currently available boosted PIs; both RTV and LPV/r have been associated with cardiac toxicity, lactic acidosis, acute renal failure, CNS depression and respiratory complications leading to death, predominantly in preterm neonates. The FDA now recommends that LPV/r **not** be administered to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days has been attained.

Infants of women with positive HIV rapid test results while the mother is in labor should begin combination ARV prophylaxis as described above. If the maternal confirmatory HIV test is positive, then ARVs should be continued in the infant for 6 weeks; if the test is negative, the infant ARVs should be stopped.

Initiation of ART is recommended for infected infants aged <12 months, regardless of clinical status, CD4+ percentage, or VL. If the infant becomes infected despite combination prophylaxis that includes NVP, the risk of NVP drug resistance is increased; expert consultation is advised when choosing ARV regimens.

Neonatal Evaluation

A baseline complete blood count (CBC) and differential should be performed on the newborn. Decisions about the timing of subsequent hematologic testing depend on baseline results, gestational age at birth, clinical condition, dose of ZDV being administered, receipt of other ARV drugs and concomitant medications, and maternal antepartum therapy. Some experts recommend more intensive monitoring of hematologic, serum chemistry and liver function assays at birth and when diagnostic HIV PCR tests are obtained for infants exposed to combination ART in utero or during the neonatal period. Because of the potential for enhanced hematologic toxicity in infants receiving a zidovudine/lamivudine-containing prophylaxis regimen, a recheck of hemoglobin and neutrophil counts is recommended 4 weeks after initiation of prophylaxis. If hematologic abnormalities are identified while the infant is receiving prophylaxis, decisions regarding continuation of prophylaxis should be individualized. Expert consultation is advised if discontinuation of prophylaxis is considered. Routine measurement of serum lactate is not recommended; but measurement of serum lactate may be considered if an infant develops severe clinical symptoms, particularly neurologic symptoms, of unknown etiology.

Follow-up of children with ARV exposure should continue into adulthood because of the unknown long-term effects of these drugs.

Diagnosis of HIV

Source: *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection*; http://aidsinfo.nih.gov/guidelines/html/2/pediatric-treatment-guidelines/0/. Accessed 6/27/12)

HIV infection can be definitively diagnosed with virologic assays in most nonbreastfed HIV infected infants by 1 month of age and in virtually all infected infants by 4 months of age. Because of transplacental passage, HIV antibody tests will be positive up to 18 months after birth and therefore are not valid for infant diagnosis. Virologic assays (HIV DNA PCR or HIV RNA assay) are used to diagnose HIV infection in infants younger than 18 months.

HIV DNA PCR or HIV RNA assay in HIV exposed infants is recommended at age 14–21 days, 1–2 months, and 4–6 months. Virologic testing at birth should be considered for infants at high risk of HIV infection (e.g., born to HIV infected mothers who did not receive prenatal ARV drugs and/or those with high VLs at the time of labor/delivery). Data do not indicate any delay in HIV diagnosis with HIV DNA PCR assays in infants who have received the ZDV regimen (*Pediatr Infect Dis J* 1995;14(11):948); however, the effect of combination ART in the mother or newborn on the sensitivity of infant virologic diagnostic testing, particularly HIV RNA assays, is unknown. Therefore, although HIV RNA assays may be acceptable for diagnosis (particularly in older infants) HIV DNA PCR assays may be optimal for diagnosing infection in the neonatal period.

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Confirmation of HIV infection should be based on two positive virologic tests from separate blood samples. Definitive exclusion of HIV infection should be based on at least two negative virologic tests (at >1 month and >4 months of age). Consider confirmation of HIV status with HIV antibody testing at 12–18 months in infants with prior negative virologic tests. In children aged ≥18 months, HIV antibody assays alone can be used for diagnosis.

Pneumocystis jirovecii Pneumonia Prophylaxis

To prevent *Pneumocystis jirovecii* pneumonia (PCP; formerly known as *Pneumocystis carinii* pneumonia), all infants born to women with HIV infection should begin PCP prophylaxis with TMP-SMZ (150/750 mg/m^2/day in two divided doses po three times weekly on consecutive days) at age 4–6 weeks, after completing 6 weeks of ZDV, unless there is adequate test information to presumptively exclude HIV infection. Dapsone and atovaquone are alternatives.

Guidelines for Postpartum Care

Infant feeding: Breastfeeding (BF) by HIV infected mothers is not recommended in the United States, even for women who are on ART and have undetectable VL, because of potential toxicity arising from drug transmission via breast milk

and the risk of drug resistance due to insufficient drug levels in breast milk if the baby is infected despite prophylaxis. Furthermore, ART may not affect the presence of cell-associated virus (intracellular HIV DNA) in breast milk, which may therefore continue to pose a transmission risk (*J Acquir Immune Defic Syndr* 2004;35(2):178).

Late HIV transmission events in infancy have recently been reported among HIV infected children suspected to have acquired HIV infection as infants as a result of consuming premasticated food; this was supported by phylogenetic comparisons of virus from cases and suspected sources and supporting clinical history. Healthcare providers should routinely inquire about this feeding practice and instruct HIV infected caregivers to avoid this practice and advise on safe feeding options (*Pediatrics* 2009;124(2):658; *J Acquir Immune Defic Syndr* 2012;59(2):207).

In most low-resource settings internationally, however, BF has significant benefits that outweigh the risks, including provision of ideal infant nutrition in the first 6 months of life, reduction of infant morbidity and mortality through protection against both diarrhea and respiratory-associated mortality in the first year of life (*Lancet* 2000;355:451), delays in the return of fertility with exclusive breastfeeding (promotes child spacing and maternal recovery from blood loss), low cost, and cultural acceptability. Therefore, current WHO recommendations regarding BF for HIV infected mothers include the following:

- When infants are HIV uninfected or of unknown status:
  - Exclusive BF for the first 6 months of life unless replacement (formula) feeding is acceptable, feasible, affordable, sustainable, and safe

  - At 6 months, introduce appropriate complementary foods and continue BF for the first 12 months of life. All BF should then stop once a nutritionally adequate and safe diet without breast milk can be provided.

- When infants are HIV infected:
  - Exclusive BF for the first 6 months of life and continue BF as per recommendations for the general population (up to 2 years or beyond)

In addition, data from several recent randomized controlled trials support the use of extended infant NVP prophylaxis or continuation of maternal triple ARV prophylaxis throughout BF to further reduce the risk of perinatal transmission (*Lancet* 2008;372(9635):300; *N Engl J Med* 2010;362:2271; *N Engl J Med* 2010;362:2282; *N Engl J Med* 2008;359:119). The WHO now recommends one of these two strategies when ongoing maternal ART is not indicated (World Health Organization. *Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants*. 2010 version. http://whqlibdoc.who.int/publications/2010/9789241599818_eng.pdf. Accessed 3/26/12).

Care for mother and infant: HIV infected mothers may neglect their own care while trying to provide appropriate care for their infants and other children or family members. The immediate postpartum period is an important time to assess new mothers' psychological, emotional, and physical health. New

mothers should be monitored for signs of postpartum depression or worsening of underlying psychiatric disorders and referred to mental health services if necessary. In addition, this is an important time to review the completeness of preventive health interventions, including immunizations and cervical cancer screening. The care of other chronic medical conditions should be reviewed. It is essential that women be linked with comprehensive medical and supportive care services, including HIV specialty care; primary medical and gynecologic care; family planning; mental health or substance abuse treatment services; and assistance with food, housing, transportation, and legal/advocacy services, if needed. A team approach with multiple support services may also help to provide optimal care. Similarly, the HIV-exposed infant should be linked into ongoing pediatric care, with HIV diagnostic tests as described above and appropriate HIV specialty care if HIV infected.

Antiretroviral Treatment

Whether to continue or discontinue ARVs after delivery: Decisions regarding continuation of ARV drugs after delivery should take the following into account: current recommendations for initiation of ART (available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed 5/17/13), current and nadir CD4+ cell counts and trajectory, HIV RNA levels, clinical symptoms/disease stage, presence of other indications for ART (e.g., chronic hepatitis B, HIV-associated nephropathy), adherence issues, HIV infection status of the woman's sexual partner, and patient decision after careful counseling.

Following delivery, women who meet the indications for ART should continue therapy without interruption. Doses of some PIs may be increased during late pregnancy; for women continuing therapy, available data suggest that standard doses can be used again starting immediately after delivery.

When ARV drugs have been given in pregnancy to women with CD4+ cell count >500 cells/microliter, the decision to stop or to continue ARV drugs postpartum has become increasingly controversial because of increasing evidence of benefit in starting therapy at higher CD4+ levels and recommendations for earlier initiation of ART (http://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-treatment-guidelines/0/. Accessed 5/17/13) and because therapy interruption when ART has been given for treatment in nonpregnant adults has been associated with increased morbidity (*J Infect Dis* 2008;197:1145).

At issue is the potential impact of postpartum ARV discontinuation on the short- and long-term health of the mother. This is especially important as women may have multiple pregnancies, resulting in episodic receipt of ARVs. To date, studies of pregnant women with relatively high CD4+ cell counts who stop therapy after delivery have not shown a risk for increased disease progression (*J Infect Dis* 2007;196(7):1044; *HIV Med* 2009;10(3):157; *Infect Dis Obstet Gynecol* 2009:456717). Unplanned changes in ARV regimens and discontinuations of treatment in the postpartum period have led to viral load rebound (*HIV Clin Trials* 2011;12(1);9).The risks versus benefits of stopping therapy postpartum in women with high CD4+ counts is being evaluated in the ongoing PROMISE study.

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The potential benefits of continuing ART in women with higher CD4+ counts must be weighed against possible drug toxicity, cost, and the risk of development of viral resistance with suboptimal adherence, which may be more likely during the postpartum period (*AIDS Care* 2008;20(8):958; 6th International AIDS Society Conference on HIV Pathogenesis and Treatment and Prevention 2011; Abstract #1016).

Women who have uninfected sexual partners should continue ART postpartum to reduce risk of HIV transmission (*New Engl J Med* 2011;365:493). Safe sexual practices should continue to be recommended.

The decision to continue therapy after delivery should be discussed with the woman and decisions made prior to delivery. Until definitive evidence is available to guide this decision, continuation of therapy in women with high CD4+ cell counts should be based on individualized discussions with the woman and consideration of willingness and ability to commit and adhere to lifelong therapy.

Stopping ARV Drugs Postpartum

For women whose antepartum regimen included an NNRTI and who plan to stop ARV prophylaxis after delivery, consider one of the following two options: 1) stop the NNRTI first and continue other ARVs for a period of time; or 2) switch from an NNRTI to a PI prior to interruption and continue the PI with the other ARVs for a period of time before electively stopping. The optimal interval between stopping an NNRTI and the other ARV drugs is not known; at least 7 days is recommended. Given the potential for prolonged detectable NNRTI concentrations for more than 3 weeks in patients taking EFV-based therapy, some experts recommend continuing the other ARVs or substituting a PI plus two other agents for up to 30 days. A recent study of 412 women who received single-dose nevirapine and were randomized to receive zidovudine/lamivudine, tenofovir/emtricitabine, or lopinavir/ritonavir for either 7 or 21 days found an overall new nevirapine resistance mutation rate of 1.2% when assessed by population genotype at 2 and 6 weeks following completion of treatment, with no difference by length of treatment. However, low-frequency nevirapine-resistant mutations at codons 103, 181, and 184 detected using allele-specific PCR emerged significantly more often in the 7-day arms (13/74 [18%]) than in the 21-day arms (3/66 [5%], P = .019). (*Clin Infect Dis* 2013; 56(7):1044).

Women whose antepartum regimen did not include an NNRTI and who plan to stop ARV prophylaxis after delivery should stop all ARVs at the same time.

Adherence support: For women continuing ARVs postpartum, adherence support should be available during the postpartum period and adherence should be assessed at each clinical visit. Because of the physical recovery from giving birth, the stresses and demands of caring for a new baby, and possible postpartum depression, the new mother may be particularly vulnerable to problems with adherence to ARV treatment. Providers should be especially aware that depression or drug or alcohol use/abuse may negatively affect adherence and should screen postpartum women for these conditions.

It is essential that access to and continuity of ART as needed for maternal health be ensured. Simplification of an ARV regimen may be considered. If a woman is not able to adhere to her regimen, temporary interruption of ART may be needed while strategies are devised to improve adherence.

Contraception and Condom Use

Discussions about contraception and safe sexual practices should continue throughout pregnancy and should be reviewed and reinforced at the postpartum visit. Lack of breastfeeding is associated with earlier return of fertility; ovulation returns as early as 6 weeks postpartum and potentially even earlier in some women, putting them at risk for pregnancy shortly after delivery (*Obstet Gynecol* 2011;117(3):657). Interpregnancy intervals <18 months have been associated with increased risk of poor perinatal and maternal outcomes in HIV-uninfected women (*J Obstet Gynaecol* 2010;30(2):107). Because of the stresses and demands of a new baby, women may be both more receptive to the use of effective contraception and more at risk for nonadherence to contraceptive methods and unintended pregnancy. This is an important concern when the woman is on an EFV-containing regimen or other drugs that are potential teratogens. An ideal contraceptive strategy for women with HIV infection is to provide simultaneous protection against both unintended pregnancy and HIV transmission or sexually transmitted disease acquisition or transmission, often called "dual protection" (i.e., condoms plus a highly effective contraceptive) (*Sex Transm Dis* 2002;29(3):168). The use of longer-term, reversible contraceptive methods (e.g., injectable, implants, and/or IUD) should be included as options.

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National Perinatal HIV Hotline

This toll-free hotline provides free clinical consultation on all aspects of perinatal HIV, including infant care: 1-888-448-8765.

Dolutegravir (Tivicay, DLG)

FDA approved 8/13. It is classified as FDA Pregnancy Category B.

Standard adult dose: ARV-naïve or ARV-experienced but integrase inhibitor naïve patients: DLG 50 mg once daily

ARV-naïve or ARV-experienced but integrase inhibitor naïve if given with EFV, fos-APV/r, TPV/r, or rifampin; or integrase inhibitor experienced: DLG 50 mg twice daily

Formulation: 50 mg tablets

Adverse effects: The most common adverse reactions of moderate to severe intensity and incidence ≥2% are insomnia and headache. Hypersensitivity reactions have been reported in 1% or fewer study subjects and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury. Patients with underlying hepatitis B or C may be at increased risk for abnormal liver enzymes.

Drug Interactions: Drugs that are metabolic inducers may decrease the plasma concentrations of dolutegravir. Dolutegravir should be taken 2 hours before or 6 hours after taking cation-containing antacids or laxatives, sucralfate, oral iron supplements, oral calcium supplements, or buffered medications. DLG should be given as 50 mg twice daily when coadministered with rifampin.

Use in pregnancy: Insufficient data to recommend use: No studies of dolutegravir use in human pregnancy. Insufficient data to assess for teratogenicity in humans. No evidence of teratogenicity in mice, rats, or rabbits. Placental transfer and PK in pregnancy are unknown

Chapter 9:

Psychosocial Issues, Mental Health, and Substance Abuse

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Chapter 9: Psychosocial Issues, Mental Health, and Substance Abuse

Chapter 9 at a Glance

Psychosocial Issues, Mental Health, and Substance Abuse

Although healthcare providers for women living with HIV focus primarily on the physical manifestations of the condition, understanding the psychosocial, cultural, mental health, and substance abuse issues faced by HIV infected women is important to optimizing care. By developing a comprehensive treatment plan for the HIV infected woman that includes emotional support and treatment for coexisting psychosocial and mental health conditions, the care provider can help the woman to feel that the entirety of her experience is being addressed. This chapter reviews the principal psychosocial, cultural, mental health, and substance abuse issues relevant to women with HIV infection and makes recommendations for provider response, evaluation, and management.

Major Psychosocial and Cultural Issues Faced by Women with HIV Infection

A woman with HIV infection potentially faces many psychosocial issues that can significantly affect her ability to access or accept care. For many women, HIV infection is just one additional challenge in a life filled with poverty, abuse, substance use, and other hardships, and it may not even be perceived as the biggest problem.

Gender inequality: Gender inequality contributes to the spread of HIV infection (Table 9-1) and magnifies many of the problems women experience after becoming infected. Compared with men, women often have both less control over their sexuality and less power in many other spheres of their lives.

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Table 9-1
Gender Norms that Contribute to the Spread of HIV Infection

Men
- Gender norms related to masculinity can encourage men to have more sexual partners and older men to have sexual relations with much younger women
- Homophobia stigmatizes men who have sex with men, making them more likely to keep such activity covert and to have a female partner as a cover

Women
- Women and girls often have less information about HIV and fewer resources to take preventive measures
- Because of economic dependency and unequal power relations, women are often unable to negotiate safer sex practices
- Women may be subjected to forced sex, which can cause tears and lacerations in the vaginal mucosa and anal lining, thereby increasing the risk of HIV transmission
- Women who fear interpersonal violence may be less likely to disclose their HIV serostatus

Sources: Adapted from *Gender Issues–HIV & AIDS*. United Nations Development Fund for Women; *Gender, Women, and Health: Gender Inequalities and HIV*. World Health Organization (WHO). 2012

Race/ethnicity: In the United States, women living with HIV are disproportionately African-American or Hispanic. Many of these women have experienced stigma related to their race, ethnicity, or country of origin, and HIV may be particularly stigmatizing within their own communities. Language and cultural beliefs about health may act as barriers to care, and there may be lack of awareness and health literacy definicts, as well as other myriad social and structural barriers. Recent studies also highlight sometimes disparate treatment by health care providers. Healthcare providers must offer respect, awareness, and acceptance of cultural differences and proactively address these health disparities. They should develop a basic knowledge of a patient's culture, such as the involvement of family members in decision making (important in many Hispanic cultures), the use of alternative therapies or traditional healers (common in some African cultures), and rituals relating to birth and death. Language differences should be addressed with appropriately trained medical interpreters; in general, family members should not be asked to interpret.

Economic problems: HIV infected women are more likely than HIV infected men to be poor, unemployed, and uninsured or under-insured (*Clin Inf Dis* 2007;45:S255); women may be less likely to be able to keep their healthcare appointments because of a lack of transportation and may be unable to afford their medications. Poverty may lead some women to exchange sex for money, food, or other material support, placing them at increased risk for acquiring HIV. Poverty may also lead women to stay in abusive relationships.

Childbearing and childcare: The woman with HIV infection often has children, one or more of whom may also be HIV infected. She may be stigmatized if she becomes pregnant or expresses the desire to have children. Caring for her children will generally take precedence over caring for herself and lack of childcare may be a further barrier to accessing care.

Other caretaking: The woman with HIV is often a caretaker for other family members, who may include her husband or partner, aging parents, and/ or grandchildren. Attending to these responsibilities may take priority over meeting her own needs and may result in the woman neglecting her own care.

Cultural issues and societal perceptions/pressures: Perceptions and expectations of women, including HIV infected women, vary in different cultures and societies. These expectations commonly center on childbearing, sexuality, and submission to men. Women are often expected to be virgins when they marry, to have several children after marriage, and to submit to sex or violence within relationships without complaint or choice. When women do not meet the expectations placed on them, they may feel guilt and shame and may pay a heavy price in terms of stigma or even safety.

Stigma/disclosure: Stigma has profoundly adverse effects on the prevention and treatment of HIV in women. For example, disclosure of one's HIV status can help with medication adherence, relationship authenticity, and prevention of transmission (*J Nurs Scholarsh* 2004;36(2):122); however, because of stigma, women who are infected may not disclose their status to a partner, family, or friends for fear of rejection, abandonment, or violence. The HIV infected woman may not feel comfortable insisting that her partner use a condom, fearing that the request may arouse suspicion about her serostatus. She may

be at increased risk for nonadherence because she does not want to take her antiretroviral medications in front of others, fearing that people may ask questions about the pills and her reasons for taking them. Table 9-2 presents issues women may need to consider prior to disclosing their HIV serostatus.

Table 9-2	
Decisions and Considerations Regarding Disclosure of HIV Status	
Decisions	**Considerations**
Who will make the disclosure?	Will the patient disclose for herself or designate someone else to do so on her behalf?
Who will be told?	Partners? Children? Family? Friends? Employer? Coworkers? Health care providers?
When will disclosure take place?	Immediately after diagnosis or after a period of adjustment? Before disclosure is made by someone else? Any time that feels right?
Under what circumstances will disclosure be made?	What are the necessary conditions for disclosure to occur?
How much information will be shared?	Will the patient tell all the details of her diagnosis?
What are the reasons for disclosure?	Is disclosure necessary to obtain needed services? To have the support of friends and family? To prevent transmission of infection? To prevent someone else from telling?
Are there any reasons not to disclose HIV status?	What are the times and circumstances when it may be best not to disclose (e.g., is there a possibility of harm?)?

Source: *Qual Health Res* 2006;16(10):1350

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Interpersonal violence: More than four million women a year in the United States are harmed by their husbands, boyfriends, or other intimate partners (*JAMA* 2010;304:596). Although no statistics are available on the number of HIV infected women who are victims of interpersonal violence (IPV), Gielen et al. (*Trauma Violence Abuse* 2007;8:178) found in a review of studies on IPV and HIV that HIV infected women appear to experience IPV at the same rates as uninfected women. Rates of adult lifetime physical or sexual IPV were roughly equivalent across studies and between HIV infected and uninfected women; more than 60% of women, regardless of HIV status, reported experiencing IPV. Abuse was both more frequent and more severe among HIV infected women, however, than among HIV uninfected women.

IPV is more complex for HIV infected than uninfected women. Those who are in abusive relationships are at risk for potential re-infection with HIV and for infection with other STDs because men who are violent are more likely to engage in risky sexual practices (*Sex Health* 2010;7:25). Abusive male partners are more likely than other men to be HIV infected; therefore, women who experience IPV have a higher incidence and prevalence of HIV (*Science*

2010;329:145). Women learn the futility of resisting their partners' attempts to control the timing and circumstances of sex because of their experiences of male dominance in sexual relationships. Women who are depressed, abusing substances, or dissociating from post-traumatic stress disorder (PTSD) are more likely to be at risk of IPV (*Science* 2010;329:145).

Because IPV is so common in many women's lives and because there is help available for women who are being abused, care providers should ask every patient about domestic violence, with such questions as the following: (ACOG Committee Opinion No. 518; *Obstet Gynecol* 2012;119:412)

- Within the past year, have you been hit, slapped, kicked, or otherwise physically hurt by someone?
- Are you in a relationship with a person who threatens or physically hurts you?
- Has anyone forced you to have sexual activities that made you feel uncomfortable?
- Have you ever been the perpetrator of violence?

If the woman is newly diagnosed, the clinician should ask about concerns she may have if/when her partner learns of her HIV serostatus.

Special Considerations

Homelessness: Structural and societal factors contribute to the increased numbers of homeless women, particularly since the economic recession of 2008 (*Curr HIV/AIDS Rep* 2007;4:181). The deinstitutionalization of mental health services, low wages, limited employment opportunities for women with few job skills, and difficulties receiving and maintaining government entitlements all contribute to homelessness among women.

Women are particularly susceptible to less visible forms of homelessness, such as staying with friends or family, "couch surfing," or exchanging sex for shelter. Transitions in and out of homelessness occur frequently for women in this vulnerable position. Riley et al. reported that female gender was one of the strongest predictors of poor health among homeless adults (*Curr HIV/AIDS Rep* 2007;4:181).

Women without stable housing are more likely to use illicit drugs, have multiple sex partners, and report poor physical and mental health compared with their sheltered counterparts. Exchanging sex for money, drugs, housing, food, and safety exposes women to violence and sexually transmitted infections, including potential infection or re-infection with HIV, yet women without stable housing may resort to this strategy for survival and may be unable to negotiate safer sexual practices. With competing needs for housing and food, and perhaps also for the care of children, appropriate health care may not be a priority for HIV infected women, especially if they are asymptomatic. Women who are homeless are more likely to use emergency health care services and to use health services in general inconsistently. They may feel that the stigma they already experience as a result of HIV infection is compounded by their marginal housing situation and may be less likely to search for assistance with either housing or health care (*Curr HIV/AIDS Rep* 2007;4:181). Care providers should be consistent in asking about their HIV infected patients' living situations,

whether or not they have enough food, and whether or not they have access to electricity and water, as these basic needs must be met before women can effectively manage their HIV infection.

Incarceration: The prevalence of HIV infection among incarcerated women is roughly double that among incarcerated men (*J Assoc Nurses AIDS Care* 2009;20:50). Life circumstances outside of prison tend to be very different for incarcerated women than for incarcerated men: women have higher levels of poverty, more exposure to violence and abuse, more substance abuse, and are more likely to face unstable living conditions. Incarcerated women also are more likely than incarcerated men to have used sex work to buy food and drugs; they are thus at greater risk than men for HIV infection.

Privacy is necessarily limited in prison, which may make inmates who are concerned about disclosure of their HIV status reluctant to access healthcare. Lack of medical privacy, or the lack of privacy when taking one's medications in prison, has been shown to be a barrier to adherence to antiretroviral therapy (ART) for the imprisoned (*J Assoc Nurses AIDS Care* 2009;20:50). By denying medical privacy to inmates, prisons inadvertently may be reducing ART adherence rates and increasing the risks of treatment failure and drug resistance, which could have public health consequences upon the release of inmates to the community. Positive interactions with prison healthcare providers, including time for private conversations about medications, can help HIV infected incarcerated women adhere to an ART regimen. Similarly, individualized decisions regarding the method of medication administration (e.g., keeping one's own medications, directly observed therapy) can also improve adherence. Education of prison staff, healthcare providers, and inmates can reduce the stigma associated with HIV infection, improve a woman's desire to protect her health, and increase adherence behaviors (*J Assoc Nurses AIDS Care* 2009;20:50).

Lesbian and transgender patients: Special issues, particularly relating to stigma and discrimination, face the HIV infected patient who is lesbian or transgendered. It is important that healthcare providers inquire about sexual practices in a nonjudgmental fashion (e.g., "Do you have sex with men, women, or both?") and also ask about specific practices in order to best advise about safe sex. Because many of these patients have had negative experiences with the healthcare system or with individual healthcare providers, it is critical to openly discuss concerns they may have related to care as a lesbian or transgendered person and to actively work to build trust and foster mutual respect.

Mental Health Issues

General Considerations

Mental health problems are common in the setting of HIV infection in women. Psychiatric illnesses often co-occur with HIV infection and have been linked with poor medication adherence and with the risk of suicide (*AIDS Care* 2009;21:1432). In one study of subjects with a dual diagnosis of HIV and

mental illness, HIV infected women were more likely than HIV infected men to have a serious mental illness, defined as a diagnosis of schizophrenia or major affective disorder, and at least one inpatient or two outpatient treatment contacts with healthcare providers related to these diagnoses (*Psychiatr Ser* 2009;60:974). The most common causes of psychiatric hospitalizations for HIV infected women include mood, anxiety, and psychotic disorders. Alcohol/substance abuse is significantly associated with mood, adjustment, anxiety, personality, and psychotic disorders. The most vulnerable women are those who are triply diagnosed (i.e., with HIV infection, a chronic mental illness, and a substance abuse disorder).

The cost of managing patients with multiple diagnoses is high. One study found that health care expenditures for triply diagnosed patients were nearly twice as high as those for people with HIV infection in general (*AIDS Care* 2009;21:1547). Inpatient care (36%), medications (33%), and outpatient services (31%) each accounted for roughly one-third of expenditures; costs were highest for patients on Medicare or Medicaid, not in stable residences, or with poor physical health or high viral loads (*AIDS Care* 2009;21:1547). Women were more likely than men to have poor access to care, defined as no outpatient medical visits, at least one emergency room visit without an associated hospitalization, and at least one hospitalization (*AIDS Care* 2009;21:1547).

Both men and women with HIV are more likely to experience a range of mental health issues, which most commonly include feelings of acute emotional distress, depression, anxiety, PTSD, and cognitive impairment (*Mental Health Screening: A Quick Reference Guide for HIV Primary Care Clinicians*. New York State Department of Health. 2012; http://www.hivguidelines.org/wp-content/uploads/mental-health-screening-06-21-2012.pdf. Accessed 7/18/2012).

Psychosis is more common among patients with HIV who abuse substances, particularly stimulants, than in the general population. With any change in mental status, a medical cause should be considered before determining that the cause is solely psychiatric.

Assessment

It is helpful to assess a patient's general psychosocial status by inquiring about the following:
- Who does the patient consider to be family?
- Does she have a social support system?
- Does she have a partner?
- What kind of work does she do? If unemployed, how does she spend her time?
- Does she have children? If yes, how many?

The care provider should also inquire about the patient's living situation, transportation needs, income adequacy, concerns for the future (including advance directives for healthcare planning), spiritual/religious support, and disclosure status.

It is important to obtain a detailed psychiatric history, including any prior use of psychotropic medications and any history of hospitalizations for mental health issues. Depression in particular can be a recurring problem and it will be helpful to know what medications or other treatments were effective for this disorder in the past. Complex psychiatric disorders require an interdisciplinary approach. Table 9-3 lists mental health disorders that should be assessed at baseline and at least annually in the HIV infected female patient.

Table 9-3	
Screening for Mental Health Disorders	
Condition	**Screening Considerations**
Alcohol and/or Substance Abuse	• The provider should inquire as to type, quantity, and frequency of alcohol and other substance use and whether the patient has experienced adverse consequences from this use • Addiction to alcohol and recreational drugs and the work required to obtain these substances can become the driving force in a patient's life, resulting in neglect of a woman's health and/or that of her children
Anxiety	• Anxiety is a common symptom in HIV infected patients; if it is severe or persistent, the patient may have an anxiety disorder. Other psychiatric disorders can also present with significant anxiety. • Anxiety can present with a wide range of physiological manifestations, including shortness of breath, chest pain, racing/pounding heart, dizziness, diaphoresis, numbness/tingling, nausea, or a sensation of choking. A medical etiology for such symptoms should first be ruled out. • Other possible presentations include fear, worry, insomnia or excessive sleeping, impaired concentration and memory, ruminations, compulsive rituals, and avoidant coping • Appetite may be affected; people may eat more or less than usual when depressed or anxious. A 24-hour diet recall or an inquiry about how a patient's clothes are fitting can help to assess changes in appetite.
Cognitive Impairment	• Because cognitive impairment may have an organic cause, current immune- system status and other symptoms should be considered • It is often helpful to ask significant others and/or family members if they have noted any change in the patient's cognitive status • The Mini Mental State Exam is a good, reliable tool for assessing cognitive impairment
Depression	• Depression is the most common mental health disorder in the HIV infected patient population, Depression may, however, be difficult to distinguish from symptoms such as fatigue. • People may eat or sleep more or less than usual when depressed • With depression it is common to wake earlier than usual and be unable to go back to sleep or to have repeated awakenings during the night • Asking two simple questions about mood and anhedonia ("Over the past 2 weeks, have you felt down, depressed, or hopeless?" and "Over the past 2 weeks, have you felt little interest or pleasure in doing things?") may be as effective as using more formal instruments to screen for depression (*Screening for Depression in Adults: Recommendation Statement*. U.S. Preventive Services Task Force. 2009; http://www.uspreventiveservicestaskforce.org/uspstf09/adultdepression/addeprrs.htm. Accessed 7/16/2012) • To obtain more information and track treatment efficacy, the Patient Health Questionnaire (see p. 350) may be helpful

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Table 9-3	*continued*

Screening for Mental Health Disorders

Condition	Screening Considerations
Post-Traumatic Stress Disorder	• Because many HIV infected women have experienced a great deal of childhood and/or adult trauma, it is important to determine if the patient has symptoms of PTSD. These symptoms can become overwhelming and can make it difficult for the woman to cope with daily living, including the self-care (e.g., taking regular medications, making medical-care visits) required for a chronic illness. • Management may require an interdisciplinary approach, including counseling to resolve the underlying cause(s) of PTSD symptoms • PTSD may produce a variety of physical symptoms (e.g., insomnia, fatigue, headaches, muscle/joint pain, gastrointestinal upset). If no physiological factors are found that account for these symptoms, the provider should consider that the cause may be PTSD.
Psychosis	• Physiologic cause(s) of symptoms must first be ruled out, particularly with an acute onset of symptoms that may include - Delusions, grandiosity, or false beliefs - Hallucinations, which are most commonly auditory but can affect any of the senses - Agitation - Suspiciousness, or being mistrusting and very guarded - Hostility, or acting in an abusive or uncooperative manner - Lack of drive or initiative - Social withdrawal - Emotional flatness or unresponsiveness - Lack of spontaneity - Concrete thought or difficulty in thinking abstractly - Paucity of speech - Poor communication skills - Stereotyped thought or inflexible thinking that may seem unreasonable - Physical symptoms that may involve poor grooming and hygiene
Suicidal and/or Violent Ideation	Determine at baseline and at periodic intervals if the patient either has a history of or is currently experiencing suicidal/violent ideation. This is particularly important in circumstances that may exacerbate a mental health disorder (see below). Suicidal and/or violent ideation may be recurring features of depression. If these features are present, emergency psychiatric care is needed.

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Source: *HIV and Suicide: Risk Assessment & Intervention*. Mountain Plains AIDS Education and Training Center. 2007

Triggers that may exacerbate an existing mental health disorder among women with HIV include the following (*The Role of the Primary Care Practitioner in Assessing and Treating Mental Health in Persons With HIV.* © New York State Department of Health AIDS Institute, 2000-2012; http://www.hivguidelines. org/clinical-guidelines/hiv-and-mental-health/the-role-of-the-primary-care-practitioner-in-assessing-and-treating-mental-health-in-persons-with-hiv/. Accessed 8/1/2012):

- Learning of an HIV diagnosis
- Disclosing HIV status to others
- Beginning ART
- Physical illness, new symptoms, signs of disease progression, adverse changes in lab values
- Hospitalization
- Death of a significant other
- Lifestyle changes, e.g., loss of job, loss of income, end of relationship, relocation, birth of a child
- Making end-of-life and permanency planning decisions
- Any major problems with children, e.g., poor performance in school, acting out, illnesses

Specific Mental Health Conditions

Depression

Women with HIV infection have high rates of depression. In a longitudinal examination of data collected from the WIHS, which followed a representative sample (n=2,792) of HIV infected U.S. women for 10 years, 53% of the women were depressed at baseline and depressive symptoms were an independent predictor of mortality (*J Acquir Immune Defic Syndr* 2009;51:399). HIV infected people with depression are also less adherent to ARV regimens (*Psychiatr* Q 2009;80:131; *AIDS Patient Care STDS* 2008;22:313). It is therefore important to assess for depression at baseline and at least annually; in a woman with a history of depression, assessment should occur at each visit. A positive response to two questions ("During the past 2 weeks, have you experienced little interest or pleasure in doing things?" "Have you felt down, depressed, or hopeless?") should prompt a more thorough assessment.

Screening tools: Although many well-established depression screening tools are available, many of them include somatic items similar to HIV-related symptoms or to the side effects of some ARV medications. See Table 9-4 for the Patient Health Questionnaire (PHQ), a tool that is designed to approximate the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR) criteria for depression but that is free of somatic items. Specifically designed for use in the primary care setting, the PHQ has been studied in 5,780 patients in primary care and medical specialty outpatient centers (*Cancer* 2011;117(1):218). A Spanish version has also been validated (*Textbook of Psychosomatic Medicine*. Arlington VA: American Psychiatric Publishing, Inc.; 2005).

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Table 9-4

Patient Health Questionnaire

Instructions: How often have you been bothered by each of the following symptoms during the past 2 weeks? For each symptom put an "X" in the box beneath the answer that best describes how you have been feeling.

Symptoms	Frequency in Past 2 Weeks			
	Not At All	Several Days	More than Half the Days	Nearly Every Day
1. Little interest or pleasure in doing things				
2. Feeling down, depressed, or hopeless				
3. Trouble falling or staying asleep, or sleeping too much				
4. Feeling tired or having little energy				
5. Poor appetite or overeating				
6. Feeling bad about yourself, or that you are a failure, or have let yourself or your family down				
7. Trouble concentrating on things, such as reading the newspaper or watching television				
8. Moving or speaking so slowly that other people could have noticed—or the opposite: being so fidgety or restless that you have been moving around a lot more than usual				
9. Thoughts that you would be better off dead or of hurting yourself in some way*				

10. If you are experiencing any of the problems listed above, how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?	☐ Not difficult at all ☐ Somewhat difficult ☐ Very difficult ☐ Extremely difficult
11. If these problems have caused you difficulty, have they caused you difficulty for 2 years or more?	☐ Yes, I have had difficulty with these problems for 2 years or more. ☐ No, I have not had difficulty with these problems for 2 years or more.

* If you have had thoughts that you would be better off dead or of hurting yourself in some way, please discuss this with your health care provider, go to a hospital emergency room, or call 911.

Severity scores: For each reply, not at all = 0; several days = 1; more than half the days = 2; nearly every day = 3

Number of Symptoms: ⎯⎯⎯⎯⎯   **Severity Score:** ⎯⎯⎯⎯⎯

Source: *JAMA* 1999;282(18):1737

Scoring the PHQ: The PHQ can assist in diagnosing depression as well as in planning and monitoring depression treatment. The PHQ score has three components: 1) number of depressive symptoms; 2) severity score; and 3) functional assessment. The number of depressive symptoms is used to aid in making the diagnosis of depression. The severity score and functional assessment are measured at initial assessment and regularly after treatment begins to determine baseline depression severity and assess ongoing patient progress.

Diagnosis (number of depressive symptoms): For questions 1–8, count the number of symptoms for which the patient checks "More than half the days" or "Nearly every day." For question 9, count the question positive if the patient checks "Several days," "More than half the days, or "Nearly every day." Use the following interpretation to diagnose depression subtypes:

- 0–2 PHQ symptoms: not clinically depressed
- 3–4 PHQ symptoms: other depressive syndrome (items 1 and 2 must be among the symptoms checked)
- 5 or more PHQ symptoms: major depression (items 1 and 2 must be among the symptoms checked)

Severity score: Assign a score to each response using the following number values:

- Not at all = 0
- Several days = 1
- More than half the days = 2
- Nearly every day = 3

Total these values to obtain the severity score. Use the following interpretation to determine severity:

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- 0–4: not clinically depressed
- 5–9: mild depression
- 10–14: moderate depression
- 15 or higher: severe depression

Functional assessment: The final two questions on the PHQ ask the patient how emotional difficulties or problems affect work, home life, or relationships with other people, and if the difficulty has lasted for 2 years or more.

1. If the patient responds to question 10 with "Very difficult" or "Extremely difficult," then his/her functionality at work, at home, or in relationships with other people is significantly impaired.

2. If the patient has had difficulty with these problems for 2 years or more (question 11), then consider the diagnosis of dysthymia (chronic depression), which may require different management strategies from those used to treat acute depression.

Several general medical disorders may be considered in the differential diagnosis of major depressive disorder (Table 9-5).

Table 9-5

Differential Diagnosis of Major Depressive Disorder	
Condition	**How Differentiated from MDD**
Adjustment disorder with depressed mood	Sadness is rarely as profound as with MDD; little anhedonia; no vegetative symptoms; identifiable precipitant; responsive to environmental change; suicidal ideation and intent may still occur; severe cases may respond to antidepressants
Bipolar disorder	Racing thoughts; increased energy; decreased need for sleep; irritability or angry outbursts; hypersexuality; symptoms may coexist with depressed mood in a mixed bipolar state
Delirium	Fluctuating mental status with altered level of consciousness; distractibility; inability to focus or sustain attention; dysarthric speech; agitation; medical etiology; onset usually acute
Dementia	Less concern with cognitive decline; more gradual changes; may respond with laughter; worse at night; specific neurological deficits; CT or MRI scan often abnormal
Grief	Onset associated with loss; able to respond to positive changes in the environment with enjoyment or less sadness; decreasing severity over time; preoccupation with deceased or loss; "psychotic" symptoms related to the deceased (i.e, seeing or being visited by the deceased); rare suicidal intent, although reunion fantasies may exist
Medication- or substance-induced mood disorders	Onset with use of steroids, anticholinergics, sedative-hypnotics, anticonvulsants, anti-Parkinsonian drugs, beta-blockers, anti-TB medications, sympathomimetics, AZT, d4T, and all illicit drugs (urine toxicology screen, medication history)
Organic mood disorder	Identifiable etiology linked by time; may be associated with cognitive deficits; test for specific medical conditions (e.g., TSH, B12, VDRL or RPR, CNS evaluation); no family history

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Source: Adapted from *Guide to the Clinical Care of Women with HIV*, 5th ed. 2005;364.

Anxiety

Although depression is the most prevalent mental health problem experienced by HIV infected women, anxiety can be a problem as well. HIV infected women had significantly higher anxiety symptom scores than uninfected women (*Am J Psychiatry* 2002;159:789). Because anxiety and depression are considered by many to be two faces of a single disorder, clinicians should assess for both depression and anxiety if a woman exhibits symptoms of either disorder. Symptoms of anxiety can be very troubling for women and may require intervention. Women with HIV infection may become anxious thinking about the future, may feel uncertain about what will happen to them, and may shut down because they believe they cannot cope. Women with limited social support may be particularly susceptible to developing anxiety symptoms. Often the victims of neglectful or abusive parents themselves, many women with HIV have not been taught the coping skills that would help them successfully negotiate life's hurdles. When anxiety symptoms are severe or persistent, a

woman may have an anxiety disorder, which may manifest as generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, or PTSD (*Anxiety Disorders*. National Institute of Mental Health. 2009; http://www.nimh.nih.gov/health/publications/anxiety-disorders/nimhanxiety.pdf. Accessed 7/17/2012).

Screening for anxiety: Questions to ask include the following (*DSM-IV-TR*; Arlington, VA: American Psychiatric Association; 2000):

- Do you often worry or feel nervous?
- Are you often fearful of interacting with other people?
- Do you ever feel jittery, short of breath, or like your heart is racing?
- Do you ever feel as if you might lose control or fear that you may be "losing it"?

Screening for PTSD: If there is reason to suspect PTSD, the following questions may be helpful in screening for that disorder (*DSM-IV-TR*; Arlington, VA: American Psychiatric Association; 2000):

- In your life, have you ever had any experience that was so upsetting, frightening, or horrible that you
  - Have nightmares about it or think about it when you do not want to?
  - Try hard not to think about it or go out of your way to avoid situations that remind you of it?
  - Are constantly on guard, watchful, or easily startled?
  - Feel numb or detached from others, activities, or your surroundings?

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Wide range of manifestations: Anxiety can present with a wide range of physiologic manifestations, as outlined in Table 9-3. Just as with depression, women with a history of anxiety are susceptible to symptom recurrence. An anxiety disorder occurs when symptoms interfere with a woman's daily function, interfere with personal relationships, or cause marked subjective distress. Anxiety-like symptoms may be caused by other mental health disorders, making it difficult, for example, to distinguish depression with agitation from an adjustment disorder with anxious mood. Adjustment reactions, however, usually follow a stressful event, which is rarely the case with clinical depression. Moreover, adjustment reactions are less likely to present with the vegetative symptom complex seen in depression, including insomnia, diminished appetite, loss of pleasure/interest, feelings of guilt, and fatigue (*The Role of the Primary Care Practitioner in Assessing and Treating Mental Health in Persons With HIV*. © New York State Department of Health AIDS Institute, 2000-2012. Accessed 8/1/2012).

Underlying medical conditions, such as CNS pathologies, systemic or metabolic illness, endocrine disorders, respiratory or cardiovascular conditions, or substance intoxication/withdrawal, can cause anxiety-like symptoms, as can

certain medications. Once these have been ruled out as the source of symptoms, the clinician should determine which anxiety disorder is causing the symptoms. Table 9-6 outlines how to distinguish among various anxiety disorders.

Table 9-6

Distinguishing Among Anxiety Disorders

Disorder	Distinguishing Characteristics
Adjustment disorder with anxious mood	History of stressful situations causing nervousness or upset
Generalized anxiety disorder	Worrying/ruminating about a variety of things for months
Obsessive-compulsive disorder	Intrusive, disturbing thoughts; compulsive rituals
Panic attacks/ panic disorder	Discrete episodes of intense anxiety/fear with chest pain, pounding heart, diaphoresis, shortness of breath
Phobia	Fear/avoidance of certain situations, places, or objects
PTSD	History of a traumatic event that continues to cause great distress, with symptoms lasting more than 1 mo (if the event occurred less than 1 mo ago, this is an acute stress disorder)

Source: *The Role of the Primary Care Practitioner in Assessing and Treating Mental Health in Persons With HIV.* © New York State Department of Health AIDS Institute, 2000-2012

For some patients, if symptoms are mild, basic supportive and behavioral interventions may be sufficient. A variety of strategies may be helpful, including the following:

- Express empathy
- Educate the patient about anxiety
- Reassure the patient that anxiety can be the cause of somatic symptoms
- Identify the psychological factors that contribute to anxiety
- Prepare the patient for stressful situations and assist in the development of positive coping mechanisms
- Teach her simple breathing exercises; slow, deep, focused breathing can be helpful

Psychopharmacology

General Guidelines

The following general principles should guide the prescription of psychotropic drugs to HIV infected women (*Guide to the Clinical Care of Women with HIV*, 5th ed. 2005;365)

- **Start low, go slow:** Evidence indicates that, in general, women require lower doses of antipsychotic medications than men. Use slow upward titration as with geriatric patients (*Diabetes Care* 2004;27:596; *Am J Psychiatry* 2004;161:1324).

- **Expect the unexpected:** HIV infected patients often experience unusual side effects, common side effects at low doses, or complicated drug-drug interactions

- **Monitor dynamically:** Changes in weight or metabolism, changes in other medications, or episodes of medical illness require frequent updating and re-evaluation of dosing or choice of medications. This is particularly important with increased weight or abdominal girth, new onset of hyperlipidemia, or hyperglycemia.

- **Coordinate among disciplines:** Psychiatrists and primary health care providers should be in regular communication with each other about clinical updates, dosing changes, and major medical events

- **Suspect substances:** Depression may be complicated by alcohol use, anxiety by withdrawal syndromes, and mania by psychostimulant use. Patients often forget that when their substance consumption has decreased, their CNS sensitivity to the effects of these substances increases over time.

- **Address medication adherence:** Use medication boxes, simple regimens, written instructions, coordination with antiretroviral therapies, and patient education. Nonadherence or discontinuation may diminish the overall treatment effect if adherence is not specifically targeted (*J Clin Psychiatry* 1999;60:741).

- **Attend to potential drug-drug interactions:** Drug-drug interactions are a concern when coprescribing psychotropic and antiretroviral (ARV) medications. The primary cytochrome P450 systems at issue with psychiatric medications are CyP2D6 and CyP3A4 (*Guide to the Clinical Care of Women with HIV*, 5th ed. 2005;365). Most studies that have examined the concurrent use of antiretroviral (ARV) drugs and psychotropic medications have included few women. For drug interactions between psychotropic medications and ARVs, see Table 13-8, p. 500.

SSRIs: Selective serotonin reuptake inhibitors (SSRIs), the drugs most commonly used to treat depression, are also effective against a variety of anxiety disorders (*Depress Anxiety* 2007;24:185). The SSRIs have a range of effects, from activating or stimulating to sedating.

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Bupropion: Bupropion is often used for smoking cessation; it has no known drug-drug interactions and no sexual side effects. It may be helpful to decrease craving in patients with a history of substance abuse.

Antipsychotics: Second-generation antipsychotic agents (e.g., aripiprazole) are routinely recommended over traditional antipsychotics (e.g., haloperidol), except for acute or short-term use, because of their potential to improve psychotic symptoms and the lower associated incidence, compared with traditional antipsychotic agents, of extrapyramidal side effects and long-term risk of dyskinesia.

Side effects: Common potential side effects of all antidepressant medications include agitation, irritability, sedation, sexual dysfunction, weight gain, headache, gastrointestinal distress, dry mouth, and activation of mania. Benzodiazepine use may be complicated by tolerance, dependence and withdrawal syndromes, including rebound anxiety, and patients should be warned about sedation, cognitive effects, and slowed reflexes when using these agents. Patients who experience severe or unusual side effects, have multiple diagnoses, require multiple medications, or are not responding to routine doses of initial medications should be referred for psychiatric consultation (*Guide to the Clinical Care of Women with HIV*, 5th ed. 2005;366).

Common Psychiatric Medications

Table 9-7 lists common psychiatric medications (in alphabetical order within drug classes; order does not indicate priority for use).

Table 9-7

Common Psychiatric Medications

Disorder	Medications and Common Dosing Ranges*
Alcohol Dependence Initiate only after alcohol withdrawal for maintenance of abstinence	• Acamprosate (Campral): 333 mg tid; continue even if relapse • Disulfiram (Antabuse): up to 500 mg qd x 1–2 wk; maximum 500 mg qd • Naltrexone (Revia): 50 mg qd; must also be opioid-free x 7–10 d
Alcohol Withdrawal Doses needed may be higher with significant tolerance or combined alcohol and benzodiazepine/barbiturate dependence Observe carefully and stop treatment if signs of respiratory depression or if patient is difficult to arouse	• Alprazolam (Xanax): 0.5–1 mg bid x 7–10 d • Chlordiazepoxide (Librium): 50–100 mg initially, to be followed by repeated doses as needed until agitation is controlled; dosage then may be reduced to maintenance levels; maximum dose 300 mg qd. In acute setting, initial doses may be given IM or IV. • Clorazepate dipotassium (Tranxene): Maximum 90 mg qd; divide doses bid-tid: 　- Day 1: initial, 30 mg; then 30–60 mg 　- Day 2: 45–90 mg qd 　- Day 3: 22.5–45 mg qd 　- Day 4: 15–30 mg qd 　- Day 5 and after: 7.5–15 mg qd until patient's condition is stable • Avoid excessive reductions on successive days • Lorezapam (Ativan): 2 mg q 6h for 4 doses, then 1 mg q 6h for 8 doses
Anxiety Disorders, Panic Attacks, PTSD Unless otherwise noted, increase dose gradually to lowest effective dose	• Citalopram† (Celexa): For panic disorder, 20–30 mg qd; maximum dose 60 mg qd • Escitalopram† (Lexapro): For generalized anxiety disorder, 10–20 mg qd • Fluoxetine† (Prozac): For panic disorder, 10–60 mg qd • Paroxetine† (Paxil): 　- Generalized anxiety disorder: 20–60 mg qd 　- Panic disorder: 10–60 mg qd (immediate release); 12.5–75 mg qd (controlled release) 　- PTSD: usual effective dose is 20 mg qd • Sertraline† (Zoloft): For panic disorder and/or PTSD, 25–200 mg qd A.M. • Venlafaxine† (Effexor): For generalized anxiety and/or panic disorder, 37.5–225 mg qd in single dose (extended release) • Alprazolam† (Xanax): 　- Anxiety: 0.25–0.5 mg tid to maximum 4 mg qd in divided doses (immediate release or orally disintegrating tablet) 　- Panic disorder: 0.5 mg tid (immediate-release or orally disintegrating tablet) to maximum 10 mg qd in divided doses; 0.5–1 mg qd (extended release); usual dosing range 3–6 mg qd • Clonazepam† (Klonopin): For panic disorder, 0.25 mg bid up to maximum 4 mg qd in 2–3 divided doses • Lorazepam† (Ativan): For anxiety, 2–10 mg qd divided bid-tid • Buspirone (Buspar): For anxiety, 5 mg bid-tid or 7.5 mg bid–60 mg qd in 2–3 divided doses • Duloxetine† (Cymbalta): For generalized anxiety disorder, 30–120 mg qd; delayed-release capsules should be swallowed whole—do not cut, crush, chew, or sprinkle

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| Table 9-7 | *continued* |

Common Psychiatric Medications

Disorder	Medications and Common Dosing Ranges*
Bipolar Mood Disorder Unless otherwise noted, increase dose gradually to lowest effective dose	• Aripiprazole (Abilify): For mania or mixed episodes, 15–30 mg qd • Carbamazepine (Tegretol): 800–1600 mg in divided doses; may increase in increments of 200 mg qd, titrated slowly by blood levels (4–12 mcg/ml) • Lamotrigine (Lamictal): 25–200 mg qd • Lithium carbonate: ***Use requires ability to obtain lithium levels, as toxicity can occur at doses close to therapeutic levels*** - Acute mania: 600 mg tid (immediate-release tablet and capsule); 1800 mg qd (extended-release tablet) in 2–3 divided doses; desired serum level 1–1.5 mEq/L - Maintenance therapy: 300 mg 3–4 x qd (immediate-release tablet and capsule); 900–1200 mg qd (extended-release tablet) in 2–3 divided doses; desired serum level 0.6–1.2 mEq/L • Olanzapine (Zyprexa): 10–15 mg qd; increase in 5 mg increments at intervals not less than 24 h; maximum dose 20 mg qd • Quetiapine (Seroquel): - Depression phase: 50 mg qd (regular release and extended release), with rapid scale-up in initiation phase; usual maintenance dosage range is 400–800 mg qd, given in divided doses bid - Manic phase: 50 mg bid (regular release); increase over 4–6 d, usual dosage range 400–800 mg qd, given in divided doses bid; 300 mg qd (extended release); increase over 3 d; usual dosage range 400–800 mg qd • Risperidone (Risperdal): 2–3 mg qd; may increase in increments of 1 mg qd to maximum 6 mg qd - Valproate/valproic acid (Depakote): For acute mania, 250 mg tid (delayed release); increase rapidly to lowest effective dose; maximum 60 mg/kg/d; usual trough plasma level 50–125 mcg/mL; 25 mg/kg/d qd (extended release); increase rapidly to lowest effective dose; maximum dose 60 mg/kg/d; usual trough plasma level 85–125 mcg/mL • Ziprasidone (Geodon): For acute mania or mixed episodes, 40 mg bid with food; titrate rapidly to lowest effective dose; maximum dose 80 mg bid
Insomnia	• Diphenhydramine: 25–100 mg q hs • Eszopiclone (Lunesta): 2–3 mg q hs • Lorazepam (Ativan): 2–4 mg q hs • Temazepam (Restoril): 7.5–30 mg q hs • Trazodone (Desyrel, Oleptro): 25–50 mg q hs • Zolpidem (Ambien): 5–10 mg q hs (immediate release); 6.25–12.5 mg q hs (extended release); also available as oral spray and sublingual tablet with maximum 10 mg q hs

Table 9-7 *continued*

Common Psychiatric Medications

Disorder	Medications and Common Dosing Ranges*
Major Depressive Disorder (with or without anxiety) Unless otherwise noted, increase dose gradually to lowest effective dose	• SSRIs: - Citalopram† (Celexa): 20–40 mg qd - Escitalopram† (Lexapro): 10–20 mg qd - Fluoxetine† (Prozac): 20–80 mg qd in A.M. or 90 mg q wk - Paroxetine† (Paxil): 20–50 mg qd (immediate release); 25–62.5 mg qd in A.M. (controlled release) - Sertraline† (Zoloft): 50–200 mg qd • Bupropion† (Wellbutrin): - 100 mg bid (immediate release); increase slowly to maximum 450 mg qd in 3–4 divided doses - 150 mg once qd (sustained release); increase slowly to maximum 200 mg bid - 150 mg qd (extended release); increase slowly to maximum 450 mg qd, given as single dose • Duloxetine† (Cymbalta): Start with 20 mg bid; maintenance dose 60 mg qd; maximum dose 120 mg qd • Mirtazapine† (Remeron): 15–45 mg q hs • Venlafaxine† (Effexor): - 75–225 mg qd (immediate release) in 2–3 divided doses - 37.5–225 mg qd (extended release) in single dose

Opiate Dependence	• Buprenorphine: **Prescribing of buprenorphine for this indication is limited to qualifying physicians who have notified HHS of their intent**
	- Induction: 12–16 mg/d SL; adjust dose in 2–4 mg increments to level that suppresses opioid withdrawal effects (typical range 4–24 mg qd)
	- Rapid detoxification (with naltrexone and clonidine): 3 mg/d SL for 3 d
	- Methadone maintenance therapy:
	  ° Start 15–30 mg x 1, then 5–10 mg prn q 2–4 h prn; maximum 40 mg on day 1
	  ° Adjust dose to prevent withdrawal symptoms x 24 h, block euphoric opioid effects
	  ° Stabilize dose x 10–14 d, then decrease dose by up to 10% q 10–14 d
	  ° Doses >100 mg/d require documentation; maintenance therapy permitted only in FDA-approved program
	
	• Naltrexone:
	- Do not attempt treatment unless patient has remained opioid-free for at least 7–10 d. Verify self-reporting of abstinence from opioids in opioid addicts by analysis of urine for absence of opioids.
	- Patient should not be manifesting withdrawal signs or reporting withdrawal symptoms. If there is any question of occult opioid dependence, perform naloxone challenge test. If signs of opioid withdrawal are still observed following naloxone challenge, do not attempt treatment with naltrexone. Naloxone challenge can be repeated in 24 h.
	- Initiate treatment carefully, with an initial dose of 25 mg qd. If no withdrawal signs occur, patient may be started on 50 mg qd thereafter
	- Extended-release naltrexone also available

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Table 9-7	*continued*

Common Psychiatric Medications

Disorder	Medications and Common Dosing Ranges*

Opiate Withdrawal	• Clonidine: 0.3–0.6 mg in 3 divided doses
	• Methadone:
	  - Short-term detoxification:
	    ° 15–30 mg as initial dose, then 5–10 mg q 2–4 h prn; maximum 40 mg on day 1; adjust dose to suppress withdrawal symptoms
	    ° Stabilize dose x 2–3 days, then decrease dose by up to 20% q 24–48 h
	    ° Doses >40 mg/d require documentation
	  - Drug detoxification:
	    ° Opioid abuse: Initial dose 15–30 mg orally; additional 5–10 mg can be given 2–4 h later if needed
	    ° Adjust dose cautiously over first week based upon control of withdrawal 2–4 h post dose
	    ° Usual total daily dose 40 mg qd; keep on stable dose for 2–3 d, then decrease in 1–2-d intervals according to response
	    ° Detoxification treatment usually occurs over 21 d
	  - Opioid abuse, maintenance therapy:
	    ° Individualize maintenance doses
	    ° Titrate to a dose that prevents symptoms for 24 h
	    ° Usual maintenance doses range from 80–20 mg qd

Psychotic Symptoms and/or Schizophrenia
 	
Unless otherwise noted, increase dose gradually to lowest effective dose
 	
Periodically reassess need for treatment; d/c if ANC <1000; consider d/c if unexplained decrease in WBC
	• Aripiprazole (Abilify): 10–15 mg qd; maximum 30 mg qd
	• Olanzapine (Zyprexa): 5–10 mg qd; maximum 20 mg qd
	• Paliperidone (Invega): 6 mg qd A.M. (extended release); maximum 12 mg qd; do not cut, crush, or chew
	• Quetiapine (Seroquel):
	  - Start at 25 mg bid (regular release); usual effective range is 150–750 mg qd, in divided doses; maximum 800 mg qd
	  - With extended-release formulation, start at 300 mg qd; target dose range 400–800 mg/d; maximum 800 mg/d
	• Risperidone (Risperdal): Start at 1 mg qd or bid; maximal effect usually seen with 4–8 mg qd; do not cut or chew orally disintegrating tablet
	• Ziprasidone (Geodon): Start at 20 mg bid with food; maximum 80 mg bid

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

*All doses are for oral administration, unless otherwise noted. Many psychiatric medications are now available in extended-release, rapidly dissolving, liquid, and parenteral forms.

†Taper dose gradually to discontinue

Source: Adapted from *Guide to the Clinical Care of Women with HIV*, 5th ed. 2005;367. Dosing recommendations from Epocrates® Online

Substance Abuse

Substance *abuse* is differentiated from substance *dependence*; in the latter the impairment is more pervasive and includes physical dependence and withdrawal symptoms.

Substance Use and Addictive Disorders: DSM-V-TR Criteria
(*DSM-V-TR*; Arlington, VA: American Psychiatric Association; 2013)

The old categories of substance abuse and dependence have been replaced with the new "substance use and addictive disorders" classification. The term "dependence" was felt to be misleading, often applied to tolerance and withdrawal, which are normal responses to prescribed medications that affect the central nervous system. The new category for addictive diseases includes a variety of "substance-use disorders" broken down by drug type.

Substance use disorder:

A. A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by two or more of the following, occurring within a 12-month period:

　1. Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household)

　2. Recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use)

　3. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with spouse about consequences of intoxication, physical fights)

Tolerance, as defined by either of the following:

- Need for markedly increased amounts of the substance to achieve intoxication or desired effect
- Markedly diminished effect with continued use of the same amount of the substance

Withdrawal, as manifested by either of the following:

- Characteristic withdrawal syndrome for the substance
- Same or a closely related substance is taken to relieve or avoid withdrawal symptoms
- Substance is often taken in larger amounts or over a longer period than was intended
- Persistent desire or unsuccessful efforts to cut down or control substance use

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- A great deal of time is spent on activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance (e.g., chain smoking), or recover from its effects

- Important social, occupational, or recreational activities are given up or reduced because of substance use

- Substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., current cocaine use despite recognition of cocaine-induced depression, continued drinking despite recognition that an ulcer was made worse by alcohol consumption)

- Craving or strong desire or urge to use a specific substance

Women who have a substance use disorder expend an extraordinary amount of time and energy in pursuit of their drug of choice at the expense of their own health and the health and well-being of their children.

Scope of the problem: An estimated one in five new HIV diagnoses in women is related to injection drug use (*HIV/AIDS among Women*. U.S. Centers for Disease Control and Prevention [CDC] HIV/AIDS Fact Sheet. 2008; http://www.cdc.gov/hiv/topics/women/pdf/women.pdf. Accessed 7/26/2012) and 60% of new AIDS cases in women represent sexually acquired HIV from drug-using partners (*Medical Care of HIV-Infected Substance-Using Women.* © New York State Department of Health AIDS Institute, 2000-2012; http://www.hivguidelines.org/clinical-guidelines/womens-health/medical-care-of-hiv-infected-substance-using-women/. Accessed 7/26/2012). Few specific data exist on substance abuse disorders in HIV infected women. The WIHS found that 27% of HIV infected women reported crack, cocaine, or injection drug use (*AIDS* 1999;13:591). Crack cocaine in particular has disproportionately affected African-American women. Women who smoke crack are more likely than other women to sell sex or have an STD; women who smoke crack also have more sexual partners (*Health and Human Rights* 1998;2(4):42).

Methamphetamine (i.e., meth, speed, ice, crystal, crank) abuse is a significant problem in the United States, though it has been decreasing in recent years; in some parts of the country, methamphetamine is the third most common drug of abuse after alcohol and marijuana. Although limited data are available on methamphetamine use by HIV infected women, this drug is known to increase risky sexual behavior and has been associated with an increased proportion of drug-treatment admissions in pregnancy. (*Methamphetamine Use and Risk for HIV/AIDS*. CDC. 2007; http://www.cdc.gov/hiv/resources/factsheets/meth.htm. Accessed 8/1/2012).

Greater vulnerability: At a more complex level, the intersection of HIV infection, poverty, and race/ethnicity in HIV infected women places them on the outer fringes of society and increases their vulnerability to substance use/abuse. Substance abuse in women may begin because of childhood trauma, in an attempt to numb the pain and shame felt as a result of sexual abuse. If a woman left home in her teens because of abuse, she may resort to survival sex, and substance use may continue in order to counteract despair and shame. Women who are injection drug users (IDUs) are more likely than male

IDUs to adopt the drug-use patterns of and share needles with their partners. Although women often start using drugs and alcohol at older ages than men, some studies suggest that women become addicted more quickly, with a more "telescoped" course from use to abuse. Although the incidence of alcohol abuse or dependence is greater among men than women, women with alcohol abuse or dependence are more likely to seek medical help but less likely to be identified by their healthcare providers (*J Gen Intern Med* 2002;17:387). Drug-involved women often rely on their partners to procure the drugs they share and because women are often injected by their partners, they are "second on the needle," which increases their risk for infection with HIV. For women who have a substance abuse problem, refusing to share needles and syringes can also increase the risk of physical and sexual violence, further potentiating risks for HIV infection and re-infection (*Lancet* 2010;376:312).

Whether HIV is acquired sexually or through IDU, ample evidence exists that substance abuse plays a significant role in the lives of women who abuse drugs or alcohol (*J Assoc Nurses AIDS Care* 2004;15(5):48). Sharing injection equipment, exchange of sex for drugs, and the likelihood of risky sexual behaviors (e.g., unprotected sex, multiple sexual partners), particularly when under the influence of drugs or alcohol, are all increased in the setting of substance abuse and all increase risk for HIV (*HIV/AIDS among Women*. CDC HIV/AIDS Fact Sheet. Although reports of substance abuse in HIV infected women often focus only on IDU, noninjection drugs also play a critical role in HIV transmission due to impaired decision making and disinhibition that leads to high-risk behaviors.

Substance abuse following HIV diagnosis: Women may exhibit three patterns of substance abuse upon learning of their HIV infection. Many accelerate their use/abuse out of despair and uncertainty and/or a belief that death is imminent (*J Assoc Nurses AIDS Care* 2004;15(5):48). Some decrease their use or stop altogether, realizing that they must be able to participate in a plan of medical care if they are to survive and understanding that continued use of drugs/alcohol would likely preclude optimal care. A few nonusers initiate use of drugs/alcohol, for many of the same reasons given by those who accelerate use (*J Assoc Nurses AIDS Care* 2004;15(5):48). Continued or accelerated substance use in the context of an HIV diagnosis also adds to the stigmatization women feel, particularly those who are mothers.

9

Substance Abuse Comorbidities

HIV infected women who abuse drugs and/or alcohol are at risk of developing other medical conditions (Table 9-8). These comorbidities can be difficult to treat with coexistent HIV infection and signs and symptoms of the various conditions may be difficult to distinguish. Comorbidities may also accelerate HIV progression and/or complicate HIV management (*Guide to the Clinical Care of Women with HIV*, 5th ed. 2005). Several factors, including lower body weight, lower total body water, and lower levels of alcohol dehydrogenase, may contribute to greater sensitivity to alcohol's long-term effects among women compared with men.

Table 9-8

Medical Conditions and Sequelae Associated with Drug and Alcohol Abuse

- Bacteremia
- Cancer
- Cellulitis
- Cirrhosis
- Cognitive dysfunction
- Cutaneous abscesses
- Endocarditis
- Hepatitis (A, B, C, D and GB virus C)
- HIV
- Pneumonia
- Poor nutrition
- Septic emboli
- Sexually transmitted infections
- Thrombophlebitis
- Trauma
- Tuberculosis

Source: *Guide to the Clinical Care of Women with HIV*, 5th ed. 2005;380

The conditions listed in Table 9-8 represent only a few of the many disease states that are either directly associated with or exacerbated by substance abuse. Excessive alcohol use also places women at risk for epilepsy, psychiatric disorders, cardiomyopathy, peptic ulcer disease, pancreatitis, and malignancies. Smoking tobacco is the most common cause of lung cancer and airway diseases and has been implicated in other malignancies such as cervical carcinoma (*Guide to the Clinical Care of Women with HIV*, 5th ed. 2005;380; *Gynecol Oncol* 1994;55(1):91). Methamphetamine use has been associated with neurologic deficits, severe dental problems, arrhythmias, hypertension, seizures, depression, suicidal ideation, and psychosis (*Addiction* 2010;105:991).

Liver disease: Both HIV and alcohol abuse appear to accelerate viral hepatitis–induced liver damage and are major risk factors for progression of liver disease and death from liver disease (*Guide to the Clinical Care of Women with HIV*, 5th ed. 2005;380); *AIDS Res Hum Retroviruses* 2002;18:757). End-stage liver disease has become the leading cause of death in specific patient populations with HIV infection.

Antiretroviral therapy: Treatment with ART is associated with improved outcomes in HIV infected patients with substance abuse and comorbidities such as hepatitis (*Hepatology* 2001;34:283). This underscores the importance of the timely identification and treatment of substance abuse and its sequelae as well as HIV. In both substance abuse treatment programs and primary care clinics, strategies are needed to identify and manage HIV and recognize comorbid conditions associated with HIV and/or substance abuse or have established linkages into appropriate care (*Guide to the Clinical Care of Women with HIV*, 5th ed. 2005;381)

Identification of Substance Abuse

Problems with substance and/or alcohol abuse can be identified in several ways. Table 9-9 provides clues that may be picked up when a woman's clinical history is taken.

<div>

Table 9-9

Clues to Drug and Alcohol Abuse

Medical History	Behavior	Social History
• HIV infection • Endocarditis • Hepatitis B or C infection • Septic emboli • Septic thrombophlebitis • Pancreatitis • Cirrhosis	• Agitation • Somnolence • Disorientation • Erratic behavior • "Doctor hopping" • Frequent unexplained accidents	• Inability to retain employment • Child custody loss • Seemingly unexplainable financial difficulties • Relationship distress

Source: *Guide to the Clinical Care of Women with HIV*, 5th ed. 2005;383

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Specific questions such as the following can assess for drug use or abuse:

- Have you ever used any street drugs such as heroin, methamphetamine, ecstasy, cocaine, crack, or marijuana?
- When was the last time? How often do you use?
- Are you interested now in any substance use services or treatment?

There are also screening tools that are effective in identifying drug use, such as the ASSIST and the DAST.

If the patient has a history of substance abuse or is currently using, proceed with further evaluation and referral to a treatment program or mental health specialist. Intervention is indicated when there is evidence of adverse affects owing to substance abuse on the woman's physical and/or mental health, relationships, or job.

Assessing for alcohol abuse: Several tools are available to screen for alcohol abuse in women. One measure is the TWEAK questionnaire (*Alcohol Clin Exp Res* 1991;15(6):991):

- **T**olerance: How many drinks can you hold ("hold" version; ≥ 6 drinks indicates tolerance) or How many drinks does it take before you begin to feel the first effects of the alcohol? ("high" version; ≥ 3 indicates tolerance).
- **W**orried: Have close friends or relatives worried or complained about your drinking in the past year?
- **E**ye openers: Do you sometimes take a drink in the morning when you first get up?
- **A**mnesia: Has a friend or family member ever told you about things you said or did while you were drinking that you could not remember?
- **K**ut down: Do you sometimes feel the need to cut down on your drinking?

9

Score 2 points each for a positive response to Tolerance or Worried; 1 point each for a positive response to Eye opener, Amnesia or Kut down; the range of summed points is 0 to 7. A score of 3–7 indicates that the patient has an alcohol problem.

Another measure is the T-ACE (*Am J Obstet Gynecol* 1989;160(4):863):

- How many drinks does it take for you to feel high? (**T**olerance)
- Have people **A**nnoyed you by criticizing your drinking?
- Have you ever felt you ought to **C**ut down on your drinking?
- Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover? (**E**ye opener)

Any woman who answers "more than two drinks" on the Tolerance question is scored 2 points. Each yes to the subsequent three questions scores 1 point. A score of 2 or more is considered a positive screen and the woman should be referred to a specialist for further assessment.

The care provider can also ask about quantity and frequency of alcohol use. For women, more than seven drinks per week or more than three drinks on any one occasion may put them at risk for developing alcohol dependence (Women and Alcohol. National Institute on Alcohol Abuse and Alcoholism [NIAAA]. 2011; http://pubs.niaaa.nih.gov/publications/womensfact/womensfact. htm. Accessed 8/1/2012). One standard drink is equivalent to 12 ounces (354.9 mL) of beer, 5 ounces (147.9 mL) of wine or 1.5 ounces (44.4 mL) of 80-proof spirits (*Women and Alcohol*. NIAAA. 2011).

Physical symptoms or signs of long-term alcohol abuse include the following (*Guide to the Clinical Care of Women with HIV*, 5th ed. 2005):

- Loss of appetite, eating poorly, weight loss
- Spider angiomas on the skin
- Swelling or redness of the palms of the hands
- Redness on the face, especially the nose and cheeks
- Repeated skin sores or abscesses
- Numbness or tingling in feet and hands (this symptom could also indicate peripheral neuropathy related to HIV or ART)
- Unsteady gait
- Abnormal liver function tests, other liver problems such as cirrhosis

The physical signs of other substance abuse depend on which drug(s) are being abused. Physical examination findings are limited but may include injection marks, nasal lesions or recurrent epistaxis, poor dentition, or poor nutritional status. Signs or symptoms of intoxication or withdrawal are highly suggestive of substance use disorder. A toxicology screen or blood alcohol level may also be of use (*Ferri's Clinical Advisor*. Philadelphia, PA: Elsevier; 2011). Cocaine snorting can be suspected by observation of damaged nasal mucosa; hypodermic marks or "tracks" suggest IDU, although the absence of visible marks does not rule this out. The single most useful examination is of the eyes: nystagmus is often seen in abusers of sedatives/hypnotics or cannabis; dilated pupils are often seen in people under the influence of stimulants or hallucinogens or in withdrawal from opiates; pupillary constriction is a classic

hallmark of opioid effect. Evidence of multiple minor (or past major) injuries can also be a clue to possible substance abuse (*Guide to the Clinical Care of Women with HIV*, 5th ed. 2005;385).

Drug Testing

Drug testing for substances of abuse may be performed for clinical indications (e.g., need to exclude drugs as cause of acute change in mental status or behavior) or when required for legal indications. Drugs may be detected in almost any fluid or tissue in the body (false-positive screens for marijuana and the benzodiazepines have occurred in patients taking EFV). The most common samples used for drug tests are urine, blood, saliva, hair, sweat, and breath (*Addiction* 1999;94:1279).

Urine tests: Urine testing is the most available, useful, and reliable testing format for clinicians to use. Test kits are available for use in offices and at home that require the simple collection of a urine sample. Urine testing, however, has numerous limitations, including the ability to detect only recent drug or alcohol use. Adulterated urine samples and changes in urine acidity may prevent the quantification of illegal drugs in urine.

Other tests: Blood testing is available to many caregivers and is more accurate for the quantitative detection of drugs in the user; however, it is more expensive and more cumbersome than urine analysis. Saliva may be useful and correlates well with drug levels in the blood. Hair analysis has the advantage of detecting drug use over a 1- to 3-month period, depending on a person's hair growth rate (*Anal Bioanal Chem* 2010;397(7):2987; *J Forensic Leg Med* 2010;17:254; *Ther Drug Monit* 2010;32:318). Sweat testing is another noninvasive test that is useful for monitoring drug relapse during drug treatment. It is designed to continuously monitor a person's drug use over a period of time through a special absorbant pad placed on the skin. The pad collects microscopic amounts of sweat produced over time and is analyzed later for the presence of drugs. Breath testing is a reliable tool for measuring blood alcohol levels.

Interpretation: Drug test results may be difficult for the inexperienced care provider to interpret because they may be confounded by secondary drug exposures, chemical characteristics of the drugs to be detected, drug-level variations in different body tissues and fluids, and test-method variations. Drug testing properly used is a useful adjunct to clinical and behavioral drug-use assessment and is a useful but limited drug-use screening tool. Drug testing may also be helpful during substance abuse therapy and follow-up (*Guide to the Clinical Care of Women with HIV*, 5th ed. 2005;385).

Pregnancy: Drug screening in pregnancy should be performed only with consent; the pregnant woman must be informed of the potential ramifications of a positive test result, including any mandatory reporting requirements. Providers should be aware of laws and regulations in their jurisdictions regarding the reporting of maternal toxicology testing (ACOG Committee Opinion No. 473; *Obstet Gynecol* 2011;117:200).

9

Treatment Readiness and Harm Reduction

Unmet treatment need: Combined data from the Substance Abuse and Mental Health Services Administration's (SAMHSA's) National Surveys on Drug Use and Health conducted from 2004 to 2006 indicate that, on average, 6.3 million women annually (9.4% of women aged 18–49) needed treatment for a substance use (illicit drugs or alcohol) problem (*The NSDUH Report: Substance Use Treatment among Women of Childrearing Age.* SAMHSA. 2007; http://www.samhsa.gov/data/2k7/womenTX/womenTX.htm. Accessed 7/17/2012). Of the women aged 18–49 who met the criteria for needing substance use treatment in the previous year, 84.2% neither received it nor perceived the need for it; 5.5% did not receive treatment even though they thought they needed it. The reasons for not receiving substance use treatment among women with an unmet treatment need were as follows: 36.1% were not ready to stop using alcohol or illicit drugs, 34.4% could not cover their treatment costs because of lack of or inadequate health insurance coverage, and 28.9% did not seek substance use treatment because of social stigma.

Treatment: For women who want treatment for substance abuse, drug/alcohol use treatment programs should be provided through community resources, along with education programs, social and work skills-building programs, health care, and programs to prevent sexually transmitted infections (*Guide to the Clinical Care of Women with HIV*, 5th ed. 2005;388). Table 9-10 describes the components of drug and alcohol treatment.

Table 9-10

Components of Drug and Alcohol Abuse Treatment

Personal Needs	Treatment Needs
• Family services	• Behavioral therapy
• Housing and transport	• Clinical and case management
• Financial services	• Intake and processing
• Legal services	• Treatment plans
• HIV/AIDS services	• Pharmacotherapy
• Educational services	• Continuity of care
• Medical services	• Substance use monitoring
• Vocational services	• Self-help/peer support groups
• Child care services	• Substance education
• Mental health services	
• Family planning services	

Source: *Guide to the Clinical Care of Women with HIV*, 5th ed. 2005;388

The number of substance-abuse treatment programs is inadequate, especially for women with few or no resources and/or no insurance. Even when treatment is available, the patient may not be ready to go into treatment. Concern for children leads many women to seek treatment for substance abuse problems; however, many treatment programs do not accept women who are pregnant. Women with young children may have ongoing difficulty accessing outpatient day treatment and residential programs because of inadequate childcare

resources. Fear of the removal of children from the home by the welfare system and lack of emotional support from substance-abusing partners are other obstacles that may deter women from seeking substance abuse treatment.

Most patients do not seek treatment until symptoms and associated consequences are severe. Compared with men, women's drug-use problems tend to occur at an older age and to develop more rapidly. Additionally, women often learn of their HIV infection and other comorbid conditions later than men. The late diagnosis of drug use and other conditions may result in shorter survival. The confluence of factors that complicate health care for female substance abusers underscores the importance of the early engagement and retention of women in care (*Guide to the Clinical Care of Women with HIV*, 5th ed. 2005;388).

Harm reduction: Although barriers exist, harm reduction remains critical. Harm reduction refers to measures aimed at reducing the harm caused by substance abuse; these measures may be a first step in moving toward abstention. Harm-reduction techniques for women who are IDUs include the following: (*Cleaning Works*. 2012; http://www.thewellproject.org/en_US/Living_Well/Health/Cleaning_Works.jsp; Accessed 7/17/2012)

- Use clean sterile needles and syringes every time injection drugs are used.
- Do not share needles, syringes, cotton, or cookers with others when injecting.
- Participate in a needle exchange program if available and legal (these usually have other health promoting services [e.g., HIV/hepatitis screening, referral for treatment of substance abuse]).
- Purchase sterile equipment without a prescription from a pharmacy, if available.
- If these safer options are not adopted and needles and syringes are shared, reduce the risk of infection by always cleaning them in bleach and water immediately after use and just before reuse. Although not risk free, bleach cleaning is an important risk-reduction tool. (Hydrogen peroxide or rubbing alcohol may be substituted if bleach is not available; hard alcohol, not beer or wine, should be used if there are no other cleaning solutions available.)
- For greater cleaning effectiveness, take the set apart, remove the plunger from the barrel and soak both in bleach for at least 30 seconds.
- If the cooker (spoon) must be reused, soak it in bleach for at least 30 seconds and then rinse it with clean water.
- Because bleach loses its effectiveness with exposure to light, store all bleach for cleaning needles and works in a container that blocks light from passing through it.

9

Pharmacologic Interventions for Addiction

Managing withdrawal symptoms: Today even the most severe physical withdrawal symptoms can be managed with appropriate pharmacologic treatments that control or prevent serious medical consequences of drug or alcohol withdrawal. Medications like methadone can help to stabilize an opiate-dependent patient and facilitate a return to productive functioning. Other important pharmacologic interventions include the treatment of

comorbid conditions common in drug- and alcohol-abusing populations, such as the treatment of depression. The use of antidepreirected at the effects of drugs of abuse. Pharmacologic treatments for drug use are well known but not well understood by many healthcare providers. Several classes of medications may be used to treat, modulate, or prevent ongoing drug use (*Guide to the Clinical Care of Women with HIV*, 5th ed. 2005; *Basic Principles for Treatment and Psychosocial Support of Drug Dependent People Living with HIV/AIDS*. WHO. 2006; http://www.who.int/substance_abuse/publications/basic_principles_drug_hiv.pdf. Accessed 7/17/2012).

Opiate addiction: Opioid agonists such as methadone and buprenorphine are used to treat opiate-dependent persons. When used to treat addiction, these drugs block the ability of the illicit drugs to attach to opiate receptors, therefore thereby decreasing drug craving without causing euphoria.

The use of opioid agonists is the most misunderstood medical approach to addiction treatment. Although methadone and buprenorphine are addictive, they are successful in helping addicts stop the negative and harmful behaviors associated with drug use and begin to concentrate on developing the skills to discontinue drug use entirely. It is drug craving that is associated with drug-use relapse and criminal behavior and it is the prevention of drug craving that makes substitution medications work successfully as part of a drug treatment program (*Guide to the Clinical Care of Women with HIV*, 5th ed. 2005;389; *Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence*. WHO. 2009; http://www.who.int/substance_abuse/publications/Opioid_dependence_guidelines.pdf. Accessed 7/17/2012).

- **Methadone:** Methadone suppresses withdrawal for 24 hours (four to six times the duration of the effects of heroin) and decreases or eliminates drug craving; it is not sedating, can be dosed once per day, and can be administered orally. Furthermore, it is medically safe even when used continuously for 10 years or more.

- **Buprenorphine:** Buprenorphine is a partial opioid agonist for office-based and program-based treatment of opioid addiction. Some of the advantages of using buprenorphine are milder withdrawal symptoms, a lower risk of overdose, and availability to patients in the offices of physicians trained and certified in the medication's use. If used at the proper dosage, buprenorphine is as effective as methadone (*Guide to the Clinical Care of Women with HIV*, 5th ed. 2005;389). Recent reports show that buprenorphine/naloxone treatment can be successfully integrated into HIV clinical care in a variety of practice settings (*J Acquir Defic Syndr* 2011;56 (suppl 1):S68).

These medications are not a cure for drug dependence but are important adjuncts to care. It has been shown that while an opiate user is taking methadone, she is much less likely to commit a crime and is more likely to succeed in completing a drug treatment program. When combined with behavioral therapies or counseling and other supportive services, these pharmacologic approaches are highly effective for treating heroin addiction, particularly in those with long-term dependence and repeated prior treatment failures (*Guide to the Clinical Care of Women with HIV*, 5th ed. 2005; *Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence*. WHO. 2009).

Opioid antagonist medications such as naloxone and naltrexone block the effects of morphine, heroin, and other opiates. As antagonists, they are especially useful as antidotes. Naltrexone, which has a duration of action ranging from 1 to 3 days depending on the dose, blocks the pleasurable effects of heroin and is useful in treating some highly motivated individuals, such as professionals who do not want to lose their jobs. It is also successful in preventing relapse by former opiate dependent individuals released from prison on probation (*Guide to the Clinical Care of Women with HIV*, 5th ed. 2005). Naltrexone is now available as an extended-release formulation, given by IM injection once every 4 weeks.

Alcohol addiction: Disulfiram (Antabuse) is used in the context of alcohol abuse treatment to cause negative effects when the patient consumes alcohol. The drug interferes with alcohol metabolism, causing the production of acetaldehyde, a noxious chemical that causes severe flushing, nausea, and vomiting. The effectiveness of therapy depends on the patient's adherence to a daily medication dose. Acamprosate is a newer drug currently used in Europe that increases alcohol abstinence and decreases craving by affecting g-aminobutyric acid and glutamate brain receptors. Naltrexone also has been found to decrease alcohol craving and relapse; it was approved by the U.S. Food and Drug Administration in 1994 for the treatment of alcohol dependence (*Am J Psychiatry* 1999;156:1758; *Arch Gen Psych* 1992;49:876; *Guide to the Clinical Care of Women with HIV*, 5th ed. 2005;390). Naltrexone is now available as an extended-release formulation, given by IM injection once every 4 weeks.

Cocaine addiction: Although no effective medications are available to treat cocaine addiction, the treatment of comorbid mental health problems may improve the likelihood that a patient will stop using cocaine or crack. Pharmacologic therapies have been specifically targeted at decreasing the dysphoric effects of cocaine withdrawal. Unfortunately, studies examining multiple generations of antidepressant medications such as fluoxetine, sertraline, maprotilene, phenelzine, trazodone, and lithium have not demonstrated the success of those drugs in assisting with the permanent cessation of cocaine or crack use (*NIDA Res Monogr* 1997;175:36). Dopaminergic agents such as bromocriptine, amantadine, haloperidol, bupropion, and others have also not been proven to be effective. In studies using desipramine, carbamazine, and bupropion, however, the mental-health effect of these drugs was clinically helpful for a patient's successful drug cessation in drug treatment programs (*Guide to the Clinical Care of Women with HIV*, 5th ed. 2005;390); *Psychiatr Clin North Am* 1999;22:401).

Methamphetamine addiction: Evidence is limited on pharmacologic treatments for methamphetamine abuse; however, three double-blinded placebo-controlled trials using modafinil, bupropion and naltrexone have shown positive results in reducing amphetamine or methamphetamine use. The agonist replacement medications d-amphetamine and methylphenidate have shown promise in two studies (*Br J Clin Pharmacol* 2010;69(6):578).

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Nonpharmacologic Approaches

Behavioral and cognitive interventions: Behavioral and cognitive interventions are a vital part of drug and alcohol addiction treatment and prevention. Cognitive-behavioral therapies are based on the assumption that learning processes play an important role in the development of drug use and dependence and are therefore important to efforts to reduce use and dependence. Behavioral methods are employed to identify high-risk relapse situations, extinguish triggers to drug use, develop self-monitoring of use behavior, and establish competing coping responses. By learning to recognize situations conducive to substance use, patients can develop individual coping strategies to avoid circumstances that place them at risk for relapse. Perhaps the single most important factor for short- and long-term relapse prevention is the learning and application of individual coping skills. Avoidance of other drug users and drug-use environments are key tools for maintaining abstinence (*Guide to the Clinical Care of Women with HIV*, 5th ed. 2005).

At least 11 research-validated therapies use a variety of behavioral, social, and incentive-based systems to treat drug use. The objectives of these programs include

- removing patients from stressful environments to get care (short-term and long-term residential homes),
- providing alternatives to pharmacologic treatment (outpatient drug-free programs), and
- providing community-specific interventions (community-based programs for drug users and recently released criminals).

Several effective psychotherapy programs are based on a patient's willingness to recognize drug use as a problem and to stay off drugs, with or without incentives (*Guide to the Clinical Care of Women with HIV*, 5th ed. 2005;392).

Twelve-step programs: Twelve-step self-help groups and meetings are important nonmedical, behavioral drug-use intervention and prevention activities used by millions of people. These meetings emphasize fellowship and provide support for maintaining abstinence from alcohol, other drugs, or addictive behaviors like overeating. These programs are not intended to replace medical and behavioral drug-use treatments but are meant to add to their effectiveness. The largest 12-step groups are Alcoholics Anonymous (AA); Narcotics Anonymous (for all drug users, including alcoholics); Al-Anon, to support family members and friends of alcoholics and drug users; and Overeaters Anonymous (*Guide to the Clinical Care of Women with HIV*, 5th ed. 2005;392). Other self-help resources include Rational Recovery, which does not have the religious overtones of AA, and Moderation Management.

Pregnancy and Substance Abuse

Alcohol: Data from SAMHSA's National Surveys on Drug Use and Health, conducted in 2002 through 2007, were used to compare alcohol-drinking rates, frequency, and quantity among women aged 15–44. Those surveyed were divided into three groups: 1) pregnant women; 2) recent mothers (i.e.,

had a child within the previous 12 months); and 3) all other women in this age group. Pregnant women (11.6%) were significantly less likely to have used alcohol in the past month than recent mothers (42.1%) or all other women (54.0%). Among current alcohol drinkers, pregnant women drank alcohol on fewer days than other women. Pregnant women also had fewer drinks on their drinking days (*The NSDUH Report: Substance Use Treatment among Women of Childrearing Age*. SAMHSA, 2007; http://www.samhsa.gov/data/2k7/womenTX/womenTX.htm; Accessed 7/17/2012).

Alcohol use in pregnancy is associated with the risk of fetal alcohol syndrome, a congenital syndrome characterized by growth retardation, facial abnormalities, and CNS dysfunction. Skeletal abnormalities and structural cardiac defects are also seen in the fetal alcohol syndrome, but it is the performance deficits that are most obvious. Decreased IQ, fine-motor dysfunction, and hyperactivity are all common findings (ACOG Technical Bulletin No. 195; *Int J Gynaecol Obstet* 1994;47(1):73; *Guide to the Clinical Care of Women with HIV*, 5th ed. 2005;395).

Illicit drugs: Combined 2004 and 2005 data showed that among pregnant women aged 15–44 years, 3.9% reported using illicit drugs in the previous month. This rate was significantly lower than that among women aged 15–44 who were not pregnant (9.9 %) (*The NSDUH Report: Substance Use Treatment among Women of Childrearing Age*. SAMHSA. 2007).

Tobacco: Tobacco smoking during pregnancy is associated with increased perinatal mortality, bleeding complications in pregnancy, low-birth-weight infants and preterm delivery, and a possible increase in behavioral and learning problems among school-aged children whose mothers smoked during pregnancy (ACOG Committee Opinion #471; *Obstet Gynecol* 2010;166:1241; *Am J Psychiatry* 1996;153(9):1138). It is estimated that there could be as much as a 10% reduction in fetal and infant deaths if all pregnant women stopped smoking (*Am J Epidemiol* 1988;127(2):274).

Opiates: Opiate dependence in pregnancy is associated with a sixfold increase in maternal obstetric complications, including low birth weight, preeclampsia, 3rd-trimester bleeding, malpresentation, fetal distress, and meconium aspiration. Neonatal complications include narcotic withdrawal, which occurs in most newborns, poor postnatal growth, microcephaly, neurobehavioral problems, and increased neonatal mortality. A systematic review found a 74-fold increase in sudden infant death syndrome among children born to women who used opiates during pregnancy (*Cochrane Database Syst Rev* 2008;(2):CD006318).

Methamphetamine: Methamphetamine use in pregnancy is associated with low birth weight, small-for-gestational-age babies, and neurodevelopmental abnormalities both in neonates and in childhood (ACOG Committee Opinion No. 479; *Obstet Gynecol* 2011;117(3):751).

Cocaine: Cocaine use in pregnancy poses both maternal and fetal hazards, some of which stem from the intense vasoconstriction associated with cocaine (malignant hypertension, cardiac arrhythmias, and cerebral infarction). Cocaine has been associated with premature rupture of membranes, preterm labor

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and delivery, growth retardation, delays in cognitive development, and placental abruption. Cases of in utero fetal cerebral infarction have also been documented (*Am J Obstet Gynecol* 1987;157:686; *Guide to the Clinical Care of Women with HIV*, 5th ed. 2005;395).

HIV infection, substance use, and pregnancy: No data are available on rates of alcohol and/or substance abuse among HIV infected pregnant women. However, any substance abuse during pregnancy is of concern, especially in the setting of HIV. Substance use has been associated with an increased risk for perinatal HIV transmission (*Adv Exp Med Biol* 1993;335:211; *N Engl J Med* 1996;334:1617); although rates of perinatal transmission have decreased dramatically in developed countries, this problem has not been completely eradicated. Some residual transmission may be related to substance use among pregnant women. Exposure to drugs of abuse during pregnancy may increase mother-to-child transmission of HIV through a variety of mechanisms (*J Neuroimmune Pharmacol* 2010;5:507). A study of HIV infected mothers who were actively abusing substances found that most received inadequate or no prenatal care and that denial and substance use were the primary intrinsic barriers to disclosure and care. Substance-abusing pregnant women with HIV also may be less adherent to ART regimens during pregnancy. Attention to potent social and institutional barriers that impair the ability of the most marginalized women to disclose their HIV status and accept care is essential to maximizing the prevention of perinatal transmission (*Soc Sci Med* 2006;62(1):59). All pregnant women with a substance abuse problem should be offered treatment during pregnancy in consultation with maternal-fetal medicine and substance-abuse experts.

Treatment Retention and Relapse

Among clients discharged from substance-abuse outpatient care settings, treatment completion is highest among those who reported primary alcohol abuse and lowest among those who reported primary opiate or cocaine abuse. Both male gender and increased educational level were associated with a greater likelihood of completing outpatient treatment. Furthermore, patients who were referred to treatment by an employer, an employee assistance program, or the criminal justice system were more likely to complete outpatient treatment than patients referred by other sources (*Treatment Outcomes among Clients Discharged from Outpatient Substance Abuse Treatment*. SAMHSA. 2009; http://oas.samhsa.gov/2k9/outptTX/outptTX.pdf. Accessed 7/18/2012). Relapse is common and to be expected, and does not indicate failure or hopelessness. Indeed, women may make many attempts to stop substance abuse before succeeding; the clinician can play a major role in this journey by accepting the woman at whatever point she is in a recovery trajectory.

Antiretroviral Therapy and Substance Abuse

HIV infected women who are active substance abusers are less likely to be able to adhere to their ARV regimens than are women who are not abusing substances (*AIDS Care* 2009;21:168). A past or current history of substance

abuse, however, should not lead to automatic denial of ART; patient readiness should be assessed on an individual basis. Women previously treated for drug dependence may be more adherent that the general population or other groups. A strong patient-provider relationship, including trust and engagement with the provider, has been associated with improved ARV adherence (*AIDS Patient Care STDS* 2000;14:189).

Several ARV agents decrease methadone levels. When these agents are co-administered, the patient should be monitored for opiate withdrawal symptoms and the methadone dose increased if needed. Of note, when methadone is administered to a patient taking ZDV, the ZDV concentration is increased by >40%; the patient should be monitored for a potential increase in ZDV-related adverse effects. With newer ARV agents and dosing schedules that allow for once-daily ART regimens, directly observed therapy (DOT) in the setting of a methadone clinic may be an option for adherence support in some patients.

Tobacco

Most people with HIV infection also smoke cigarettes and are thus at high risk for tobacco-related disease and death (*AIDS Educ Prev* 2009;21(3 suppl):14; *Smoking Cessation in HIV Infected Patients*. © New York State Department of Health AIDS Institute, 2000-2012; http://www.hivguidelines. org/clinical-guidelines/adults/smoking-cessation-in-hiv-infected-patients/. Accessed 8/1/2012). Information about the tailoring of smoking-cessation interventions to HIV infected people, and specifically to HIV infected women, is sparse. The U.S. Public Health Service guidelines recommend brief, individual smoking-cessation counseling sessions in which the following five components (the "5 As") are addressed at each clinical encounter (*AIDS Educ Prev* 2009;21(3 suppl):14):

1. Ask about tobacco use at every encounter

2. Advise smokers to quit

3. Assess willingness to quit

4. Assist with quitting

5. Arrange follow-up

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Smokers' telephone quit lines, which offer free counseling and smoking cessation materials, are a cost-effective intervention with demonstrated efficacy. Other group and individual counseling interventions are available, with motivational interviewing and cognitive-behavioral interventions in particular being effective (*AIDS Educ Prev* 2009;21(3 suppl):14; *Smoking Cessation in HIV Infected Patients*. © New York State Department of Health AIDS Institute).

Pharmacological interventions, which include nicotine replacement therapy (gum, patches, lozenges, inhalers, and nasal spray), bupropion, and varenicline, have increased quit rates. Consideration of patient preferences, cost of the intervention, prior quit attempts, patient characteristics, and comorbidities

should help to determine the best intervention. A combination of nicotine replacement therapies usually works better than a single agent. Initial dosing depends on the number of cigarettes smoked per day; dosing should be tapered over the course of treatment. The usual course of treatment is 10–12 weeks. Sustained-release bupropion, alone or in combination with nicotine replacement therapy, is effective. Varenicline, which relieves withdrawal symptoms and reduces the rewarding aspects of nicotine use, has been shown to be more efficacious than bupropion; however, adverse neuropsychiatric events have been reported with varenicline and the patient should be closely monitored (*AIDS Educ Prev* 2009;21(3 suppl):14; *Smoking Cessation in HIV Infected Patients*. © New York State Department of Health AIDS Institute).

Conclusion

HIV infection in women must be considered in the context of baseline psychosocial and cultural issues, as well as potential mental health and substance abuse conditions. The willingness and ability to address these concerns compassionately, directly and effectively will play a crucial role in the effective care and treatment of the medical manifestations of HIV and in the quality of life of the HIV infected woman.

Chapter 10:
Adolescents

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Chapter 10: Adolescents

Chapter 10 at a Glance

HIV in Adolescents

The HIV epidemic continues to evolve among adolescents, defined as youth aged 13–24 years. The prevalence of disease has been influenced by improved survival of perinatally infected youth after the introduction of effective antiretroviral therapy (ART) as well as changes in incidence rates. As youth explore intimacy and sexuality and develop autonomy, adolescence becomes a time of heightened vulnerability, including risk for HIV infection. This chapter focuses on young women as it reviews the epidemiology of HIV/AIDS in adolescents and provides guidelines for HIV counseling and testing, medical and psychosocial care, and strategies for linking HIV infected and at-risk youth to care.

Epidemiology

Global Summary

Adolescents are at high risk for HIV. In 2009, 33.3 million people worldwide were living with HIV, of whom 2.6 million were newly infected. More than 40% of those new infections occurred in youths aged 15–24 years. A decline in HIV incidence among adolescents over the past decade has been attributed to improved knowledge of transmission and changes in risk behavior, including improved condom use, reduction in multiple partnerships, and delayed sexual debut (*UNAIDS Global Report 2010*, www.unaids. org/globalreport/Global_report.htm). Despite these positive trends, the prevalence in young women continues to outpace prevalence in men; rates are almost 3 times higher among young women in Sub-Saharan Africa than among men (*UNAIDS Global Report 2010*).

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U.S. Summary

In 2009, approximately 8,400 adolescents (1,670 women and 6,722 men) were newly diagnosed with HIV infection in 40 States and five U.S. dependent areas. These numbers are based on confidential name-based HIV infection reporting since at least January 2006, and they bring the cumulative total of HIV cases in this age group to 29,746 Significant racial and ethnic disparities exist: The majority of new infections occur among black/African-American and Latina youth. Most new infections in women (about 90%) occur through heterosexual contact, and 10% result from injection drug use (IDU). Of the 10,206 young women living with HIV at the end of 2008, 59% were exposed through heterosexual contact; 7%, through IDU; and the remainder, predominantly through perinatal transmission. The increase in heterosexual transmission in women has contributed to a decrease in the male-to-female ratio of AIDS cases. At the onset of the HIV/AIDS epidemic in the United States, diagnoses of AIDS were rare among adolescent women; however, in 2009 approximately one-quarter of AIDS diagnoses for this age group

occurred in women (CDC, *HIV Surveillance in Adolescents and Young Adults, July 2011.* www.cdc.gov/hiv/topics/surveillance/resources/slides/adolescents/index.htm)

Risk Factors

Adolescents are at increased risk for HIV and sexually transmitted infections (STIs) because of the interplay among behavioral, biological, and socioeconomic factors (Institute of Medicine 2011. *The Science of Adolescent Risk-Taking: Workshop Report*).

Sexual Behaviors

During adolescence, sexual activity is often initiated; risk-taking and experimentation are normative; and many sexually active adolescents fail to take appropriate prevention precautions, despite basic knowledge of HIV transmission and prevention. A majority of adolescent females with HIV are infected through heterosexual intercourse. This situation is consistent with widespread lack of awareness of the potential risk for HIV infection among sexually active adolescent and adult women. For example, among adolescents known to be HIV infected, 75% of young women are unable to identify their partners' risk factors (*Pediatrics* 1993;91:730). Moreover, for many adolescents "having sex" means heterosexual vaginal intercourse, but some adolescent females may engage in receptive anal intercourse in the belief that doing so preserves their virginity and is safer (*J Nurs Scholarsh* 2003;35:231).

High risk for STIs: Youth and inexperience are no protection against STIs. Adolescents are at high risk for STIs and account for half of all new infections diagnosed in the United States. In 2006, 1 million youth and young adults aged 10–24 were diagnosed with chlamydia, gonorrhea, or syphilis. Evidence of HPV is detected in 25% of women aged 15–19 and in 45% of women aged 20–24. In 2006, 750,000 young women under age 20 became pregnant (Guttmacher Institute. U.S. Teenage Pregnancies, Births and Abortions: National and State Trends and Trends by Race and Ethnicity January 2010 http://www.guttmacher.org/pubs/USTPtrends.pdf). The data on STIs and pregnancy are markers for unsafe sexual activity. In addition, ulcerative and inflammatory STIs increase susceptibility for HIV infection.

Youth risk behavior: According to the 2009 Youth Risk Behavior Survey (*MMWR* 2010;59 SS5:1), nearly half (46%) of all female high school students in the United States are sexually active, including 62.3% of 12th graders. African-American high school students were more likely to be sexually active than their Caucasian and Hispanic counterparts (58.3% vs. 44.7% and 45.4%, respectively). During their most recent sexual encounter, only 54% of female high school students reported using a condom. Many teens follow a pattern of sexual serial monogamy and may not consider themselves as having multiple partners. Of high school students surveyed, 11% of all females and 18% of African-American females reported four or more lifetime sexual partners.

Younger teens, particularly females, are least likely to be considered at risk or to be screened for STIs, particularly if they are asymptomatic—and the majority of STIs in females are asymptomatic. For example, chlamydia is asymptomatic in 75% of infected women, and approximately 50% of women with gonorrhea infections have no symptoms. This pattern is especially concerning because adolescent females have the highest age-specific incidence rates for both gonorrhea and chlamydia. The REACH cohort of high-risk adolescents confirmed these findings (*J Adolesc Health* 2001;29 suppl 3:49).

Young women with HIV infection (either perinatally or behaviorally acquired) are also engaging in high-risk behaviors. A study of 166 HIV infected adolescents, ages 13-21, (53% female) found that 105 were sexually experienced and that 44% reported having unprotected sex. Eighty percent of the adolescents had not informed their partners of their HIV status, and 19 females became pregnant (*J Acquir Immune Defic Syndr* 2010;55:380). These data stress the need for ongoing discussions about sexual risk behaviors.

Substance Use

More than 1 in 5 female high school students (20% to 24%) report episodic heavy drinking or current marijuana use; 12% report using inhalants, and 2% have injected illegal drugs (*MMWR* 2010;59 SS5:1). Substance use can impair judgment and increase potential for high-risk behaviors.

Biological Risk

Several biological factors also contribute to heightened risk in adolescent females. During puberty, as the cervix matures and the single-layer columnar epithelium of the cervix is replaced with thicker, multilayered squamous cells, the cellular lining becomes less susceptible to infection. Until this occurs, the cervix is much more vulnerable to STIs, particularly chlamydia and gonorrhea, which have an affinity for columnar cells and have been shown to facilitate other STI transmission. The same cervical anatomy is responsible for the increased risk of HPV infection in adolescent women. Moreover, HIV appears to increase the risk of progression of HPV disease. High-risk HPV DNA has been found in cervical samples of up to 77% of HIV infected adolescents; 70% of the adolescent women with high-risk HPV DNA had cytologic abnormality and 21% had high-grade dysplasia within 3 years of follow-up (*Arch Peds Adolesc Med* 2000;154:127). Moreover, male-to-female transmission of STIs is much more efficient than female-to-male transmission, given the larger surface area of the lower female genital tract and mechanics of sexual intercourse, which can result in mucosal trauma to women. In addition, STIs, which facilitate HIV transmission, are more likely to remain asymptomatic in women and, thus, unrecognized and untreated for a longer period.

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Socioeconomic Risk and Access to Care

Poverty, poor access to care, and lack of education and prevention skills further increase vulnerability to HIV. Additional barriers include mistrust of the healthcare system, fear of inappropriate disclosure, and providers' lack of expertise in providing care for adolescents. In addition, adolescents are the most underinsured group in the United States and are the least likely to receive office-based medical care or to use primary care services (*Bull NY Acad Med* 1993;70:219). With less access to either employer-provided insurance benefits or public insurance options, 30% of youth aged 18–24 have no health insurance (U.S. Census Bureau 2009, www.census.gov/prod/2009pubs/p60-236.pdf). Even when they have insurance coverage through their parents, adolescents may be reluctant to use it out of fear of disclosure of sensitive medical issues. Moreover, many adolescents use emergency and walk-in facilities for acute care needs. As a result, they lack a primary care provider (or medical home) that can ensure ongoing care and address prevention and health promotion needs. Because adolescence is a time when help-seeking behaviors and attitudes about health and self-care are formed, the experiences adolescents have with healthcare providers are especially important. They form the basis for future provider–client interaction, communication patterns, and relationships.

Special Populations

Specific populations of teens, including those who are lesbian, bisexual, or transgender; homeless or runaway; injection drug users; or mentally ill, are at especially high risk of HIV exposure. Also at higher risk are youth who have been sexually or physically abused, incarcerated, or placed in foster care. These youth experience increased vulnerability and multiple health and social problems because of abuse and neglect and lack of services and care. Lesbian and bisexual females may view themselves at lower risk, but those who are sexually active with gay male peers are at risk for infection because of higher HIV prevalence among gay males (*Lesbian and Gay Youth: Care and Counseling*, Columbia University Press; 1998).

Issues in HIV Care for Adolescents

Cornerstones of adolescent care include consent policies, confidentiality, accessibility, outreach, testing, and linkage to care and prevention. Even though youth prefer healthcare settings that are geared to their needs, most teens will not receive care in adolescent programs. Although most facilities are unable to offer the ideal one-stop shopping for teens, quality care can be provided by identifying a staff member and/or provider team that wants to work with adolescents and by adapting adult and family programs to meet the needs of adolescents. For example, programs can accommodate walk-ins, because youth do not often plan ahead; address payment barriers; and provide

flexible appointments that will not conflict with school or work. In 2007, the Health Resources and Services Administration (HRSA) created a comprehensive website on HIV care for youth (www.hivcareforyouth.org).

Confidentiality and Legal Issues

All States have laws that allow minors to consent to treatment without parental consent for specific health services, including emergency care, treatment for STIs, reproductive healthcare, and substance abuse treatment services. In many States, the law includes the right to consent for HIV counseling and testing. However, not all providers are aware of these rights or understand their significance for adolescents, and rights vary by State and the medical service provided. The *Compendium of State HIV Testing Laws* is available at nccc.ucsf.org and hivlawandpolicy.org. Providers should know that lack of confidentiality may cause adolescents to avoid or delay needed care. Even though parental consent may not be needed to provide an HIV test or HIV-related care, providers should carefully assess an adolescent's cognitive capacity to understand the implications of having HIV disease and should encourage the involvement of a supportive adult in the adolescent's care.

Counseling and Testing

Routine testing recommended: Since 2006, the CDC has recommended that medical providers routinely offer HIV testing to all patients aged 13–64. This recommendation is based on several factors, including the considerable number of HIV infected people who are unaware of their infection or not linked to care, advances in medical treatment that make early diagnosis and treatment life saving, and the prevention benefits of widespread knowledge of serostatus. Most youth and, often, their providers think they are not at risk of HIV infection (*J School Nurs* 2001;17:198). Most youth also prefer to have healthcare providers initiate discussions about HIV testing, prevention, and risk assessment (*Pediatrics* 2006;117:e468). All adolescents should receive HIV prevention education and should routinely be offered HIV testing. This process enables providers to identify HIV infected youth, provide ongoing medical care and support services, relieve their patients' anxiety, and reinforce preventive behaviors for youth who are not HIV infected. For adolescents who are not sexually active, counseling provides an opportunity to talk about sexual readiness, delaying intercourse, and low-risk ways to explore intimacy. Routine testing also serves to identify the few perinatally infected adolescents who have not previously been tested, often because they were asymptomatic slow progressors (*HIV Med* 2009;10:253). Teens of HIV infected parents or whose parents died of unknown causes should certainly be tested, even if they are not sexually active.

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The ACTS Program

The Adolescent AIDS Program at Montefiore Medical Center, New York, has developed a streamlined approach that enables providers to routinely incorporate HIV screening into their clinical encounters with adolescents (and clients of any age). The program, called Advise–Consent–Test–Support (ACTS), teaches healthcare providers to do the following:

- **A**dvise patients to get an HIV test, and ask if patients are ready to be tested today; if they are not, answer the patients' concerns and then encourage testing.

- **C**onsent patients according to applicable State law. As of 2011, an increasing number of States are moving away from requirements for specific written consent to an opt-out approach, in which HIV testing is included under general consent for care, as encouraged by the CDC.

- **T**est with rapid or conventional HIV test.

- **S**upport patients after testing.

For patients who are not infected, support consists of providing test results and informing patients about ways to take an active role in avoiding HIV infection. A care provider may help patients choose a prevention plan (e.g., abstinence; reduced number of partners; condom use for oral, vaginal, and anal sex). Patients should also be encouraged to get retested annually and advised about when more frequent testing is appropriate (i.e., following unprotected sex, sex with new partners, infection with an STI, or pregnancy or if there are any signs of acute HIV infection).

For HIV infected patients, support should focus on informing patients of test results, addressing immediate and short-term coping abilities, and providing links to appropriate medical care. Patients should be counseled about transmission prevention, which may entail informing sex partners personally or eliciting the help of the local health department to inform partners. Finally, patients should be encouraged to engage in safe sex.

The ACTS program is designed to facilitate practice change within the healthcare system through a four-step process:

- Obtain buy-in from clinic and administrative leadership.

- Implement planning, which includes identifying the role of all staff and process flow.

- Train care providers in the use of the ACTS approach.

- Utilize routine monitoring and evaluation to assess implementation efficacy.

ACTS has successfully increased routine counseling and testing in community health centers, school-based clinics, hospitals, cities throughout the United States, and in other countries in citywide and provincial scale-ups (see www. adolescentaids.org).

Overcoming barriers: Testing options such as rapid testing for antibodies in oral fluids are helpful with youth who are afraid of needles. Those options also allow providers to offer testing in a variety of settings, including mobile vans, school-based clinics, and drug treatment programs. Meeting adolescents' needs for flexibility, accessibility, and low- or no-fee HIV testing is important in overcoming primary barriers to accessing care and can serve as an entry point to care. Ensuring access to HIV counseling and testing is essential to enabling adolescents to receive ongoing treatment and care.

Risk assessment and counseling: HIV screening and testing can be streamlined and incorporated into the clinical visit, but prevention counseling and risk assessment takes more time. Because adolescents may have misconceptions about aspects of HIV transmission and prevention, providers should assess a youth's baseline understanding and capacity to understand basic concepts of HIV disease and viral transmission. Effective HIV counseling for adolescents should be culturally sensitive and tailored to adolescents' developmental needs, i.e. information provided at a level of comprehension consistent with the age of the client. In addition, providers should take special precautions to ensure confidentiality in institutional settings such as foster care, residential treatment, or detention centers. Elements of a youth-friendly risk assessment are summarized in Figure 10-1.

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Figure 10-1

HIV Risk Assessment for Adolescents

1. Engage and Assess

- Create a confidential atmosphere
  - Assure youth that visit is confidential and explain ability to consent for testing per local laws.
  - Assure youth that getting tested is his or her choice.
  - Acknowledge that it can be embarrassing to discuss sexual behaviors.
  - Help youth identify a supportive adult who is aware that he or she is being tested.

- Assess HIV/AIDS knowledge
  - Allow youth to verbalize his or her understanding of HIV; clarify misconceptions, then fill gaps in knowledge.
  - Assess youth's feelings about testing and previous HIV testing experiences.
  - Ask if youth knows anyone with HIV/AIDS (eg., sexual partner, family member).

- Assess sexual risk
  - Assess sexual behaviors without making assumptions about sexual orientation: Not all youth are heterosexual, and not all youth who have engaged in same-sex behavior self-identify as lesbian or gay.
  - Assess number of youth's partners, age differential, and partners' known risks.
  - Assess frequency of substance use in the context of sexual behavior.
  - Assess consistency of condom use and obstacles to use such as lack of assertiveness, desire to become pregnant, fear of violence, and religiosity.
  - Assess for history of sexual abuse or rape (coerced sex).
  - Assess for history of sex work and transactional sex.

- Assess substance use and other risks
  - Assess level of drug and alcohol use, context in which use occurs, and reasons for use.
  - Review risk of impaired judgment that may lead to unsafe sex.
  - Assess potential need for drug treatment.
  - Assess violence and substance use in home and community.

2. Reduce Risk

  - Discuss abstinence.
  - Discuss sexual activities that don't involve exchange of body fluids (e.g., outercourse or frottage).
  - Demonstrate proper use of male condom, female condom, and dental dam on anatomical model and provide opportunity for practice.
  - Rehearse (role play) effective ways to communicate risk reduction with sexual partner(s).
  - Discuss harm-reduction strategies, if youth is using drugs.
  - Develop a personalized risk-reduction plan.
  - Discuss postponing sex, if youth is not sexually active.
  - Determine referral needs (e.g., medical, psychosocial, school/vocational, substance abuse, reproductive health, legal, housing, psychiatric).

Condom use: Several intrinsic and extrinsic factors, outlined in Figure 10-2, affect condom use among adolescents. Knowledge of appropriate condom use and widespread availability of condoms are especially important in promoting risk-reduction behaviors among youth. All facilities that provide

healthcare for adolescents should make condoms available, and providers should demonstrate condom use with anatomical models. Gender and power imbalances in relationships make condom use especially difficult for adolescent women, who may have older partners and who are just beginning to develop communication and negotiation skills. Helping youth identify their personal values may increase self-esteem and help them resist pressures to engage in sexual risk behaviors.

Figure 10-2
Factors That Encourage and Discourage Condom Use

Encourage Use
- Knowledge about condoms
- Belief in effectiveness
- Discussion with healthcare provider
- Self-esteem and self-efficacy
- Communication and negotiation skills
- Availability and accessibility

Discourage Use
- Drug and alcohol use
- Relationship power imbalances
- Peer pressure
- Lack of effective sex education
- Lack of media and cultural support

Prevention

Promoting abstinence and risk reduction among adolescents is especially challenging because developmental characteristics encourage concrete, short-term thinking and experimentation and increased reliance on peers. Thus, successful primary and secondary prevention programs for adolescents are those that provide interventions to increase self-esteem and self-efficacy, build social skills, and provide basic information geared to the adolescent's developmental level, using a peer-support model (*Psychosom Med* 2008;70:598). For high-risk youth, the AIDS Risk Reduction Model (*Health Educ* Q 1990;17:53) has been widely used to foster primary and secondary prevention. The model is based on three stages of behavior change: (1) acknowledging that a behavior is risky (behavior labeling), (2) committing to change, and (3) taking action to reduce high-risk activity.

School-based programs: School-based programs that provide comprehensive health education in conjunction with school health clinics offer optimal opportunities to reinforce positive health behaviors and ensure routine screening for a range of health and mental health concerns. They are especially important to efforts to reduce risk and identify sexually active youth who are at risk for STIs and pregnancy. A comprehensive review of school-based programs designed to reduce risky behavior in teens found that adolescents who received AIDS education were less likely to engage in sexual activity and more likely to practice safer sex than peers who lacked AIDS education in school (*Public Health Rep* 1994;109:339). In particular, successful prevention programs focus on building skills, reinforcing age- and experience-based values and norms that help prevent unprotected sex, and discussing social influence and pressure. School clinics also offer an important venue for access to condoms and appropriate instruction on condom use. Although not widely available, school clinics provide an important site for HIV counseling

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and testing for in-school youth, given new rapid testing options. Ultimately, successful prevention must also involve society and the media—until youth see abstinence, condom use, and safer sex discussions incorporated into sex scenes in music videos and movies, they will not believe that these practices are the social norm.

Adolescents who are HIV infected are also in need of risk-reduction counseling to prevent transmission of HIV to uninfected sexual partners and to prevent acquisition of other STIs or reinfection with other HIV strains. Previous data show high prevalence of risky sexual behaviors and the attendant high risk of STIs among youth. (*Perspect Sex Reprod Health* 2004;36(1):6-10; *MMWR* 2010;59 SS5:1). Multiple studies of HIV infected youth reveal a significant unplanned pregnancy rate, which is further evidence of high-risk behaviors (*HIV Med* 2011;12:118).

Linking Youth to Care

Barriers to care: Linking HIV infected youth to care is essential in meeting their needs for risk-reduction education and appropriate ongoing HIV medical and psychosocial care. Barriers to care include stigma associated with HIV, lack of independent transportation, dependence on parents for health insurance or other financing for care, and feelings of vulnerability. Many HIV infected youth do not know they are infected, and many providers are not aware of available community service agencies that can address adolescents' multiple mental health and social service needs. Community outreach is a primary component in ensuring access to care for youth with HIV disease. Programs often use peer-based outreach, because adolescents are more likely to listen to their peers.

Outreach: Unlike adult women, who have more opportunities to obtain HIV testing and to access care related to their reproductive health needs, adolescents who are not pregnant require proactive outreach efforts to promote HIV testing and engage them in care. These efforts include citywide campaigns to encourage testing and to make it more widely available with direct linkages to adolescent healthcare facilities. Another crucial element is social marketing, using the media (radio, TV, Internet, and mobile phones) that youth prefer for their communication and entertainment. To effectively reach adolescents, it is crucial that social marketing be continually updated and use the words and formats preferred by youth. Every 5 years brings a new generation, and marketing and outreach must be continually updated to reach these new generations.

Linkage to care is a crucial step in ensuring that newly identified HIV infected youth can access life-saving care. Knowing where youth are identified can also help guide expanded testing and collaboration programs. A survey conducted among 12 sites in the National Institutes of Health (NIH)-funded Adolescent Trials Network assessed the referral sources for 400 HIV infected youth who were identified and linked to care in 2009 (Futterman, unpublished data). Medical sites were the referral source for almost half the patients (48%); public health departments accounted for 21% of referrals; community-based

organizations, 16%; self, friend, or family, 10%; and other, 8%. This survey highlighted the importance of medical providers as referral agents as well as the full spectrum of sites involved in youth testing.

HIV Clinical and Psychosocial Care

Although the natural history of HIV infection in adolescence is still being defined, the course of disease among youth who acquire HIV sexually appears to follow that of adults. Descriptive studies of HIV infected adolescents in care consistently show that most youth enter care with significant immune dysfunction and that clinical status varies markedly by transmission category. Most HIV infected youth acquire their infection sexually and enter care while asymptomatic but with enough immune dysfunction to qualify for initiation of ART. In the NIH- and HRSA-funded REACH cohort (a national prospective study with sites in 13 cities to identify the course of disease in adolescents), 49% of HIV infected females and 66% of HIV infected males had CD4+ cell counts below 500/mm^3 at study entry. Although a similar percentage of females and males had AIDS at study entry (16% of females and 18% of males), viral loads were higher in the males: 9% of females but 23% of males had viral load above 50,000 copies/mL (*J Adolesc Health* 2001;29 suppl 3:8). The higher CD4+ cell count values and lower viral loads, yet similar percentage of AIDS among adolescents, provide a different perspective for the debate about whether females progress to AIDS at lower viral load and higher CD4+ cell counts.

In contrast, youth who are perinatally infected often have a much more serious course during adolescence, reflecting the effects of long-term infection. In many cases, the course of illness in adolescence also reflects the often complex patterns of resistance that result from treatment with serial mono or dual therapy that was based on earlier standards of care and medication availability. Of note, one study that predated the era of highly active antiretroviral therapy showed that among perinatally infected children, one-fifth remained asymptomatic with CD4+ cell counts > 500/mm^3. With the introduction of HAART, the subpopulation of perinatally infected youth will continue to grow as more survive and age into adolescence. Dramatic declines in mortality associated with HAART were demonstrated in the PACTG-219 study (*J Acquir Immune Defic Syndr* 2010;53:86), but those gains are tempered by the fact that mortality rates still remain 30 times greater than in uninfected matched cohorts.

Perinatally infected youth are often confronted with their own physical disabilities, which may include multiorgan system disease, delayed puberty, body dysmorphisms, and developmental delay. Their difficulties may be compounded by isolation, stigma and, often, the death or illness of one or more parents. At the same time, HIV infected youth are challenged by the tasks of adolescence, including the emerging sense of self and the need for independence. Some youth are first told of their infection during adolescence

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even after having taken medications for years. Clinicians also need to be aware that some slow-progressing perinatally infected youth might not even be diagnosed until adolescence.

Physical Exam, Laboratory Tests, and Immunizations

Privacy is an important consideration in the adolescent physical exam, because most adolescents have a high level of modesty that is often compounded by anxiety about physical changes and a lack of understanding about their anatomy. Physical examinations for adolescents should follow guidelines used for adults; however, when prescribing medications, providers should use the Tanner staging of puberty, presented in Table 10-1, which characterizes development of breasts, genitalia, and pubic hair (*Comprehensive Adolescent Health Care*, 2nd ed. St. Louis: Mosby; 1998).

Table 10-1

Classification of Sex Maturity Stages (Tanner Scale)

Stage	Pubic Hair	Breast	Penis	Testes
I	Preadolescent	Preadolescent	Preadolescent	Preadolescent
II	Scanty, long, slightly pigmented, downy	Breast bud stage; elevated breast and papilla; increased areolar diameter	Slight enlargement	Enlarged scrotum and testes; pink; changed skin, texture
III	Darker, coarser, curlier	Enlarged breast and areola with no contour separation	Increased length	Increased size
IV	Adult type, but less; no spread to medial surface thighs	Areola and papilla form secondary mound	Glans enlarged; increased breadth	Enlarged, skin darker in color
V	Adult distribution with spread to medial thighs	Mature stage; projection of nipple	Adult size	Adult size

Adapted from *Growth at Adolescence*, 2nd ed. Oxford, England: Blackwell Scientific Publications; 1962.

Routine screening: Because sexually active adolescents are at very high risk for STIs, providers should routinely screen with cervical cytology and for chlamydia, gonorrhea, syphilis, and hepatitis B and C; they also should follow TB screening guidelines for adults with HIV infection. Pregnancy testing should be performed when indicated by history or exam findings, and it should always be considered with missed menses, abnormal bleeding, or development of pelvic pain.

Immunizations: Adolescents require more immunizations than adults; immunizations are listed in Figure 10-3. HIV infected adolescents can safely receive most childhood vaccines, although efficacy may vary. Those with severe immunosuppression (CD4+ cell count <200/mm^3; CD% <15%) should not receive MMR or varicella vaccine. Oral polio and intranasal influenza vaccine are contraindicated in HIV infected patients. The CDC provides vaccination guidelines, including catch-up schedules, for patients older than 18 years of age (www.cdc.gov/mmwr/preview/mmwrhtml/mm5901a5.htm) and younger than 18 years of age (www.cdc.gov/vaccines/recs /schedules/default.htm).

Because immunizations may briefly boost viral load, they should be scheduled on the same day as or after viral load measurements. At present, CD4+ cell counts and viral load measurements are interpreted as for adults and used to guide treatment.

Figure 10-3
Immunizations for Adolescents

- Measles, mumps, and rubella (MMR) booster if CD4+ cell count is stable >200/mm^3
- Diphtheria-tetanus toxoid (TdaP) booster
- Hepatitis B vaccine (3 in series)
- Hepatitis A vaccine (2 in series; not routine for females, but recommended for males who have sex with males)
- Influenza (yearly)
- Pneumococcal vaccine (PPSV-23) >age 2 years and booster 5 years after
- HPV (3 in series) age 9–26
- Varicella zoster vaccine for contacts (not currently approved for HIV infected people; can consider for those with CD4+ cell count >200/mm^3)
- Meningococcal conjugate vaccine (MCV4; 2 in series) age 11–12, booster at age 16–18

Source: *AIDS Clin Care* 1999;11:17. Reprinted with permission.

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HIV Treatment

Medication dosing: Adolescents have not been studied extensively in the clinical trial system; thus, few direct data about dosing regimens are available. The U.S. Department of Health and Human Services (HHS) has included the treatment recommendations (based on expert opinion) for postpubertal adolescents with adult treatment guidelines. Because pubertal changes may affect pharmacokinetics, dosage is based on Tanner staging rather than on age. For example, pediatric dosing should be used for adolescents who have entered or are in early puberty (Tanner stage I/II), whereas dosing for adolescents in midpuberty (Tanner III/IV) should be based on whether they have completed the growth spurt. Adolescents who have completed puberty (Tanner V) should receive adult dosages (www.aidsinfo.nih.gov). Factors that should be considered in choosing the initial treatment regimen for adolescents include results of viral resistance testing (genotype or phenotype), pill burden, potential side effects, and likelihood of adherence.

ART and contraception: Note that several key medications commonly prescribed to adolescents have significant interactions with antiretroviral medications, including combined estrogen/progestin contraceptives, which may be less effective and/or cause more side effects when taken with antiretrovirals. Clinicians may consider switching to progestin-only methods, such as depot medroxyprogesterone acetate or the etonogestrel implant, both of which provide very effective and longer term contraception without the need to take daily pills. Concomitant use of a barrier method of contraception should be stressed. Efavirenz has been associated with risk of birth defects; since pregnancy is often unplanned in youth, this medication should generally be avoided in young women, unless other effective and well-tolerated options are not available. Currently, clinicians are advised to avoid tenofovir until patients reach Tanner IV/V. (For more information on drug–drug interactions, see the U.S. Public Health Service adult and adolescent guidelines at www.aidsinfo.nih.gov).

Adherence: Treatment adherence, which is challenging for adults, can be especially challenging for adolescents, who struggle with a range of developmental tasks that require them to balance dependence with increasing autonomy. As with any successful work with adolescents, the first step in promoting adherence is to establish a solid therapeutic alliance. Providers must develop a systematic approach that facilitates adherence by addressing four areas of interaction: (1) building trust, (2) assessing and facilitating readiness, (3) helping teens initiate and practice a new treatment regimen, and (4) providing ongoing support for adherence. This approach is outlined in Figure 10-4, which describes the EARS approach: Engage, Assess, Ready, Support. This approach addresses barriers to maintaining a complex medication schedule for adolescents, such as lack of privacy in school, home, or residential settings; the need to develop a reminder system; and the incongruity of having a serious illness while exhibiting few visible indicators of disease. In a Los Angeles adolescent HIV/AIDS program, the most common reasons for missing medication reported by youth include forgetfulness, side effects, the inconvenience of having to take so many pills, and the fact that taking the medication is a continual reminder of being HIV infected (*J Adolesc Health* 1998;22:160). Patients should be screened for depression, a known cause of nonadherence (*Arch Pediatr Adolesc Med* 2005;159:764).

Figure 10-4
Adherence: Use Your EARS

Engage
- Establish therapeutic alliance and build trust—the goal is to have youth participate actively in all aspects of treatment.
- Address immediate needs: health, housing, insurance, family, and partners.
- Educate about HIV infection—transmission, disease course, and benefits of medications.

Assess
- Stage of HIV infection
- Mental and cognitive abilities
- Physical ability to take medicines
- Support systems and disclosure issues (family and friends)
- Readiness to begin medications

Ready
- Decide with adolescent on a regimen that integrates clinical needs with lifestyle—show different pills and combinations.
- Solidify support systems: family, treatment buddy, or both.
- Practice chosen regimen with surrogate vitamins; distribute medications into a weekly medication planner and program 1-day pill timer with the adolescent.
- Address adherence barriers discovered in the practice run.

Support
- Provide ongoing support with frequent clinic visits and phone contact.
- Acknowledge and address side effects.
- Develop strategies to ensure tolerability and regularity.
- Facilitate interactions with other youth who are taking medications.

Source: *AIDS Clin Care* 1999;11:17. Reprinted with permission.

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Psychosocial Issues

An understanding of adolescent development is crucial to working effectively with adolescents as partners in their healthcare. In addition to the physical changes of puberty, adolescence consists of a series of cognitive and psychosocial phases that are key to successful maturation yet are greatly confounded in the setting of HIV infection. The Adolescent AIDS Program has identified five key issues that adolescents with HIV/AIDS must address in coping with their changing health status: (1) receiving an HIV diagnosis; (2) disclosing HIV status to parents, partners, and others; (3) coping with HIV disease; (4) becoming symptomatic; and (5) preparing for death (*J Adolesc Health* 1993;14 supp:S1). Family members can play a key role in the care of the HIV-infected adolescent if they are engaged and supportive.

Receiving an HIV diagnosis: Providers should instill a sense of hope and encouragement when giving adolescents an HIV diagnosis. Asymptomatic youth must learn to balance healthy denial and preoccupation with HIV infection. Concrete thinking makes it difficult for some youth to integrate the concept of disease latency and asymptomatic infection. Support is essential in helping youth integrate this life-changing information. Individual and peer-group interventions with psychologists and social workers can help

facilitate adjustment. Psychotropic medication may be needed to manage preexisting psychiatric problems or anxiety and depression that may accompany the diagnosis.

Disclosure of HIV status: After learning of an HIV diagnosis, adolescents face the hurdle of deciding whom to inform and when to disclose their HIV status. Although the involvement of a supportive adult is ideal, telling parents is difficult for many adolescents, who fear losing their parents' love and support or worry about hurting them. The need to rely on adults because of illness sharply contrasts to the developmental need to establish independence and identify with one's peer group. For gay or substance-using youth, disclosure to one's parents may be especially threatening because they may have to reveal their HIV status, sexuality, and drug use all at once, which could lead to rejection, harassment, or violence. Disclosure becomes a particularly salient issue with advancing disease or initiation of ART because it is difficult to conceal medications from the people with whom one lives. Adolescence is one of the most observed times of life—young people often do not have space to call their own, and privacy is especially compromised for youth living in crowded homes or residential programs. In school, institutional bathrooms provide no seclusion for taking medications.

Disclosure to sexual partners is both ethically compelling and complicated. Of course, HIV infected adolescents should inform their sexual partners and engage in safer sex, but youth face several unique challenges in disclosing their HIV status. The adolescent social/sexual world is smaller, more intense, and often shorter lived than that of adults, so confidentiality is more easily compromised. Providers should be aware that adolescents in earlier stages of sexual development might have fewer partners, which could make an anonymous disclosure easier to figure out. If one person knows, then everyone in an adolescent's group might easily find out. Fear of rejection and loss of confidentiality are thus major concerns in disclosing to sexual partners. Providers should offer to help with disclosure and offer guidance in determining when it is safe and appropriate for a youth to disclose her HIV status. Role-playing and working through scenarios ahead of time can help an adolescent manage potential fears and concerns. Collaboration with the local public health department can also facilitate partner notification and identification of sexual networks.

Coping with HIV disease: Given the prognostic significance of viral load and CD4+ cell count, adolescents need to understand how these markers relate to the course of their HIV disease. However, these concepts are often difficult to understand for youth, who may be concrete thinkers. Adolescents also need guidance in learning how to interpret changes, because fluctuation in results may cause some youth to panic. Providers can help by explaining that variation is common and that fluctuations in values will not prevent adolescents from leading satisfying and productive lives.

Becoming symptomatic: The appearance of HIV-related symptoms can be especially disturbing for adolescents, who may have only superficially acknowledged their HIV status. The onset of HIV symptoms may pierce their denial. For some youth, becoming symptomatic may encourage them to fight HIV and may enhance treatment adherence and self-care. Others, however,

may feel overwhelmed and lose their motivation to care for themselves. When symptoms occur, providers should explain their significance, correct misconceptions, and ensure that adequate services and support are available.

Preparing for death: Many adolescents have limited experience with death and have naïve perceptions about what to expect. Introducing the topic by talking about living wills and healthcare proxies before HIV becomes too advanced is a practical way to help youth begin to deal with issues related to death. When clinically appropriate, providers can help adolescents explore their feelings about dying by discussing options for dying in the hospital or at home, talking about funeral or memorial services, and exploring child custody or permanency planning with adolescent parents.

Mental Illness and Substance Use

Mental illness and substance abuse are significant comorbidities for HIV infected adolescents. Accurate screening, diagnosis, and treatment are essential to helping adolescents cope with their HIV disease and successfully maintain their ART regimen. Case studies of adolescents and young adults with HIV indicate a high prevalence of depression, bipolar disorder, and anxiety; these mental health issues often predate an HIV diagnosis (*Arch Pediatr Adolesc Med* 2000;154:240). Similarly, many HIV infected adolescents report alcohol and drug abuse. Of adolescents in the REACH study, 14% percent of females and more than 25% of males reported weekly use of alcohol in the prior 3 months. During the same period, 7% of females and 20% of males reported using hard drugs (*J Adolesc Health* 1998;22:300; *J Adolesc Health* 2001;29 suppl 3:57). In addition, a high proportion of HIV infected youth report childhood sexual abuse, which has many psychological and behavioral sequelae, including depression, posttraumatic stress disorder, substance abuse, suicidality, and HIV risk behaviors.

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Age Transitions

As medical care continues to improve, a considerable number of HIV infected adolescents will be healthy enough to graduate from pediatric to adolescent to adult programs. Emerging adults require programs and providers that can address their developmental needs. They face the concurrent challenges of healthcare maintenance, medication adherence, and chronic illness within the context of maturing sexuality and establishing an independent life. The issues of transition to adult care have been addressed in the literature for other chronic illnesses, but HIV infection has some unique features. Young people can be quite reluctant to leave their established and trusted providers and care teams. In response, many adolescent HIV programs have increased their upper age limit from 21 to 24 years. However, there comes a time when transfer to adult care is appropriate. Most successful programs begin the transition process months before it occurs. Patients and staff work together to develop skills such as dealing with the medical system (making and keeping appointments),

maintaining entitlements (health insurance and housing), learning to give a medical history and track symptoms, learning to take and be responsible for medications, and learning when to report emerging symptoms. Patients must also learn self-management skills, including setting and achieving life goals such as education and employment or careers.

Summary

The high risk of HIV in adolescent females underscores the need to develop realistic prevention programs that build prevention skills. It also highlights the need for routine HIV counseling and testing for all sexually active teens in all programs that provide care for adolescents. Youth at high risk for HIV should be identified and engaged in primary care as soon as possible. Outreach is an important component of programs that seek to link HIV infected youth to care. Although most HIV infected youth will not receive services in adolescent programs, services can be readily adapted to provide a youth-centered approach by making such basic accommodations as flexible hours, low or no payment for services and care, and engaging providers who are knowledgeable about adolescents. Information on relevant clinical trials should be made available to adolescents as well. Wide dissemination of information to healthcare providers about providing adolescent-related HIV care should take place, such as use of Tanner staging for determining appropriate medication dosages.

Adolescents with HIV need intensive individual and group support to maintain their health and reduce transmission to others. Healthcare providers in all settings that serve adolescents need to assist in making services visible, flexible, affordable, confidential, culturally appropriate, and available for all adolescents.

Chapter 11:

Palliative and Supportive Care

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Chapter 11: Palliative and Supportive Care

Chapter 11 at a Glance

Therapy to Improve Quality of Life

Address Four Domains of Suffering

Palliative care is defined as therapy intended to improve quality of life, irrespective of quantity (*NEJM* 2004;30:2582). The term *palliative* is derived from the Latin *pallium* (cloak) and means to protect (or "cloak") from illness and suffering. Palliative care seeks to address the four domains of suffering—physical, psychological, social, and spiritual. Ideally, it involves an interdisciplinary team approach for pain and symptom management as well as for nonphysical needs that may arise during the course of illness. Those needs may be met with psychosocial support for marginalized patients, identification of substance abuse and mental health issues and provision of appropriate services, and advance care planning. When appropriate, care may also include facilitating transitions to end-of-life care, including hospice. High-quality palliative care begins at disease diagnosis and is delivered simultaneously with life-prolonging therapy throughout the course of illness (Figure 11-1). As a patient's illness progresses, palliative care takes on an increasingly important role.

Palliative care encompasses end-of-life care, including hospice. In the United States, patients on Medicare may choose to disenroll from Medicare and enroll in the Medicare hospice benefit, which requires a physician to certify that the patient is in the last 6 months of his or her life. This separation between palliative care in general and hospice is artificial and applies only in the United States. In other countries, the terms palliative care and *hospice* are often used synonymously (*Cancer J* 2010;16:423).

Supportive care is used in the literature and in practice to delineate a similar model of care. Supportive care is designed to support a patient and his or her family and caregivers during an illness that is not imminently terminal but is curable or has a good chance of recovery or survival. Supportive care describes many ambulatory programs, particularly in the areas of oncology and cardiac disease. Supportive care settings also include a focus on the four domains of suffering and an interdisciplinary model of care.

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Figure 11-1
Palliative Care's Place in the Course of Illness

Diagnosis of Serious Illness

Life-Prolonging Therapy

Palliative Care

Medicare Hospice Benefit

Death
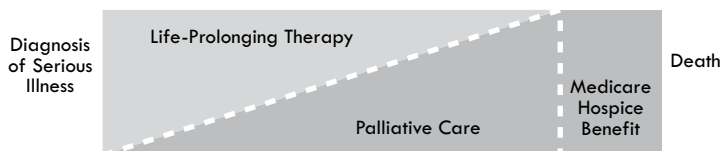
Source: National Consensus Project for Quality Palliative Care. *Clinical Practice Guidelines for Quality Palliative Care*, 2nd ed. 2009. Copyright © 2009 by the National Consensus Project for Quality Palliative Care. Used with permission.

Rapid Expansion in the United States

The number of hospital-based palliative care programs increased from 658 in 2000 to more than 1151 in 2005 (*J Palliat Med* 2008;11:1094); in 2009, 41.6%% of all deaths in the United States took place under the care of a hospice program (http://www.nhpco.org/files/public/Statistics_Research/ Hospice_Facts_Figures_Oct-2010.pdf). A recent high-profile study showed that an early outpatient palliative care intervention improved quality of life and extended survival as much as cisplatin-based chemotherapy for patients with metastatic non-small-cell lung cancer. Although this result is not necessarily generalizable to other patient populations, it is encouraging (*NEJM* 2010;363:733). Additionally, palliative care is an increasingly accepted part of care not only for patients with cancer but also for those with other chronic diseases, such as congestive heart failure (CHF), chronic lung disease, and HIV.

Interdisciplinary Approach

As noted above, the delivery of comprehensive palliative care should involve an interdisciplinary team consisting of physicians, nurses, social workers, pastoral care representatives, and mental health care providers. High-functioning teams also successfully incorporate midlevel care providers, such as nurse practitioners, physician assistants, pharmacists, pain management specialists, and integrative therapists (massage, music, and art) as well as volunteers. The National Quality Forum has produced a document of preferred practices that delineate the parameters or measures of quality for palliative care programs; it should be referenced when initiating or enhancing delivery of palliative and supportive care (National Quality Forum 2006. *A national framework and Preferred practices for Palliative and Hospice Care Quality: A Consensus Report 2006*).

HIV as a Chronic Disease

Alleviate Suffering of Chronic Disease

Before the introduction of effective ART in the mid-1990s, the trajectory of HIV/AIDS was a downward spiral, and all care was palliative. HAART transformed HIV from a disease with a uniformly poor prognosis into a chronic disease with a slowly progressive course and occasional exacerbations, much like chronic obstructive pulmonary disease (COPD), CHF, and chronic malignancies. Patients began to have the potential for normal or nearly normal life spans. In the post-HAART era, the focus understandably shifted toward optimal use of life-prolonging medications. Palliative care for HIV was seen as mostly of historical significance, appropriate only for patients facing imminent death from AIDS (*JAMA* 2003;290:806, *Annals Int Med* 1998;129:899). However, symptom burden remains high despite ART (*Int J STD AIDS*

2006;17:400). Therefore, in the current treatment era, palliative care should be applied throughout the disease continuum to alleviate suffering associated with living for many years with a chronic disease.

HIV Disease Burden and the Role of Palliative Care

Today, HIV palliative care focuses on quality of life, maximized functional status, and treatment of complicated comorbidities (Figure 11-2). Unfortunately, the burden of HIV disease in the current treatment era remains high for several reasons.

Prevalence: Even though the number of new HIV diagnoses among US women has declined slightly from 2008–2011, HIV prevalence continues to increase as more infected individuals are living longer because of ART (http://www.cdc. gov/hiv/surveillance/resources/reports/2010report/index.htm).

Pain and symptom burden: Patients living with HIV disease have significant pain and physical and psychological symptoms. Most studies of pain and symptoms in HIV come from the early treatment era, but emerging evidence indicates that pain and symptom burden remains high despite advances in therapy (*J Pain Symptom Manage* 2009;38:882).

Aging patients: As a result of effective ART, the population of patients with HIV is aging. In addition, a number of patients with HIV experience premature aging and are at increased risk for cardiovascular disease, metabolic complications, neurologic sequelae, frailty, osteoporosis, and malignancies, among other age-associated conditions (*AIDS Patient Care STDS* 2006;20:782, *J Acquir Immune Defic Syndr* 2008;49:S77, *J Acquir Immune Defic Syndr* 2009; 50:299, *Top HIV Med* 2010; 18:45, *J Acquir Immune Defic Syndr* 2003;33:281, *J Acquir Immune Defic Syndr* 2009; 52:203). Aging and comorbidities likely add to pain and symptom burden.

Death: People still die of HIV in the United States; 2010 data from the U.S. Centers for Disease Control and Prevention indicate that the death rate in women with HIV disease has leveled off at 4–5 deaths per 100,000 since 1998. Increasingly, death is occurring among non-Hispanic blacks, residents of the South, and people aged 45 years and older (http://www.cdc.gov/hiv/surveillance/resources/reports/2010report/index.htm). Death from HIV has shifted "from fate to tragedy" (*Ann Intern Med* 1998;129:899) and is often due to nonadherence to medical care and ART, psychiatric and substance abuse comorbidities, and marginalization from the medical system.

Non-AIDS–related death: HIV patients die more often of non-AIDS–related causes, such as cardiovascular, hepatic, and pulmonary disease; non-AIDS malignancies; and substance abuse. They are at greater risk for those diseases than is the general population (*Ann Int Med* 2006;145:397, *J Acquir Immune Defic Syndr* 2006;43:27, *J Acquir Immune Defic Syndr* 2009;52:203).

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Thus, the role of HIV care providers is to alleviate suffering while treating the primary disease. If for no other reason, HIV providers today must learn and use the principles of palliative care to address the burden of HIV as a chronic disease. Additionally, evidence increasingly shows that management of symptoms in patients with HIV improves quality of life (*AIDS Behav* 2004;8:151, *CID* 2008;46:941), adherence (*J Acquir Immune Defic Syndr* 2002;31:211, *AIDS Beh* 2003;7:109, *Ann Behav Med* 2007;34:46, *AIDS Care* 2009;21:244), and virologic outcomes (*J Acquir Immune Defic Synd* 2010; 54:500). Palliative care for patients with HIV can be delivered by HIV primary care providers in addition to palliative care specialists when necessary.

Figure 11-2
Key Facts About Palliative Care in HIV

- Palliative care does not equate to end-of-life care and is not the same thing as hospice.
- Symptom burden in HIV patients, even in the current treatment era, remains high.
- Incorporating principles of palliative care, including pain and symptom management, early in the disease course can alleviate suffering and may improve quality of life, adherence, and virologic outcomes.
- Palliative care for patients with HIV can be delivered by HIV primary care providers in addition to palliative care specialists when necessary.

Pain and Nonpain Symptoms

This section focuses on pain and nonpain symptoms in ambulatory patients with HIV. As with other serious conditions prevalent in patients with HIV, such as syphilis and hyperlipidemia, pain must be assessed and treated, if present, in every patient.

Pain and other symptoms in patients with HIV are generally thought to result from several factors:

- Disease-related factors may include the acute effects and long-term sequelae of opportunistic infections (e.g., headache in cryptococcal meningitis, contractures resulting from a distant history of PML), AIDS-defining and non-AIDS-defining malignancies, and the effects of HIV itself or the body's immune response to it (e.g., peripheral neuropathy).

- Treatment-related factors may include the medications used to treat HIV disease (e.g., dideoxynucleoside-related peripheral neuropathy and protease inhibitor–related gastrointestinal distress)

- Other factors may include the nonspecific effects of a chronic illness and other causes of pain and symptoms unrelated to HIV (e.g., shortness of breath in COPD or edema in CHF)

Prevalence of Nonpain Symptoms

In the current treatment era, symptoms remain prevalent, and it is essential to pursue the cause of the symptom by searching for treatable underlying etiologies. Simultaneously, an effort should be made to relieve the symptoms. This approach does not detract in any way from the evaluation; in fact, attention to symptom management may increase the likelihood of the patient returning for regular followup and enhance overall quality of life.

Most data on nonpain symptoms in patients with HIV comes from the early treatment era. In 1996, a study of 434 ambulatory patients with HIV found an average of 17 symptoms on the Memorial Symptom Assessment Scale (MSAS), a 32-symptom instrument (*Pain* 1996;68:315). The most prevalent physical symptoms other than pain were lack of energy, difficulty sleeping, and dry mouth (86%, 74%, and 69% respectively). A recent study of 350 ambulatory HIV patients in the current treatment era found a median of 9 symptoms (*J Pain Symptom Manage* 2009;38:882). The most common symptoms were lack of energy (65%), drowsiness (57%), and difficulty sleeping (56%). Numbness and tingling (44%) were also common, as were psychiatric symptoms, such as feeling irritable (50%), worrying (48%), and feeling sad (45%).

Assessment of Nonpain Symptoms

As part of an overall systems review, it is important to ask patients specifically about the types of symptoms mentioned above—namely, lack of energy, difficulty sleeping, psychological problems, and neuropathic pain. A systematic approach to assessment is more important than the specific instrument used. The MSAS is often used for research, but it may be too cumbersome for routine use in the clinical setting. If that is the case, then a standard symptom assessment tool that meets the needs of an individual clinical practice setting is recommended. When assessing physical symptoms, a patient should be asked about the degree to which a symptom causes bother or distress—i.e., not at all, a little bit, somewhat, quite a bit, or very much, as illustrated in Figure 11-3. For psychological symptoms, a patient should be asked about the frequency with which a symptom occurs—i.e., rarely, occasionally, frequently, or almost constantly. If a patient reports a symptom that is particularly distressing, then the response to these questions may be followed over time.

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Figure 11-3
Key Questions in Assessing Nonpain Symptoms

| How distressing is this symptom? | Not at all | A little | Somewhat | Quite a bit | Very |

| How often do you experience this symptom? | Rarely | Occasionally | Frequently | Almost constantly |
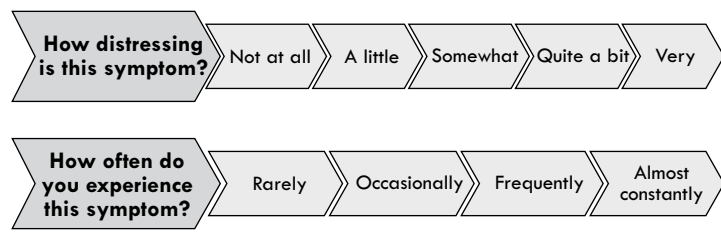
Management of Selected Symptoms

Clinicians should always investigate the cause of symptoms, particularly for potentially curable etiologies. While investigating a symptom, it is also important to begin to manage the symptom.

In a patient with HIV infection, multiple factors should be taken into consideration, including the stage of illness, current ART and other medications, and total symptom burden. As noted above, patients may have multiple simultaneous symptoms that require a comprehensive, patient-centered approach that focuses on the effect on quality of life of each symptom. Symptom clustering also should be considered (e.g., inadequately treated pain that leads to depression, sleep disturbance, shortness of breath, anxiety, poor appetite, and fatigue), so as not to overlook appropriate medications that may successfully treat multiple symptoms simultaneously. Discontinuation of nonessential medications that may cause a disturbing symptom should be explored as well.

Table 11-1 lists common nonpain symptoms with appropriate medication classes. A comprehensive listing of all symptoms and medications with dosages is beyond the scope of this chapter. Treatment of psychiatric and psychological symptoms is addressed in Chapter 9. It is also important to keep in mind that symptoms certainly will change and evolve as a patient's disease progresses. Therefore, use of medications may change over time as well.

Table 11-1

Common Nonpain Symptoms in HIV Patients

Symptom	Common Medications/ Classes Used in Treatment	Important Points/Notes
Fatigue	• Psychostimulants (dextroamphetamine, methylphenidate) • Steroids (dexamethasone, prednisone) • Other agents, depending on comorbidities (testosterone, opioids, sleep agents)	• Determine whether etiology is reversible. • Energy conservation counseling and/or an appropriate graduated exercise regimen may be helpful.
Weight loss/ anorexia	• Steroids (dexamethasone, prednisone) • Megestrol • Mirtazapine • Dronabinol	• Evaluate for inadequately treated comorbidities • Consider dietary or nutrition consultation. • Likely not reversible near end of life.
Insomnia	• Benzodiazepines (lorazepam, temazepam) • Antidepressants (trazodone, mirtazapine) • Chloral hydrate • GABA receptor nonbenzodiazepines (zolpidem, zaleplon) • Melatonin receptor agonist (ramelteon)	• Emphasize nonpharmacologic sleep hygiene. • Avoid chronic long-term use of meds.
Nausea/ vomiting	• Dopamine agonists (haloperidol) • Dopamine antagonists (prochlorperazine, chlorpromazine, promethazine) • Gastric motility agents (meclizine, hydroxyzine) • Antihistamines (meclizine, hydroxyzine) • Anticholinergics (scopolamine, glycopyrrolate) • Anxiolytics (lorazepam) • Steroids (dexamethasone) • 5-HT3 antagonists (ondansetron, granisetron)	• Thoroughly evaluate for mechanism and/or etiology. • Remember bowel history and avoid constipation. • Combinations of agents may be helpful. • 5-HT3 antagonists may have limited utility near end of life. • Sedation is a common limiting side effect.
Dysphagia/ odynophagia	• Antifungals (fluconazole, nystatin) • H2 antagonists (famotidine, ranitidine) • Proton pump inhibitors (omeprazole) • Steroids (dexamethasone) • Anticholinergics (hyoscyamine, glycopyrrolate) • Oral solutions (viscous lidocaine)	• Treatment of oropharyngeal comorbidities is crucial. • Complicates many other symptoms. • Very common near end of life. • Combinations of agents in oral solution may be helpful.

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Table 11-1	*continued*	

Common Nonpain Symptoms in HIV Patients

Symptom	Common Medications/ Classes Used in Treatment	Important Points/Notes
Cough	• Guaifenesin (immediate or sustained release) • Nebulized saline • Guaifenesin with dextromethorphan • Guaifenesin with codeine or other opioid • Benzonatate	• Difficult to treat in many instances. • Treat underlying comorbidities when possible. • Provide smoking cessation counseling when appropriate. • May be productive or nonproductive.
Hiccups	• Chlorpromazine • Baclofen • Simethicone • Haloperidol • Anticonvulsants (gabapentin, valproic acid, carbamazepine)	• Search for reversible causes; usually self-limiting. • Relation to meals is important. • Nonpharmacologic measures may be beneficial. • Holding breath, gastric distention, vagal maneuvers may be helpful.
Pruritus	• Topical preparations (camphor–menthol lotion • Lidocaine ointment, hydrocortisone • Antihistamines (diphenhydramine, hydroxyzine) • Steroids (dexamethasone, prednisone) • Antidepressants (doxepin, mirtazapine, paroxetine)	• May have multiple etiologies. • Soaps, detergents, and fabrics are common offenders. • Cool environment is usually better than warm.
Dyspnea/ shortness of breath	• Immediate-release opioids (morphine, oxycodone, hydromorphone) • Benzodiazepines (lorazepam, alprazolam) • Nebulized medications (furosemide, fentanyl)	• Troublesome, common symptom near end of life. • Nonpharmacologic treatment (fan, relaxation, etc.) may be most helpful. • Opioids are a mainstay near end of life. • Nebulized meds are somewhat controversial.
Xerostomia	• Saliva substitutes • Chemical stimulants • Muscarinic agents (pilocarpine, cevimeline)	• Encourage ice, frozen fruits, etc. • Sour candies may increase saliva production. • Use humidified oxygen when appropriate. • Use muscarinic agents only with caution.

Prevalence of Pain

Most studies of pain in patients with HIV were conducted in the early treatment era. The largest study surveyed 274 patients, 62.6% of whom reported frequent or persistent pain during the 2 weeks prior to the survey. The mean rating of pain intensity was 5.4 on a scale of 1 to 10, and the mean rating for interference with general activity was 5.7 on a scale of 1 to 10. Pain prevalence in women was similar to that in men, but women reported significantly higher pain intensity. Pain was associated with the presence of AIDS-defining conditions (*Pain* 1996;68:315). In a study of symptoms in HIV patients in the current treatment era, 55% had pain, 60% of whom reported the symptom frequently. Pain was associated with female gender, advanced disease, and absence of antiretroviral (ARV) medications (*J Pain Symptom Manage* 2009;38:882). In a recent study, muscle aches and joint paints were one of the two symptoms most associated with the physical component of health-related quality of life in patients with HIV (*AIDS Behav* 2011; 15:853). Another recent study found that up to 15% of HIV Outpatient Study patients used prolonged analgesic therapy each year; variables associated with the initiation of prolonged analgesia included both HIV and non-HIV related factors. (*Clin J Pain* 2011;27:699).

Although more research is needed to understand HIV patients' pain in the current treatment era, the available data suggest that pain is widely prevalent in this population. Studies from the early treatment era suggest that pain is underrecognized and undertreated (*BMJ* 1997;314:23, *J Pain Symptom Manage* 1999;18:263, *Pain* 1996;65:243) and has a negative effect on quality of life (*AIDS Behav* 2004;8:151, *CID* 2008;46:941). Multisite pain syndromes are common as well–patients have musculoskeletal, neuropathic, and visceral pain syndromes simultaneously. Multisite syndromes may have distinct etiologies and require specific evaluations and treatments that can further complicate care plans, medical regimens, and patients' emotional response to their illness. Although referral to a pain specialist may be useful for patients with a history of previous substance abuse, it behooves the primary care provider to attempt to clarify the types of pain present to ensure adequate follow-up.

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Assessment of Pain

Brief Pain Inventory (BPI; *Ann Acad Med Singapore* 1994; 23 (2): 129): Many approaches to the assessment of pain in patients with chronic illness are available. Because no tool has been validated specifically in patients with HIV, having a systematic approach to assessing pain is more important than using a specific tool. A standard approach that is consistent with the intent of the BPI is generally recommended (*Ann Acad Med Singapore* 2004;23:129).The BPI has been validated in patients with chronic nonmalignant pain (*J Pain* 2004; 5:133) and has been used in studies of patients with HIV (*Pain* 1996; 68: 315). In its entirety, the BPI may be too long for many clinical settings, but when appropriate, it should be incorporated into a patient's ongoing pain assessment and treatment plan.

Pain evaluations should begin by simply asking whether the patient has had pain that affects quality of life during the past week. If the patient answers yes, in addition to usual questions about pain (e.g., location, quality, exacerbating and alleviating factors, duration), a few brief follow-up questions, illustrated in Figure 11-4, may be asked:

- **Severity:** How severe is your pain right now on a scale of 0 to 10, where 0 is *no pain* and 10 is *pain as bad as you can imagine?* On average? At its worst? At its least? (A pain scale, shown in Figure 11-5, may be used to help patients answer this question.)

- **Relief:** What current medications or therapies do you use to help alleviate your pain? How much relief do you get from these therapies, on a scale of 0% (*no relief*) to 100% (*complete relief*)? It is important to ask and document all medications or therapies that have been successful in the past; also emphasize reports of allergies or sensitivities to particular opioids or other pain medications.

- Interference: How much does the pain interfere with your general activity on a scale of 0 to 10, where 0 is *no interference* and 10 is *complete interference?* How does much does it interfere with your mood? Walking ability? Normal work? Relations with other people? Sleep? Enjoyment of life?

The answers to these questions can be followed over time.

Figure 11-4
Key Questions in Assessing Pain

On a scale of 0 to 10 → **How severe is your pain?** → On a scale of 0% to 100% → **How much relief do you have with your current therapy?** → On a scale of 0 to 10 → **How much does pain interfere with your life?**
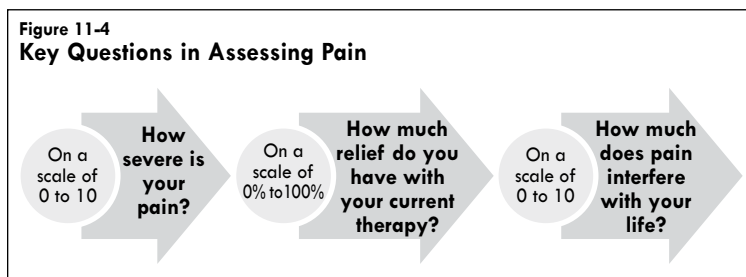
Several additional questions, noted below, may be especially helpful if patients have longstanding or multisite symptomatology. Discussing the questions below can build a therapeutic relationship that helps patients become more active in their care plan.

- Which of your pain locations is the worst today?

- When was the last time you remember being pain free?

- What are your goals, or what would be an acceptable pain score for you?

- If we meet these goals, what kinds of things would you like to do that you are not currently doing?

- What would be your time frame for acceptable pain relief?

- How do your emotions or stress affect your pain?

Figure 11-5
Pain Scale

0	1	2	3	4	5	6	7	8	9	10
No Pain		Mild Pain			Moderate Pain		Severe Pain			
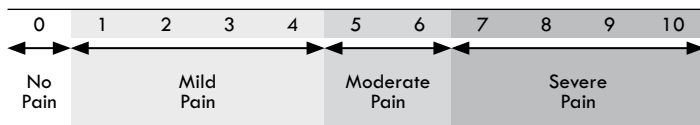
Approach to Pain Management

Initial medication selection: Although it has not been validated specifically in patients with HIV, the World Health Organization's (WHO's) pain ladder is a well-accepted approach to pain management (Figure 11-6).

Figure 11-6
WHO Pain Relief Ladder

Step 3: Severe Pain
Opioid (morphine, hydromorphone)
± Nonopioid analgesics
± Adjuvants

Step 2: Moderate Pain
Opioid (codeine, hydrocodone, oxycodone)
± Nonopioid analgesics
± Adjuvants

Step 1: Mild Pain
Nonopioid ± Adjuvants
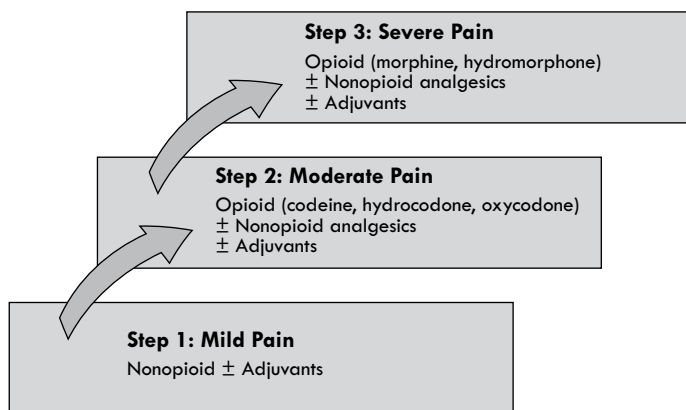
Source: World Health Organization. *WHO's Pain Relief Ladder*. Copyright © 2012. World Health Organization. Adapted with permission.

Principles for Use of WHO Pain Ladder

Initiation: Initiate pain medications according to the appropriate step on the WHO Pain Ladder. In the outpatient setting, this step may entail use of oral instead of intravenous medications, even for patients with moderate to severe pain. In the inpatient setting and in patients with severe pain, pain medications administered intravenously or subcutaneously may be needed for acute pain relief in opiate-naïve patients.

Starting doses for opioid-naïve patients with normal renal and hepatic function are listed in Table 11-2. The medication should be given every 4 hours around the clock, not on an as-needed basis. In addition to the around-the-clock doses, prescribe a breakthrough dose that is 10% of the total daily opioid dose, given every hour if the pain is not controlled.

Long-acting pain medication: Once pain is fairly well controlled, if it is expected to continue and not improve (e.g., pain related to a fracture that is healing), then it is appropriate to change to a long-acting pain medication for ease of administration.

- Calculate the dose of a long-acting medication by adding all doses taken in 24 hours (including breakthrough doses). Oral long-acting medications are usually given 2 or 3 times per day, so the total daily dosage must be divided by this number to get the amount of each dose.

- Fentanyl patches and methadone are preferred in patients with renal and hepatic failure (when using methadone, consult with a palliative care or pain specialist). Provide a breakthrough dose every 1 hour as needed; the breakthrough dose should be 10% of the total daily dosage.

- Adjust for incomplete cross-tolerance; see below.

Adjusting for incomplete cross-tolerance: When exposed to a new opioid, a patient will not have had the opportunity to become tolerant to that opioid's side effects. Therefore, as a rule of thumb, when converting between opioids or converting to long-acting medications, decrease the dosage by 25% to 50%. This adjustment is called "adjusting for incomplete cross-tolerance" to the new drug. Use an equianalgesic table, such as Table 11-2.

Fentanyl patches should never be used in opioid-naïve patients. To convert short-acting medications to fentanyl, see Table 11-3. To convert fentanyl back to short-acting medications, see Table 11-4. Note that liquid formulations, rectal suppositories, and sprinkles that can be mixed with food may be prescribed for patients who have with difficulty swallowing pills.

Most well-localized and acute pain can be controlled with the use of the pain ladder (*JAMA* 1995; 274:1870). Once a patient is on an appropriate dosage, side effects (except for slowed bowel motility) generally resolve within 7–10 days.

Table 11-2

Oral Opioid Dosing

Drug	Starting Doses for Naïve Patients	Equianalgesic Doses	Renal Impairment	Hepatic Impairment
Codeine	30-60 mg	200 mg	Avoid	Avoid
Oxycodone	5-10 mg	20 mg	Adjust dose and frequency	Adjust dose and frequency
Hydrocodone	2-4 mg	30 mg	Adjust dose and frequency	Adjust dose and frequency
Morphine (short-acting)	15-30 mg	30 mg	Avoid	Adjust dose and frequency; avoid in severe disease
Hydromorphone	2-4 mg	7.5 mg	Preferred, but decrease dose and frequency	Adjust dose and frequency

Source: © *Pain Management Guidelines*. Hertzberg Palliative Care Institute. May 2008. Adapted with permission.

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| Table 11-3 | | | |

Converting the Current Opioid to a Fentanyl Patch*

Morphine, po mg/24 h	Oxycodone, po mg/24 h	Hydromorphone, po mg/24 h	Replace with Fentanyl Patch at Following Dose (mcg/hr q 72 h)
10–19	20–39	8–14	12
20–44	40–89	15–33	25
45–74	90–149	34–55	50
75–104	150–209	56–78	75
105–134	210–269	79–100	100
135–164	270–329	101–123	125
165–194	330–389	124–145	150
195–224	390–449	146–168	175
225–254	450–509	169–190	200
255–284	510–569	191–213	225
285–314	570–629	214–235	250
315–344	630–689	236–258	275
345–374	690–749	259–280	300
375–404	750–809	281–303	325
405–434	810–869	304–325	350
435–464	870–929	326–348	375
465–494	930–989	349–370	400

*PRN dosing for breakthrough pain: The breakthrough dose of oral morphine for a patient on a fentanyl patch is roughly 1/3 the fentanyl patch dose (e.g., if the patient is prescribed a fentanyl patch of 75 mcg/h q 72 h, the breakthrough dose is short-acting morphine 25 mg po q 1 h prn. If you want to use an opioid other than morphine, use the equianalgesic table to convert. As always, when starting a new opioid, adjust for incomplete cross-tolerance.

Source: © *Pain Management Guidelines*. Hertzberg Palliative Care Institute. May 2008. Adapted with permission.

| Table 11-4 |

Converting a Fentanyl Patch to Another Opioid*

Fentanyl patch dose (mcg/hr q 72 h)	Replace With One of the Following Opioids (Total mg/24 h)**		
	Morphine po mg/24 h	Oxycodone po mg/24 h	Hydromorphone po mg/24 h
12	45	30	11
25	90	60	22
50	180	120	45
75	270	180	67
100	360	240	90

*PRN dosing for breakthrough pain: The breakthrough dose of oral morphine for a patient on a fentanyl patch is roughly 1/3 the fentanyl-patch dose (e.g., if the patient is prescribed a fentanyl patch of 75 mcg/h q 72 h, the breakthrough dose is short-acting morphine 25 mg po q 1 h prn. If prescribing an opioid other than morphine, use the equianalgesic table to convert. As always, when starting a new opioid, adjust for incomplete cross-tolerance.

**Divide recommended doses (mg/24 h) into 6 equal doses given q 4 h.

Source: © *Pain Management Guidelines*. Hertzberg Palliative Care Institute. May 2008. Adapted with permission.

Opioid Titration

For many patients, pain is not adequately relieved by the initial low-dose opioid. When that is the case, the care provider must titrate the patient's opioid dose to pain relief. Moderate pain requires titration every 24 hours, whereas severe pain may require more frequent titration. A patient may be instructed to alert the care provider if severe pain continues or if more than three to four doses of the breakthrough pain medication are taken, at which time the patient's total daily dosage may be increased by 25% to 50% for mild to moderate pain and by 50% to 100% for severe pain. Patient or caregiver diaries of breakthrough pain medication dosing are helpful in opioid titration. Patients undergoing titration should be seen frequently, as often as every week, and called as often as is necessary between appointments to ensure adequate pain relief.

Bowel Regimen

Constipation is expected with opioids and will not resolve without pharmacologic intervention. Unlike other side effects, tolerance does not develop over time with long-term opioid therapy. Therefore, all patients receiving opioids must also be started on a bowel regimen at the time of opioid initiation. A combination of a stool softener and a mild stimulating agent (such as docusate, 100 mg orally twice daily, and senna, 2 tablets daily) may be an effective initial regimen. If this regimen is ineffective, then the doses of these agents can be increased or an osmotic agent (such as lactulose, sorbitol, or polyethylene glycol) can be added. If those measures do not work, then

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a laxative suppository (e.g., Dulcolax) and enemas may be used. The newer agent methylnaltrexone can also be prescribed in severe refractory cases, but it is quite expensive, requires a subcutaneous injection, and can be used only once every 2 to 3 days.

Side Effects of Opioids

Table 11-5 outlines common side effects of opioids. Although respiratory depression is a much-feared side effect, it is unusual unless an opiate-naïve patient is given a large initial parenteral dose. Use of the Pain Ladder method and the starting doses described above is a safe approach. Patients should be counseled that side effects usually dissipate after a week of therapy.

Table 11-5	
Common Side Effects of Opioid Analgesics	
Constipation	Requires prescription of bowel regimen at the SAME TIME opioids are prescribed.
	Tolerance does NOT develop.
Drowsiness	Resolves after 24–36 h.
	Extended sleeping can be from exhaustion; may need psychostimulant, such as methylphenidate.
Nausea	Prescribe antiemetic with first opioid prescription.
	Resolves in several days; may need around-the-clock dosing initially.
Urinary retention	Uncommon side effect.
	Rotate opioids or adjuvants; may require catheter drainage of bladder.
Itching/ twitching	May indicate toxic levels due to impaired renal function.
	Lengthen interval; rotate opioids.

Nonopioid Analgesics

The most commonly used nonopioid analgesics are

- acetaminophen (starting dose 650–1000 mg orally every 6 hours, not to exceed 2-3 g/day in an adult with normal hepatic function or 2 g/day in patients with impaired hepatic function);

- ibuprofen (200-800 mg orally every 8 hours); and

- tramadol (50-100 mg orally every 4-6 hours, not to exceed 400 mg orally daily).

Prescribing opioids and nonopioids separately, as opposed to in combination pill form (e.g. oxycodone–acetaminophen) is better practice because it allows providers to titrate up opioids without exceeding the maximum dose of a nonopioid.

Adjuvants

Adjuvant medications are used to enhance the analgesic efficacy of opioids, to treat concurrent symptoms that exacerbate pain, and to provide independent analgesia. They may be used at all stages of the WHO Pain Ladder. Commonly used adjuvants include antidepressants, antipsychotics, anxiolytics, psychostimulants, anticonvulsants, and corticosteroids. Consider use of adjuvants for any patient with pain. In particular, it may be helpful to consider the mechanism of pain when selecting an adjuvant. For example, a patient with neuropathic pain may benefit from the anticonvulsant gabapentin, whereas a patient with colon cancer and liver metastases and right upper-quadrant pain may benefit from steroids for capsular pain. A complete discussion of initiation of adjuvant pain medications is beyond the scope of this chapter. However, care providers who are treating pain syndromes should be generally familiar with these medications and comfortable with the starting dosage while consulting with a pain management or palliative medicine specialist.

Adjuvants used in selected circumstances include:

- anticonvulsants (e.g., gabapentin, pregabalin, and carbamazepine) and GABA-receptor agonists (e.g., baclofen) for neuropathic pain;

- transdermal agents (e.g., the lidocaine patch) for postherpetic neuralgia and other localized pain syndromes;

- antidepressants, including tricyclic antidepressants (e.g., amitriptyline) and selective serotonin reuptake inhibitors (e.g., paroxetine, citalopram); and

- corticosteroids (e.g., dexamethasone) for pain due to increased intracranial pressure, pain due to bowel or bladder obstruction, bone pain, and spinal cord compression (Textbook of Palliative Medicine, 2006)

Adjuvant medications may be particularly helpful when patients have comorbid conditions such as depression, weight loss, or cachexia. Antidepressants may be beneficial for patients experiencing what has been described in the past as a "whole body" or more central-type chronic pain syndrome. As noted above, several adjuvant medications may be more helpful in patients who have a neuropathic component to their pain syndrome.

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Peripheral Neuropathy

Distal sensory polyneuropathy is the most common neurologic complication found in patients with HIV (*Neurol Clin* 2008;26:821). Prevalence estimates of clinically evident peripheral neuropathy in patients with well-controlled HIV in the current treatment era range from 13% to 49% (*Clin Infect Dis* 2005;40:148, *Arch Neurol* 2010;67:552, *Neurology* 2006;66:867).

Cause: Distal sensory polyneuropathy is thought to be caused by the direct effects of HIV on peripheral nerves. It is more common in patients with advanced disease and in those taking certain ARVs (i.e., DDI and d4T). It can occur at any CD4+ cell count. Risk factors include age greater than 40, CD4+ cell count nadir below $50/mm^3$, diabetes, and use of DDI and d4T (*Clin Infect Dis* 2005;1:148, *Arch Neurol* 2010;67:552, *Clin Infect Dis* 2005;40:148, *Neurology* 2006;66:867).

Clinical presentation: Typical clinical presentation is numbness and tingling in the feet, which may progress up the legs and, less commonly, to the hands and arms in a stocking–glove distribution. The neuropathy is usually only sensory, but in rare cases it may have a motor component.

Diagnosis: Diagnosis is clinical. Workup should include tests to exclude other causes of peripheral sensory neuropathy (e.g., B12 level, diabetes screening, hepatitis C virus (HCV) testing, thyroid function tests, renal/hepatic function, serum and urine protein electrophoresis, syphilis screening, and careful review of the medication list for neurotoxic medications).

Recommended approach to treatment: Remove neurotoxic drugs, such as implicated ARVs and isoniazid, and treat coexisting conditions found on initial evaluation.

- **Antiepileptic drugs:** Initiate gabapentin 100 mg p.o. 3x/day with titration to a maximum dose of 3,600 mg daily (*J Neurol* 2004;251:1260) as tolerated.

- **Antidepressants:** Although studies in patients with HIV have not shown benefit over placebo (*Neurol* 1998;51:1682, *JAMA* 1998;280:1590), amitriptyline commonly continues to be used in this setting because of its efficacy in patients with diabetic neuropathy (*Neurol* 1987;37:589).

- **Topical agents:** Capsaicin has been shown to improve symptoms of peripheral neuropathy and may be used in combination with oral agents (*J Pain Symptom Manage* 2008;35:299, *Neurology* 2008;70:2305).

- **Opioids:** In recalcitrant cases, opioids may be added and have shown efficacy in many studies.

Patients With Substance Abuse Comorbidities

Managing pain in patients with a history of substance use is a particularly challenging problem that HIV care providers often face. Basic principles for pain management in substance users are outlined below. (Also see Chapter 9, *Psychosocial Issues, Mental Health, and Substance Abuse*.)

Approach to Pain Management in Substance Users With HIV Disease

- Substance users with HIV disease deserve pain control; we have an obligation to treat pain and suffering in all of our patients.

- Accept and respect the report of pain.

- Be careful about the label *substance abuse*; distinguish between tolerance, physical dependence, and *addiction* (psychological dependence or drug abuse) and *pseudoaddiction* (opioid-seeking behavior in a patient with undertreated pain).

- Not all substance users are the same; distinguish between active users, patients in methadone maintenance, and those in recovery.

- Individualize pain treatment.

- Utilize the principles of pain management outlined for all patients with HIV disease and pain (WHO Pain Ladder).

- Set clear goals and conditions for opioid therapy: Set limits, recognize drug abuse behaviors, make consequences clear, use written contracts, and establish a single prescriber.

- Use a multidimensional approach: pharmacologic and nonpharmacologic interventions, attention to psychosocial issues, team approach.

- Utilize pain diaries along with standard protocols for refills and periodic urine drug screens.

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Advanced Illness

Syndrome of Imminent Death

It is important to recognize when a patient is actively dying. Several features characterize the syndrome of imminent death. Early on, patients may be bedbound, have delirium, and have decreased oral intake. As they progress, they may become increasingly obtunded; develop noisy secretions (i.e., the *death rattle*); and eventually become comatose and febrile, with periods of irregular breathing interrupted by long pauses (*Syndrome of Imminent Death*, 2nd ed. Fast Facts and Concepts #3, July 2008; available at http://www.

eperc.mcw.edu/EPERC/FastFactsIndex/ff_003.htm. Accessed 9/15/2012). Figure 11-7 describes key physical and emotional aspects of care at the end of life. This guide is formatted for use as a pocket guide for care providers.

Figure 11-7
Pocket Guide to End-of-Life Care

Pocket Guide to End-of-Life (EOL) Care [side 1]

Comfort Measures at LIFE'S END

L Lips, mouth, and eyes moistened—use ice chips and artificial saliva and tears

I Incontinence of bowel and bladder expected—use catheter, bed pads

F Fevers expected—use around-the-clock antipyretics, oral or suppository

E Eliminate all but essential meds

S Symptom management—be aggressive

E Eating—less is expected; diet as desired

N Nursing call orders—revise

D Decubitus—skin care and/or turning every 2 hours

Pocket Guide to EOL Care [side 2]

Provide RPC (see below): Once the difficult decision to write a *Do Not Resuscitate (DNR)* order has been made, more remains to be done for a dying patient and the family. After writing a *DNR* order, remember to reverse your thinking and write an order to Provide *RPC*.

R = Reassurance: Continue to care for the patient and family. • Control symptoms that interfere with quality of life. • Find effective ways to cope with stress and to grieve. • Let patient and family concerns direct how and where care is provided.

P = Presence: Be there to talk with the patient and the family. • Visit regularly. • Sit down and hold a hand. • Listen respectfully.

C = Caring: Provide comfort measures. • Honor the individual. • Share touch and laughter.

Life Review: Facilitate life review, important conversations, and the exchange of important words: Thank you • I love you • Please forgive me • I forgive you • Goodbye

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Prognosis, Prognostication, and Hospice

The National Hospice and Palliative Care Organization has published guidelines hospice eligibility for patients with noncancer diagnoses, including HIV (*Hosp J* 1996;11(2):47). These widely used guidelines generally apply to patients who truly are at the end stage of their disease process and are no longer taking ART, although this is not always the case. The current guidelines were developed and published during a different era of HIV treatment, and they should be viewed as guidelines, not as absolute criteria. A brief summary and reference of hospice criteria for the diagnosis of advanced HIV is provided in Table 11-6.

Table 11-6

Guidelines for Determination of Hospice Eligibility

Patient meets the following criteria:

CD4+ cell count <25 cells/mm³

or

persistent viral load >100,000 c/mL (2 or more assays at least 1 month apart)

and

Patient has at least one of the following conditions:

• CNS lymphoma
• Untreated or refractory wasting (loss of >33% lean body mass)
• *Mycobacterium avium* complex bacteremia, untreated, refractory, or treatment refused
• Progressive multifocal leukoencephalopathy
• Systemic lymphoma with advanced HIV and partial chemo response
• Refractory visceral Kaposi's sarcoma
• Renal failure in the absence of dialysis
• Cryptosporidium infection
• Refractory toxoplasmosis
• Palliative Performance Scale of <60% (*J Palliat Care* 1996;12(1):5; *J Pain Symp Manage* 1999;18(1):2)

Supporting documentation:

• Chronic persistent diarrhea >1 y
• Persistent serum albumin <2.5 g/dL
• Concomitant active substance abuse
• Age >50 y
• Absence of ART and prophylactic meds
• Advanced AIDS dementia complex
• Toxoplasmosis
• CHF, Stage IV
• Rapid decline or other comorbidities

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

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Prognostication: Prognostication in patients with HIV is increasingly complex. Patients may present after a long history of inability to adhere to therapy, perhaps as a result of substance abuse or psychiatric comorbities, and with low CD4+ cell counts, high viral loads, and opportunistic infections. These patients often have dramatic responses to initiation of ART. They initially may appear hospice appropriate, but if started on ART, they may improve quickly. Sadly, some patients have sought treatment too late or have difficulty with medication adherence and continue to need hospice services. Others are appropriate for hospice services on the basis of comorbid conditions such as cirrhosis secondary to HCV or malignancy. These patients will have a disease course and life expectancy more consistent with the comorbid condition rather than their HIV disease, despite remaining on ART.

Goals of hospice: In the United States, hospice is an interdisciplinary program that delivers care for patients and families who have elected to live the final portion of their lives in nonhospital settings, such as home, skilled nursing facilities, or designated residential hospices. This choice allows patients to accomplish their personal goals and live life as fully as possible. In hospice, close attention is paid to management of pain and other symptoms and to relief of all suffering, whether physical, psychological, social, or spiritual. As noted earlier, criteria for hospice have been established, and all hospice admissions are certified by two physicians who verify that a patient's life expectancy is likely to be 6 months or less if his or her disease follows its expected course.

No penalty exists for estimating someone's life expectancy incorrectly. For instance, a patient with HIV infection who has a CD4+ cell count of 10/mm³ and recently received induction therapy with amphotericin for cryptococcal meningitis and is unable to adhere to ART would meet diagnostic criteria on the basis of her prognosis if her disease follows its expected course. If she outlives this estimate, the hospice medical director must determine whether the patient's prognosis is still 6 months or less if the disease follows its usual course. For as long as this is the case, the patient may remain in hospice. Therefore, it is reasonable to consider hospice referral for patients hospitalized for opportunistic infections who are not improving on appropriate therapy or who do not wish to continue receiving life-prolonging treatments.

Limitations of hospice: Hospices receive capitated payments from Medicare at a low daily rate. They must pay for all of a patient's care with that money; therefore, a hospice may have limited ability to provide expensive medications, whether or not those medications are considered palliative. These fiscal constraints limit the ability of many hospices to provide ART. The decision to provide expensive medications is made on a case-by-case basis. Medications that are relatively inexpensive and likely to prevent symptoms from occurring, such as maintenance fluconazole therapy, are more likely to be allowed.

It is possible that after receiving intensive symptom control and attention to social, spiritual, and psychological needs, a patient may decide to initiate ART. She may revoke the hospice benefit at any time and resume care under usual insurance coverage. The majority of hospice patients are those with end-stage malignancies. HIV was listed as a primary diagnosis for only 0.5% of all 2008 hospice admissions in the United States (http://www.nhpco.org/files/public/Statistics_Research/Hospice_Facts_Figures_Oct-2010.pdf. Accessed December 28, 2011). The percentage of HIV-infected patients who die while enrolled in hospice is not known. Hospice care was the standard of care for many patients in the early HIV era. Now, it is just one aspect of what is available through palliative and supportive care referral and evaluation. Practitioners of palliative and supportive care may help patients and their families access hospice programs in their communities.

One common question is whether or when to discontinue ART for HIV-infected patients in hospice. ARV medications may cost thousands of dollars per month, and because hospice is paid at a relatively low capitated daily rate,

continuing those medications may be cost prohibitive to enrolling in hospice. Decisions about ART in such circumstances must be made on a case-by-case basis with careful consideration of the medications' added benefit, if any.

Advance Care Planning

HIV practitioners play a particularly important role in facilitating patient and family (or caregiver) dialogues regarding patient wishes and advance care planning. At various points during the course of a disease, opportunities exist for patients to define important aspects of their care. Those decisions should be revisited periodically, especially when circumstances change (e.g., new partner, change in clinical condition). Attention should be paid to cultural or spiritual beliefs that may affect end-of-life decisions.

Key Decisions in Advance Planning

- Surrogate decision makers: Laws regarding default surrogate decision makers vary by State. In general, it is usually preferable for a patient to choose and document a surrogate decision maker who can speak for the patient in the event that the patient lacks the capacity to make decisions.

- Preferences for artificial nutrition and hydration, resuscitation, and life support

- Custody or guardianship of children

- Preferred location of care at the end of life, if appropriate (e.g., home vs. hospital)

- Discontinuation of ART therapy

Ideally, the patient will discuss these issues with her treating provider, who should document the patient's preferences in an easily accessible place in the patient's medical record. It is also important that the patient discuss these issues with her surrogate, who may be in the difficult position of making decisions for the patient when the patient can no longer speak for herself.

Palliative medicine practitioners who are specifically trained to discuss these difficult and complex issues can help HIV providers have these important discussions. In addition, as a patient's illness advances and symptom burden increases, issues involving psychosocial conflict, spiritual distress, and cultural belief systems may become even more prominent and are amenable to palliative care attention.

The journey of many patients with HIV may be associated with loss of traditional family support systems. This loss can lead to complicated grief and caregiver burden, if not addressed. Once again, an interdisciplinary team facilitated by palliative and supportive care practitioners may be beneficial as a patient's clinical condition worsens. One additional advantage of hospice care in the terminal phases of HIV illness is that hospice is required to provide follow-up bereavement care for the primary caregivers for 1 year following the death of a patient enrolled in hospice.

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Grief and Bereavement

Grief is a normal reaction to a major loss. Its manifestations vary but may include physical, cognitive, behavioral, and emotional elements, such as a feeling of numbness, loss and longing, restlessness, frequent crying, difficulty sleeping, loss of appetite, and somatic complaints. The expected duration of grief is 1 to 2 years, after which most people return to their previous level of functioning. Risk factors for complicated grief—grief of longer duration or greater intensity than expected—include protracted illness; difficult terminal symptoms; death from a stigmatizing disease; death of a spouse, child, or other close relative; lack of social or financial support; and the bereaved person's own history of psychiatric or substance abuse (*Textbook of Palliative Medicine*, 2006). All of these factors are highly prevalent in patients with HIV. Many patients may also suffer from anticipatory grief as their condition worsens, and some have a variant of a grief response to loss at the time of their diagnosis (i.e., in sensing the loss of good health).

Physicians caring for patients with HIV need to be available to patients' family and friends during the bereavement process. Health care providers can use five principles of bereavement support to care for patients and families during this difficult time:

- View patient and family as one unit of care.
- Enable open discussion of illness and death-related concerns.
- Provide emotional support.
- Facilitate practical assistance.
- Respect cultural, ethnic, and religious practices.

Caring for the Caregiver

Caregiver burden is the "physical, emotional, and financial toll of being a caregiver" (*Gerontologist* 1986;26:253, *Am Fam Physician* 2000;62:2613). Caregiver burden has most often been studied in spouses of patients with dementia; results indicate high rates of depression, worsening physical health, and increased mortality (*Am Fam Physician* 2000;62:2613). People caring for patients with HIV may have HIV themselves; therefore, it is important to recognize a patient's caregiver(s) and assess for lack of social support and signs of caregiver burden, including stress, depression, and isolation (*Gerontologist* 1980;20;649).

Incorporating Principles of Palliative Care Into Everyday Practice

The HIV care provider's role is often that of a general internist for patients with HIV. To provide excellent primary care for this patient population, it is important to screen for common conditions. Providers routinely perform Pap smears; recommend mammography and colonoscopies; and screen for hyperlipidemia, syphilis, and many other conditions. Primary providers should also routinely screen for pain and symptoms, because these are just as common as other conditions, and are important to patients' quality of life.

Providers should screen patients for pain and symptoms at every visit. This task can be done quickly, as outlined earlier. Management of pain and other symptoms can be handled by the HIV care provider, and if necessary, patients may be referred to a palliative care or pain specialist. In caring for patients and their caregivers, the primary HIV care provider and interdisciplinary team can incorporate purposeful dialogue with patients regarding advance care planning and preferences if they experience disease progression.

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Chapter 12:

Occupational Exposure and Postexposure Management

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Chapter 12: Occupational Exposure and Postexposure Management

Chapter 12 at a Glance

HIV, HBV, and HCV Exposures Are Common

Exposures to HIV and hepatitis B and C (HBV and HCV) are common among healthcare workers, approximately 70% of whom are women (U.S. Bureau of Labor Statistics, 2007; Report 1002:30). Although universal precautions, safety devices, and other factors have reduced occupational exposures to bloodborne pathogens (BBPs), exposures continue to be a persistent problem in healthcare settings, and only a fraction of them are formally reported (National Institute for Occupational Safety and Health Pub. No. 2000-135). Safety measures, along with widely practiced HBV immunization and postexposure prophylaxis (PEP) for both HIV and HBV, have decreased the incidence of BBP transmission to healthcare workers over the past decade.

This chapter is designed to help the managing clinician decide whether PEP should be administered and to provide guidance for postexposure management.

Postexposure Management Should Not Be Delayed

Because HIV PEP efficacy depends on the timing of the first administered dose of antiretroviral (ARV) drugs, postexposure management is urgent and should not be delayed. The need for PEP is determined by assessing the risk and severity of the exposure and the source patient's risk for HIV or hepatitis infection. Although time to initiation is critical to PEP efficacy, it is equally important to determine when PEP is not warranted.

If Consultation Is Needed

PEPline: Consultation is available 24 hours per day from the National HIV/AIDS Clinicians' Consultations Center's Post-Exposure Prophylaxis Hotline (PEPline): 888-448-4911. PEPline provides expert guidance in managing healthcare worker exposures to HIV, HBV, and HCV. Callers receive immediate PEP recommendations.

Reporting

No nationwide central service exists for reporting healthcare worker exposures. All healthcare facilities must comply with Occupational Safety and Health Administration guidance in developing institutional policies for postexposure protocols, including institution-based reporting systems, systemwide prevention initiatives to minimize occurrence of work-related exposures, and incorporation of PEP into institutional occupational healthcare programs.

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Universal Precautions to Prevent Exposure

The phrase "universal precautions" is used to indicate that all patients should be considered potentially infectious and that safety measures should be applied universally, regardless of known risk factors, to prevent exposure to HIV, HBV, and other BBPs. Protective equipment and practices are used in the healthcare setting to protect healthcare workers and patients:

- **Gloves** are recommended for use in all procedures in which contact with infectious body fluid is likely (e.g., pelvic exam, phlebotomy, transfer of body fluid samples to a specimen cup).

- **Masks** are recommended for use when there is risk of blood or other infectious body fluid splash (e.g., during incision and drainage, insertion of chest tube, intubation, surgery).

- **Goggles or other eye protection** is recommended for use when there is risk of blood or other infectious body fluid splash.

- **Gowns** should be worn during surgery or with other procedures where there is significant risk of blood or other infectious body fluid splash or contamination of clothing.

- **Puncture-proof containers** should be available to dispose of used needles, scalpels, and other disposable sharp supplies. Needle and scalpel safety devices are also available in many higher resource settings.

- **Operating room and emergency department precautions:** Avoid direct hand-to-hand transfer of sharp instruments in the operating room and emergency department; instead, pass sharps from hand to pan or emesis basin to allow for greater control in handling.

The need for safety precautions should be made on the basis of the risk of the medical procedure being performed. Gloves and other precautions are not needed when contact with infectious body fluid is unlikely, as when shaking hands with a patient or performing a routine examination.

Exposure and Transmission

Transmission Risks

For BBP transmission to occur, an exposure must involve infectious body fluid from a source infected with a BBP, and it must involve a mechanism by which BBPs can be transmitted. If both factors are not present, then no risk of transmission exists and no further evaluation is required.

Figure 12-1
Body Fluids and BBP Transmission Risk

Body fluids that CAN transmit BBPs:

☑	Blood	☑	Cerebrospinal fluid
☑	Semen	☑	Pericardial fluid
☑	Vaginal fluids	☑	Peritoneal fluid
☑	Amniotic fluid	☑	Pleural fluid
☑	Breast milk	☑	Synovial fluid

Body fluids that DO NOT transmit BBPs (unless visibly bloody):

☒	Saliva	☒	Urine
☒	Vomitus	☒	Feces

Decreasing transmission: If an exposure occurs despite universal precautions, several steps can be taken immediately to decrease transmission risk:

- **Mucous membrane exposure:** Rinse area thoroughly with water or saline.

- **Skin exposure:** Wash thoroughly with soap and water.

- **Needlestick:** Wash area thoroughly with soap and water. Do not squeeze or pinch, because doing so may increase blood flow to the area and hypothetically facilitate transmission.

Risk and mechanism of exposure: Percutaneous exposures are of substantially higher risk for transmitting BBP than mucous membrane or cutaneous exposures. The risk associated with each mechanism of exposure is outlined in Table 12-1.

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Table 12-1

Associated Risk When Exposure Source Patient Is HIV Infected

Route of Exposure	Risk of Exposure	Risk Determinants	Risk Qualifiers
Percutaneous*	~ 1/300 episodes	↑ Larger gauge hollow-bore needle ↓ Solid needle or instrument	• Risk of transmission from percutaneous exposures is increased with hollow-bore needles, visibly bloody devices, and deep injury. • Solid devices, such as lancets or suture needles, have rarely been involved in HIV transmission. • It is common for a discarded or found needle to cause percutaneous injury; however, in U.S. healthcare settings, found needles have been implicated in only 3 cases of transmission. Outside of the United States, no documented cases of transmission of HIV from a found needle have occurred.
Mucous† membrane	~1/1000 episodes	↑ Large volume ↓ Small volume	• Mucous membrane exposures usually involve infectious fluid contact with the eyes or mouth. The keratinized skin around the mouth that borders on mucous membrane is an effective protective barrier.
Cutaneous†	<1/1000 episodes	Compromised skin integrity	• Cutaneous exposures can transmit virus, but risk is present only when skin integrity is compromised (e.g., chapping, abrasion, open wound or burn, dermatitis). Prolonged contact with nonintact skin may increase risk of transmission. • Intact skin is an effective barrier that protects against transmission of BBPs.

Note: ↑ = increased risk; ↓ = decreased risk. Other abbreviations are defined in the list of Abbreviations and Acronyms, p. ix.

  * A substantial proportion of percutaneous exposures occur in dental offices; however, no transmissions from patient to provider have been reported in the dental setting. The lack of transmission is likely a result of the nature of dental instruments, most of which are solid, and the use of very small-bore needles for anesthetic injection. It is also plausible that neutralizing antibodies present in saliva may decrease chances of virus transmission.

  † Human bites expose both the biter (cutaneous exposure) and the bitten (mucous membrane exposure).

Source: *MMWR Recomm Rep* 2005;54(RR-9):1

Postexposure Assessment and Management

Baseline Laboratory Workup

If the exposure is considered one that may transmit BBP, then baseline testing for HIV, HBV, and HCV should be performed on the exposed healthcare worker and the source, when possible. Recommended tests are summarized in Table 12-2.

PEP efficacy depends upon timing of first dose: Do not wait for baseline test results to proceed with the decision to administer PEP, unless the results of the source patient's rapid HIV will be available within 1–2 hours. If the source patient's baseline rapid HIV Ab test is positive, then assume it represents a true positive result, and proceed with PEP while awaiting confirmatory Western blot results. If the confirmatory Western blot test is negative, then PEP can be stopped.

Table 12-2

Recommended Postexposure Baseline Laboratory Tests

Baseline Tests	Source Patient	Exposed Person
HIV Ab or p24 antigen-HIV antibody (HIV Ag/Ab)	Yes	Yes
HIV Western blot or immunofluorescence antibody	Yes, if HIV rapid test positive	Yes, if HIV rapid test positive
HIV RNA PCR	Yes, if status is known to be positive, but recent viral load is not known	No
HCV Ab	Yes	Yes
HCV RNA PCR*	Yes	No
HBsAg	Yes	Yes, if immune status is unclear
HBsAb	No	Yes, if immune status is unclear

Note: Test abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

* With CD4+ cell count <200 cells/mm^3, a negative HCV Ab test may represent a false negative result, and HCV RNA can clarify HCV status of exposure source.

Source: *MMWR Recomm Rep* 2001;50(RR-11):1

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Window Period

The window period for HIV Ab seroconversion—after infection has occurred but before antibodies develop—can cause anxiety for both the patient and the provider around postexposure management. However, if the source patient's HIV test is negative at the time of the exposure, then PEP is not

recommended. Note that in the United States, no reports of HIV transmission to a healthcare worker from an exposure source who was in the window period have occurred (*MMWR* 2005;54(RR-9)).

Implications for postexposure management: The window period should be taken into consideration in postexposure management only when it is highly likely that a high-risk source patient is in a window period. This situation may occur when, in the 30 days prior to the exposure, the source patient shared needles with other drug users, was incarcerated, engaged in unprotected sex with multiple male partners (if male), could have been exposed through sex work (*MMWR* 2006;55:421), or had a potential exposure in a country with high HIV seroprevalence.

In assessing the likelihood of a source patient being in the window period, determine whether the patient has a history of recent illness consistent with possible acute HIV infection (see Chapter 4, *Primary Medical Care*). If acute HIV infection is suspected, then PEP should be started while confirmation of the source's HIV RNA level is pending. In acute infection, HIV RNA level is usually very high and risk of transmission is great.

U.S. Public Health Service Guidelines for PEP

Time is of the essence in initiating PEP: If PEP is indicated or is being considered, then time is of the essence for efficacy: The optimal time to start PEP is within hours of exposure, not days. The first dose should be given as soon as possible. Seventy-two hours post-exposure is considered as the outer limit of opportunity to initiate PEP; however, a delay of that scale is believed to compromise PEP efficacy. The 72-hour outside limit recommendation is based on animal studies; no human data are available. Initiating PEP after a longer interval (e.g., 1 week) might still be considered for exposures that represent a very high risk of transmission. PEP should be administered for 4 weeks.

Regimen: The USPHS no longer recommends that the severity of exposure be used to determine the number of drugs to be offered in a PEP regimen. A regimen containing 3 (or more) ARV drugs is now recommended routinely for all occupational exposures to HIV. These include newer ARV drugs that are better tolerated and have better toxicity profiles than agents previously recommended for PEP. Medications included in a PEP regimen should be selected to minimize side effects and toxicity, and optimize convenience in terms of dosing schedules to enhance likelihood of completion. Exposure to a source patient with an undetectable serum viral load does not eliminate the possibility of HIV transmission, and PEP should still be offered. Because of concerns about tenofovir effect on renal function, this regimen is not recommended to persons with renal problems, which should be assessed before prescribing this PEP regimen. The PEPline at 888-448-4911 is available for additional advice and recommendations.

Table 12-3

Recommendations for Postexposure Prophylaxis After Precutaneous Injury or Mucous Membrane and Nonintact** Skin Exposures

Exposure Source	Recommendation
HIV-infected	Three (or more) drug PEP
Unknown HIV status	Generally no PEP is warranted. Consider PEP* for source with HIV risk factors; discontinue if source is found to be HIV-uninfected.
Unknown source (e.g., a needle from a sharps disposal container; splash from improperly disposed-of blood)	Generally no PEP is warranted. Consider PEP* in settings where exposure to HIV-infected persons is likely.
Not HIV infected	No PEP is warranted.

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix.

*"Consider PEP" indicates that PEP is optional and the decision to administer should be made case by case, on the basis of an individualized discussion between the provider and the exposed person. Higher risk source patients include injection drug users who have shared needles, sex workers, men who have unprotected sex with multiple male partners, and people who have been incarcerated.

*Followup is indicated only if there is evidence of compromised skin integrity (e.g., dermatitis, abrasion, open wound).

Source: *Infect Control Hosp Epidemiol* 2013;34(9):875–892

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PEP regimens: Current options for PEP, along with recommended toxicity monitoring, are listed in Table 12-4.

Table 12-4

Human Immunodeficiency Virus (HIV) Postexposure Prophylaxis (PEP) Regimens (all given for one month)

Preferred HIV PEP Regimen

RAL 400 mg PO twice daily
Plus
TDF/FTC 300/200 mg (Truvada) once daily

Alternative Regimens
(May combine 1 drug or drug pair from the left column with 1 pair of nucleoside/ nucleotide reverse-transcriptase inhibitors from the right column)

RAL	TDF/FTC
DRV/r	TDF + 3TC
ETR	ZDV/3TC
RPV	ZDV + FTC
ATV/r	
LPV/r	

The following alternative is a complete fixed-dose combination regimen, and no additional antiretrovirals are needed: EVG/COBI/TDF/FTC

Alternative Antiretroviral Agents for Use as PEP Only with Expert Consultation
ABC
EFV
T20
FPV
MVC
SQV
d4T

Antiretroviral Agents Generally Not Recommended for Use as PEP
ddI
NFV
TPV

Antiretroviral Agents Contraindicated as PEP
NVP

Note: Laboratory monitoring for drug toxicity should occur at baseline and 2 weeks after starting PEP and should minimally include CBC, renal and hepatic tests.

Source: Updated US Public Health Service Guidelines for the Management of Occupational Exposures to Human Immunodeficiency Virus and Recommendations for Postexposure Prophylaxis. *Infect Control Hosp Epidemiol* 2013;34(9):875.

Resistances

Important factors that should increase suspicion of resistance include (1) history of problems with medication adherence, (2) failure to achieve undetectable viral load on ARV medications, (3) development of detectable viral load after previously undetectable levels while on ARV medications, and (4) previous genotypic or phenotypic test results demonstrating resistance to one or more ARV drugs. If resistance is suspected, consultation with an HIV expert is recommended, but this should not delay initiation of PEP. In instances of known or suspected exposure use of ARV agents to which the patient is unlikely to be resistant is recommended for PEP.

Drug–Drug Interactions

Interactions between drugs in the PEP regimen and the exposed person's current medications may be a problem, and expert consultation may be indicated, especially when an expanded regimen is chosen. Most commonly, interactions involve the protease inhibitor component, such as LPV/r, DRV/r, and ATV/r. Table 12-5 lists several common drug–drug interactions. See also Tables 13-8 to 13-9, pp. 500–512.

Table 12-5

Commonly Prescribed Drugs and Interactions With Concurrent Use of Protease Inhibitors

Medication	Effects of Concurrent Use With PIs	Options and Recommendations
Acid reducers		
Antacids	ATV levels ↓	Use another PI or d/c antacids.
H$_2$ blocker(s)	ATV levels ↓	Use another PI if continuing H$_2$ blocker treatment or d/c H$_2$ blocker; may also space dosing of H$_2$ blocker 12 h apart from PEP administration.
PPIs	ATV levels ↓	Use another PI if continuing PPI treatment or d/c PPIs.
Anticoagulants		
Warfarin	Warfarin levels ↓	Monitor INR closely.
Anticonvulsants		
	Antiseizure medication levels may be altered to supra- or subtherapeutic levels	Use RAL as alternative to PIs.
Antidepressants		
SSRIs	SSRI levels ↓	Titrate dose to clinical efficacy if needed.
Tricyclic antidepressants	Tricyclic levels ↑	Toxicity monitoring is advised.

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Table 12-5	*continued*

Commonly Prescribed Drugs and Interactions With Concurrent Use of Protease Inhibitors

Medication	Effects of Concurrent Use With PIs	Options and Recommendations
Antipsychotics		
	Antipsychotics ↓ to subtherapeutic levels	Titrate dose as needed; use RAL as alternative to PIs.
Antimycobacterials		
Rifabutin	RBT levels ↑	Adjust RBT dose; consult expert.
Rifamycin	PI ↓ to subtherapeutic levels	Contraindicated with all PIs; use RAL as alternative to PIs.
Benzodiazepines		
	Midazolam and triazolam levels ↑	Contraindicated with PIs; use RAL as alternative to PIs.
Cardiac medications		
Calcium channel blockers	Calcium channel blocker levels ↑	Use RAL as alternative to PIs.
Corticosteroid		
Fluticasone	Fluticasone levels ↑	Contraindicated with PIs; use RAL as alternative to PIs.
Herbal remedy		
St. John's wort	↓ PI to subtherapeutic levels.	Contraindicated with PIs.*
Hormonal contraceptives		
Combined oral contraceptives	Ethinyl estradiol and progestin levels ↓ with certain PIs	Use backup barrier method.
Lipid-lowering drugs		
Statins	Statin levels ↑	Lovastatin and simvastatin are contraindicated; caution is advised with other statins. Consider time-limited d/c of statins for duration of PEP; use RAL as alternative to PIs.
Narcotics/Treatment for opioid dependence		
Methadone	Methadone levels ↓	Monitor for opiate withdrawal; titrate methadone dose if necessary.

Note: ↑ = increase; ↓ = decrease. Other abbreviations are defined in the list of Abbreviations and Acronyms, p. ix.

Adverse Drug Reactions and Symptom Management

Potential for PEP interference: Side effects can be a limiting factor in PEP adherence. They generally decrease after the first few days but sometimes can last the duration of the 28-day PEP course. Gastrointestinal side effects (nausea, vomiting, diarrhea) are most common, especially with expanded regimens that include a PI. Zidovudine/lamivudine (Combivir) can cause headache, fatigue, and nausea. Tenofovir/emtricitabine (Truvada) is much better tolerated than Combivir and is given as once daily dosing. Antiemetic and antidiarrheal medications can be prescribed to help with PEP adherence. If side effects are severe, consider changing to a better tolerated regimen. With the current preferred PEP regimens, toxicities are rare, generally not life threatening, and reversible.

Pregnancy

Not a contraindication for PEP: Indications for PEP are the same for pregnant and nonpregnant women. Acute HIV infection during pregnancy carries a particularly high risk for perinatal transmission because of high viral loads in early infection. When deciding whether to administer PEP and choosing the specific drug regimen, the risk of ARV exposure to the fetus and the potential adverse effects for the pregnant woman should be weighed against the benefit of decreased risk of HIV transmission to the mother and the fetus.

PEP regimens for pregnant women: Information about the use of newer antiretroviral agents administered as PEP to HIV-uninfected pregnant women is limited. Expert consultation is recommended. EFV is not recommended as part of a PEP regimen in the first trimester. If EFV-based PEP is used in women, a pregnancy test should be done to rule out early pregnancy and nonpregnant women receiving EFV-based PEP should be counseled to avoid pregnancy until after PEP is completed.

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Breastfeeding

Weigh risks and benefits: Both HIV itself and ARV medications can be found in breast milk. Some guidelines recommend that breastfeeding be avoided for 6 months postexposure. This recommendation is to prevent infant exposure to HIV should transmission occur and to avoid potential PEP drug toxicities in the infant. However, because breastfeeding offers significant benefits and because HIV is rarely transmitted to an exposed person (particularly when PEP is administered), the PEPline advises that mothers be informed of the potential risks and make their own decisions regarding breastfeeding. Because most transmissions are diagnosed by 6 weeks postexposure and almost all are detected by 3 months, a reasonable choice for some women may be to pump and discard breast milk initially and then reinitiate breastfeeding when they have reached a point at which no transmission can be safely assumed.

Follow-Up Postexposure Laboratory Monitoring

Following an exposure, laboratory followup is recommended for up to 6 months. If HCV transmission has occurred or if the exposed person is already HCV positive, followup is extended to 12 months, because rare instances of HIV transmission have not been captured until then [*MMWR* 2005;54(No. RR-9)].

Recommended postexposure laboratory monitoring includes the following:

- **6 weeks:** HIV Ab; HCV RNA PCR
- **3 months:** HIV Ab; HCV Ab
- **6 months:** HIV Ab; HCV Ab
- **12 months:** HIV Ab when concurrent HCV infection is present in the exposed person

Use of 4th generation HIV Ag/Ab combination tests allows for earlier detection of HIV infection. If these tests are used, HIV follow-up testing may be concluded 4 mo after exposure.

HIV RNA PCR is not recommended for follow-up testing unless the exposed person presents within 4 to 6 weeks postexposure with symptoms consistent with acute HIV infection, because false positives (usually at low levels of virus, i.e., <10,000 copies/mL) occur and can cause diagnostic dilemmas and unnecessary anxiety.

Hepatitis B and C Postexposure Management

Hepatitis B

Although widely utilized HIV PEP has been effective in decreasing HIV transmission to healthcare workers, the decrease in HBV transmission is attributed primarily to immunization of healthcare workers. Among nonimmunized healthcare workers, HBV confers a significant risk of transmission—as many as 2–3 infections per 5 needlestick exposures from HBV-infected individuals. As a result, HBV vaccination and documentation of immunity for healthcare workers has become a pre-employment requirement in most U.S healthcare settings. Immunization has helped to decrease transmission rates substantially and has virtually eliminated the need for HBV follow-up testing. However, some healthcare workers may not have received the full vaccination series or may not have responded adequately to vaccination.

Guidelines for HBV PEP: When a healthcare worker does not have documentation of adequate immunity (evidenced by HBsAb titer of >10 mIU/mL at any point in the past), specific guidelines for HBV PEP and follow-up, specified in Table 12-6, should be followed.

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Table 12-6

Recommendations for Postexposure Prophylaxis After Exposure to HBV

Source Status	Unvaccinated Exposed Person	Previously Vaccinated Exposed Person*		
		Known Responder†	Known Nonresponder‡	Antibody Response Not Known
HBsAg positive	HBIG† x 1 and initiate HBV vaccine series immediately	No treatment	HBIG† x 1 and initiate revaccination or HBIG x 2 with second dose separated from first by 4 wk‖	Test exposed person for HBsAb; if response is adequate,‡ no treatment is necessary. If response is inadequate,§ administer HBIG† x 1 and vaccine booster; recheck HBsAb titer in 3–4 mo. If titer is still inadequate§ for immunity, complete full second series of vaccinations.
HBsAg negative	Initiate HBV vaccine series	No treatment	No treatment	No treatment
Unknown or not available for testing	Initiate HBV vaccine series. If known high-risk source, may treat as if source were HBsAg positive.	No treatment	If known high-risk source, treat as if source were HBsAg positive.	Test exposed person for HBsAb; if response is adequate,‡ no treatment is necessary. If response is inadequate,§ administer vaccine booster and recheck HBsAb titer in 1–2 mo. If titer is still inadequate§ for immunity, complete full second series of vaccinations.

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

* People who have previously been infected with HBV are not at risk of reinfection and do not require PEP.

† HBIG (dose = 0.06 mL/kg intramuscularly).

‡ Responder = documented adequate levels of HBsAb (≥10 mIU/mL).

§ Nonresponder = inadequate levels of HBsAb (<10 mIU/mL).

‖ The option of giving 1 dose of HBIG and reinitiating the vaccine series is preferred for nonresponders who have not completed a second 3-dose vaccine series. Two doses of HBIG are preferred for people who have completed a second vaccine series but have failed to respond.

Source: *MMWR Recomm Rep* 2001;50(RR-11):1

Hepatitis C

Postexposure management: When a source patient is HCV infected, the risk of transmission following needlestick exposure is about 1 in 50. No PEP is available for HCV exposure, but early follow-up to identify transmitted infection and, when indicated, to offer early treatment is recommended. Direct viral testing with HCV RNA PCR at 6 weeks, before HCV Ab seroconversion has occurred, allows early identification of transmission and subsequent referral for evaluation and potential treatment. The rate of spontaneous clearance of HCV infection is about 25% in otherwise healthy people; however, with early diagnosis and treatment, HCV clearance can be increased to 90% or greater.

HIV Infected Healthcare Providers

No national standards limit clinical practice for HIV infected healthcare providers. The 1991 guidance (published before availability of effective combination ART) on prevention of HIV and HBV to patients during exposure-prone invasive procedures states that infected healthcare workers "should not perform exposure-prone procedures unless they have sought counsel from an expert panel and notify prospective patients of healthcare worker's seropositivity prior to undergoing an exposure-prone procedure" (*MMWR* 1991;40(RR-8)). However, States vary in implementation of this guidance (*JAMA* 2000;284:1965). Mandatory testing of healthcare workers is not recommended. Other organizations have published safe practice guidance for healthcare professionals who are involved in invasive procedures (*CID* 2005;40:1665), but no universally accepted guidelines exist for specific limitations.

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Chapter 13:

Pharmacologic Considerations in HIV Infected Pregnant Patients

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Chapter 13: Pharmacologic Considerations in HIV Infected Pregnant Patients

Chapter 13 at a Glance

Introduction

Information included in this chapter may include off-label recommendations for specific drugs or indications.

The information presented in this chapter includes detailed information about pharmacologic agents commonly used in the treatment of HIV infected women and drugs often used in pregnancy or as complementary therapies, with particular emphasis on issues related to their use in pregnancy.

Risk versus benefit: The decision to administer drugs to a pregnant woman depends on the potential therapeutic benefit versus the potential risk to the mother and/or the developing fetus. Clinicians are often advised to avoid prescribing drugs for pregnant patients because human safety data in pregnancy are lacking for many, if not most, medications; however, effective treatment for HIV, opportunistic infections, and other serious medical conditions should not be withheld in pregnancy. There are important considerations when selecting agents to treat women with HIV to prevent mother-to-child transmission and to prevent or treat opportunistic infections or other related or coexisting conditions. In general, when more than one effective treatment is available, the regimen with the best evidence for safety in pregnancy should be chosen. When animal studies suggest teratogenic or embryotoxic risk and human studies are lacking or also of concern, expert consultation is recommended.

Caveats: The literature on drug safety in pregnancy should be interpreted with caution and with the following caveats: animal studies (including studies of mutagenicity, carcinogenicity, and teratogenicity), which are the basis for most data on safety in pregnancy, are often inconsistent across species and may not accurately reflect risk in human pregnancy. For example, animals are often administered doses 5 to 20 times higher than those given to humans and the clinical applicability of such dosing to human treatment may not be clear. In humans, drug dose, intensity of exposure, placental transfer, and gestational age at exposure may all affect the presence or magnitude of risk. Teratogenic potential does not reflect the expected frequency of malformations; adequately controlled human studies are necessary to establish the degree of risk. A drug with teratogenic potential may be appropriate for use when there are no safer alternatives and when the benefits are expected to outweigh the risk.

It is now standard practice to treat HIV infected patients with a combination of antiretroviral (ARV) agents, which makes it difficult to assess the safety of a single agent, and information about the safety of newer ARVs in pregnancy is limited; additional prospective clinical data are needed. Clinicians are encouraged to report all in utero exposures to the Antiretroviral Pregnancy Registry (800-258-4263; fax: 800-800-1052; http://www.apregistry.com/). The registry is a collaborative effort of pharmaceutical manufacturers with an advisory committee of obstetric and pediatric practitioners; the group collects observational data on ARV exposure during pregnancy to assess the potential teratogenicity of these drugs.

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Pharmacokinetics of Drugs in Pregnancy

Although many physiologic changes occur during pregnancy, few trials have been conducted to evaluate the clinical significance of these changes to the pharmacokinetics of commonly used drugs. Physiologic changes that may affect drug pharmacokinetics include delayed gastric emptying, decreased intestinal motility, increased volume of distribution (average increase, 8 L), increased renal blood flow (25%–50%), and increased glomerular filtration rate (by 50%) (*Fundamentals of Gynecology and Obstetrics*, Philadelphia: J.B. Lippincott Co; 1992; *J Obstet Gynaecol* 1974;81:588; *J Obstet Gynaecol Br Commonw* 1970;77:900).

Pharmacokinetic parameters of NVP given as a single dose of 200 mg at the onset of labor were similar to but more variable than those in nonpregnant adults, possibly because of incomplete absorption associated with altered gastrointestinal function during labor (*J Infect Dis* 1998;178:368). Data suggest that NVP levels may be detectable as long as 3 weeks after a single dose given at onset of labor (11th Conference on Retroviruses and Opportunistic Infections, February 8, 2004 [abstract 41LB]). Pregnancy does not change the pharmacokinetics of ABC, ZDV, 3TC, d4T, or ddI (*J Infect Dis* 1998;1778:1327; 6th International Conference on AIDS, June 20, 1990 [abstract FB17]; *J Infect Dis* 1999;180:1536). On the other hand, FTC serum concentrations are slightly lower in the third trimester. Similarly, third-trimester TDF concentrations are lower, but trough concentrations are adequate. The clinical significance of these findings remains to be determined (see Table 8-7, pp. 285–298).

Serum concentrations of the protease inhibitors (PIs) that have been studied in pregnancy (ATV, IDV, RTV, and SQV) appear to be lower in pregnancy when the agents are given as single, unboosted PIs (*Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*; http://www.aidsinfo.nih.gov. Accessed 8/6/12). When boosted with RTV, SQV levels are adequate (*HIV Clin Trials* 2001;2:460), and adequate NFV levels are achieved when it is given at a dose of 1250 mg bid; in the third trimester, however, concentrations were lower and more variable (9th Conference on Retroviruses and Opportunistic Infections, February 2002 [abstract 795w]). When the old formulation of LPV/r capsules was administered to pregnant patients, LPV serum concentrations were lower during the third trimester. A pharmacokinetic study with the new LPV/r tablets is ongoing. Some experts recommend increasing the LPV/r dose to three tablets twice per day to compensate for the decreased LPV concentrations during the third trimester; other experts, however, recommend using the standard dose with close monitoring (*Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States*). In patients with PI mutations, a higher dose (e.g., three LPV/r tablets twice per day) should be considered in the third trimester. Use of newer ARVs (e.g., RAL, MVC, DRV, TPV, ETR) or older ARVs with limited clinical data in pregnancy (e.g., ENF, FPV) should be reserved for cases in which the benefit outweighs the risk to the pregnant woman and/or when better-studied agents are not options because of concerns for safety, tolerability, or effectiveness.

Sex-Based Differences in Response to HIV Treatment

Clinical response: There are conflicting data on sex differences in clinical response to ARV treatment. Several studies have documented sex differences in CD4+ lymphocyte counts and HIV viral loads (VLs), indicating that women have higher CD4+ cell counts and lower HIV RNA levels early in the course of infection; however, differences in VL tend to dissipate several years after initial infection and rates of progression are similar in men and women (*J Infect Dis* 1999;180:666; *N Engl J Med* 2001;344:720; *Clin Infect Dis* 2002;35:315). Early studies suggested poorer outcomes for women, but when controlled for later presentation and lower rates of care and/or treatment with effective antiretroviral therapy (ART), these sex-based differences in HIV disease course generally disappeared (*J Acquir Immune Defic Syndr* 2000;24:475; *AIDS* 2001;15:1115). Several studies have shown sex differences in ART prescription and utilization, even with free access to ART and CD4+ cell counts <200 cells/mm^3 at baseline (*J Acquir Immune Defic Syndr* 2000;24:475; *Women's Health Issues* 2006;16:104; *J Acquir Immune Defic Syndr* 2003;32:499; *J Acquir Immune Defic Syndr* 2005;38:96; *South Med J* 2007;100:775). A recent retrospective cohort study with 6,657 person-years follow-up found that women had an increased risk of death, even after adjustment for HAART use (hazard ratio, 1.62; p = .002) (*J Infect Dis* 2009;199:991); however, other large cohort studies found comparable or lower rates of clinical progression and death in women compared with men (*J Women's Health* 2007;16:1052; *AIDS* 2007;21:835; *HIV Med* 2006;7:520). Virologic and clinical responses in clinical trials are comparable between men and women, although most trials have not been powered to detect gender differences. A recent open-label Phase 3b study specifically designed to enroll a high proportion of women examined treatment responses to DRV-RTV plus an investigator-selected optimized background regimen and found no significant difference in virologic response by sex, although women were more likely to discontinue therapy for reasons other than virologic failure (*Ann Intern Med* 2010;153:349).

Adverse drug events: A number of studies have shown a higher incidence, greater severity, or altered presentation of adverse drug events in women compared with men (*Expert Rev Anti Infect Ther* 2005;3:213). Women with higher CD4+ cell counts appear to be at the greatest risk for symptomatic, potentially fatal, and often rash-associated liver toxicity associated with NVP (*J Acquir Immune Defic Syndr* 2004;35:538; *Clin Infect Dis* 2004;38 Suppl 2:S80). Lactic acidosis related to prolonged exposure to nucleoside reverse transcriptase inhibitors appears to occur more frequently in women (*AIDS* 2007;21:2455). Women also may be at greater risk for some metabolic complications of ART, such as central fat deposition, and they appear less likely to have triglyceride elevations (*HIV Med* 2001;2:84; *J Acquir Immune Defic Syndr* 2003;34:58). Women are at greater risk of osteopenia and/or osteoporosis, especially after menopause, and this may be worsened in the setting of HIV and ART (*AIDS* 2006;20:2165). Although data are limited, women may metabolize and respond to specific ARV drugs differently from men, which may result in higher drug concentrations and a greater likelihood of adverse effects (*Annu Rev Pharmacol Toxicol* 2004;44:499; *Pharmacol Res* 2008;58:173; *Gend Med* 2007;4:106). Therefore, close monitoring for adverse drug events is recommended when initiating ARV therapy in women. It is also

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important that clinicians recognize barriers to initiating and continuing ARV therapy in women because competing priorities, such as child and family care and issues related to stigma and disclosure, can interfere with ART adherence.

Table 13-1

U. S. Food and Drug Administration Categories for the Use of Prescription Drugs in Pregnancy

A	Adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of risk during later trimesters)
B	Animal reproduction studies fail to demonstrate a risk to the fetus and adequate and well-controlled studies of pregnant women have not been conducted
C	Safety in human pregnancy has not been determined, animal studies are either positive for fetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the fetus
D	Positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks
X	Studies in animals or reports of adverse reactions have indicated that the risk associated with the use of the drug for pregnant women clearly outweighs any possible benefit

Note: At the time of publication of this guide, the FDA was preparing a revision of drug categories for pregnancy and lactation that will likely do away with the current letter categories

Table 13-2

Pregnancy Categories for Antiretroviral Agents in ARV-Naïve Women

Preferred	Drugs or drug combinations are designated as preferred for use in pregnant women when clinical trial data in adults have demonstrated optimal efficacy and durability with acceptable toxicity and ease of use; pregnancy-specific pharmacokinetic data are available to guide dosing; and no evidence of teratogenic effects on the fetus or established association with teratogenic or clinically significant adverse outcomes for the mother, fetus, or newborn are present
Alternative	Drugs or drug combinations are designated as alternatives for initial therapy in pregnant women when clinical trial data in adults show efficacy but any one or more of the following conditions apply: there is limited experience in pregnancy; there is a lack of data on teratogenic effects on the fetus; or there are dosing, formulation, administration, or interaction issues for that drug or regimen
Not Recommended	Drugs and drug combinations listed in this category are not recommended for therapy in pregnant women because of inferior virologic response, potentially serious safety concerns for the mother or fetus, or pharmacologic antagonism. In addition, some drugs are listed in this category because they are not currently recommended in ARV-naïve adults and adolescents due to limited data. These agents may eventually move to a different category as more data becomes available.
Insufficient Data to Recommend	Although approved for use in adults, the drugs and drug combinations in this category do not have pregnancy-specific pharmacokinetic or safety data available or such data are too limited to make a recommendation for use for pregnancy

Source: *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. 2013*

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Note: At the time of publication of this guide, the FDA was preparing a revision of drug categories for pregnancy and lactation that will likely do away with the current letter categories

Table 13-3

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Acyclovir (Zovirax®) **FDA pregnancy category: B**	• 5–10 mg/kg IV q 8 h • 200–800 mg po 3–5x qd	• Toxicities are infrequent • GI intolerance: nausea, vomiting, diarrhea • Renal toxicity, esp. with rapid IV infusion • Dizziness • Transaminase elevation • Pruritus • Headache	Not teratogenic, but has potential to cause chromosomal damage at high doses Antiviral drug with the most reported experience in pregnancy; appears to be safe—no increased risk of birth defects or patterns of defects (*Birth Defects Res A Clin Mol Teratol* 2004;70(4):201)	Can be used in pregnancy for treatment or suppression of HSV infections and treatment of uncomplicated chicken pox or shingles; however, valacyclovir can be considered for convenient dosing and better pharmacokinetics IV acyclovir recommended for severe HSV or VZV if parenteral therapy indicated Suppressive therapy with either valacyclovir or acyclovir is recommended starting at 36 wk gestation for pregnant women with recurrences of genital herpes to reduce need for Cesarean delivery (*Obstet Gynecol* 2007;109:1489) No known benefit of suppressive therapy for women who are seropositive for HSV-2 without a history of genital lesions

Table 13-3 continued

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Albendazole (Albenza®) **FDA pregnancy category: C**	Microsporidiosis: 400 mg po bid x 3 wk	• Diarrhea • Abdominal pain • Elevated transaminase • Hepatotoxicity • Reversible pancytopenia and neutropenia	Teratogenic (skeletal malformations) and embryotoxic in rodent and rabbit studies at exposure levels lower than those estimated with therapeutic human dosing No adequate, well-controlled studies in early human pregnancy A recent randomized trial including albendazole for treatment of soil-transmitted helminth infections in 2nd trimester found no evidence of teratogenicity or other adverse pregnancy effects (*Am J Trop Med Hyg* 2008;79(6):856)	Not recommended for use in 1st trimester. Consider use later in pregnancy only if benefits outweigh potential risks.
Amphotericin B (Fungizone®) **FDA pregnancy category: B**	Usual adult dose: 0.3–1.2 mg/kg IV qd **Fluconazole-resistant candida esophagitis:** 0.3 mg/kg IV qd **Cryptococcal meningitis:** 0.7 mg/kg (plus 5FC)	• Fever and chills (40%– 50%) • Renal tubular acidosis (30%–40%); dose dependent and reversible in absence of prior renal damage and dose <3 g (reduced with hydration and sodium loading) • Hypokalemia (20%) • Hypomagnesemia • Anemia • Phlebitis and pain at infusion site • Hypotension • Nausea, vomiting • Metallic taste • Headache	Animal studies demonstrated no evidence of teratogenicity Extensive clinical use has demonstrated no evidence of teratogenicity	Preferred initial regimen for treatment of serious fungal infections in pregnancy Evaluate neonates born to women on chronic amphotericin B for renal dysfunction and hypokalemia at delivery

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Table 13-3 continued

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Artemisinin-based combination therapy (Artemether/lumefantrine) **FDA pregnancy category: C**	Artemether/lumefantrine (20 mg/120 mg tab) 4 tabs po as single initial dose; 4 tabs again after 8 h, and then 4 tabs bid (AM and PM) for next 2 d (total course of 24 tabs)	Generally well tolerated with occasional nausea, dizziness, headache, rash	Some preclinical studies found possible teratogenic effects and increased embryolethality with early 1st-trimester exposure to artemesinins in a variety of animal species, including at levels below equivalent human therapeutic dose Some data suggest pregnancy may lower levels of artemether/lumefantrine and dihydroartemisinin; optimal dosing strategies in pregnancy have not been determined	Considered first-line treatment during 2nd and 3rd trimesters for women with uncomplicated *Plasmodium falciparum* and severe malaria
Artesunate **FDA pregnancy category: C**	**U.S. IND protocol (available through CDC):** 4 equal doses of 2.4 mg/kg over 3 d, followed by oral treatment with atovaquone-proguanil, doxycycline, clindamycin, or mefloquine to avoid emergence of resistance **WHO recommendations:** IV artesunate 2.4 mg/kg IV or IM given on admission (time = 0), then 12 h and 24 h, qd in low-transmission area or outside malaria endemic area	Generally well tolerated with bradycardia, nausea, and dizziness occasionally reported	No evidence of physical or neurological abnormalities during development observed with 1st trimester exposure in small studies (*Malar J* 2007;6:15)	Alternative treatment of *P. falciparum* in 2nd and 3rd trimesters along with clindamycin WHO recommends artesunate as a first-line agent in 2nd and 3rd trimesters In 1st trimester, until more evidence becomes available, both artesunate and quinine may be considered

Table 13-3 *continued*

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Atovaquone (Mepron®) **FDA pregnancy category: C**	**PCP treatment or prophylaxis:** 750 mg po bid **PCP prophylaxis:** 1500 mg po qd **Toxoplasmosis treatment:** 1500 mg po bid + pyrimethamine or sulfadiazine	• GI intolerance: nausea, vomiting, diarrhea • Headache • Rash • 7%–9% require d/c because of side effects	Atovaquone did not increase malformations in rats and rabbits, although doses used were limited by toxicity to half the human dose Human data are limited No adverse effects in mothers or newborns found with use of atovaquone in combination with other antimalarials in about 90 pregnant Thai women in 2nd or 3rd trimester (*Trans R Soc Trop Med Hyg* 2003;97(5):592; *Eur J Clin Pharmacol* 2003;59(7):545; *J Infect Dis* 2005;192(5):846)	Alternative regimen for PCP prophylaxis and treatment Third-line treatment and prophylaxis for toxoplasmosis
Atovaquone– proguanil (Malarone®) **FDA pregnancy category: C**	**Malaria treatment:** atovaquone 1000 mg/proguanil 400 mg (4 tabs, single dose) po qd x 3 d **Malaria prevention:** atovaquone 250 mg/proguanil 100 mg (1 tab) qd, starting 1–2 d before travel and continuing for 1 wk after leaving endemic area	Generally well tolerated with occasional GI intolerance, headache, asthenia, dizziness, and rare cases of severe rash.	Preclinical studies have shown no increased risk of defects Limited human data Plasma levels appear lower in pregnancy	Can be used for malaria prophylaxis for travel to chloroquine-resistant regions Alternative treatment for *P. falciparum* in 2nd and 3rd trimesters

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Table 13-3 *continued*

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Azithromycin (Zithromax®) **FDA pregnancy category: B**	**MAC prophylaxis:** 1200 mg po q wk **MAC treatment:** 500 mg or 600 mg po qd + ethambutol +/- rifabutin	• GI intolerance (4%): nausea, diarrhea, abdominal pain • Vaginitis • Reversible hearing loss (more common with 500 mg x 30–90 d) • Elevated transaminase	Animal studies show no harm to fetus Two studies including >300 women found no increased risk of congenital anomalies with azithromycin exposure in pregnancy (*Sex Transm Dis* 2006;33(2):106; *BMC Pregnancy Childbirth* 2006;6:18)	Recommended for MAC prophylaxis or treatment in pregnancy Also used in treatment of Bartonellosis
Boceprevir (Victrelis®) **FDA pregnancy category: X**	800 mg po tid (in combination with peginterferon + ribavirin)	• Headache • Fatigue • Nausea • Elevated LFTs	No human data	Not recommended for use in pregnancy Because goal of HCV treatment is to prevent long-term sequelae, treatment in pregnancy is rarely indicated
Caspofungin (Cancidas®) **FDA pregnancy category: C**	70 mg IV load on day 1, then 50 mg IV qd (infuse over 1 h)	• Generally well tolerated • Histamine-mediated symptoms including rash, facial swelling, pruritus and sensation of warmth have been reported • Rare: fever, phlebitis, nausea, vomiting, headache, eosinophilia, proteinuria, increased alkaline phosphatase, hypokalemia	Embryotoxic: animal data with exposure comparable to human dosing resulted in incomplete ossification of skull, torso, and talus/calcaneus No human data	Avoid in 1st trimester. Use later in pregnancy should be based on consideration of benefit versus potential risk.

Table 13-3	*continued*			
Use of Antimicrobial Agents in Pregnancy				
Drug Name	**Dosing**	**Adverse Effects**	**Animal Data and Human Experience in Pregnancy**	**Comments**
Chloroquine (Aralen®) **FDA pregnancy category: C**	***P. vivax, P. ovale, P. malariae, and chloroquine-sensitive P. falciparum:*** chloroquine phosphate 1 g salt (600 mg base) 1x; then 500 mg salt (300 mg base) 6 h later; then 500 mg at 24 h and 48 h po Chloroquine HCl 160–200 mg (base) IM or IV q 6 h (IV n/a in U.S.)	• Visual disturbances • Hemolysis with G6PD deficiency • GI intolerance • Pruritus • Alopecia • Headache • Confusion • Dizziness • Severe skin rash • QTc prolongation	No evidence of increase in malformations Extensive experience with use in pregnancy	Drug of choice for malaria prophylaxis and treatment of sensitive strains in pregnancy
Cidofovir (Vistide®) **FDA pregnancy category: C**	**CMV retinitis induction:** 5 mg/kg q wk x 2 wk, then q 2 wk; give concurrently with probenecid and hydration **Probenecid regimen:** 2 g given 3 h prior to cidofovir and 1 g given at 2 h and 8 h after infusion (total 4 g) >1 L normal saline 1 or 2 h immediately before cidofovir infusion	• Nephropathy (dose dependent); reduced with hydration and probenecid • Probenecid side effects: chills, fever, headache, rash, nausea (30%–50%) • Uveitis • GI intolerance • Neutropenia • Metabolic acidosis	Embryotoxic and teratogenic (meningomyelocele, skeletal abnormalities) in rats and rabbits No experience with use of cidofovir in human pregnancy	Not recommended for use in pregnancy

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Table 13-3 *continued*

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Clarithromycin (Biaxin®) **FDA pregnancy category: C**	**MAC prophylaxis:** 500 mg po bid **MAC treatment:** 500 mg po bid + ethambutol +/- rifabutin	• GI intolerance: diarrhea (4%) • Headache • Reversible dose-related hearing loss • Taste disturbances	Studies in monkeys show growth retardation, cleft palate, embryonic loss Two studies, each with slightly >100 women with 1st-trimester exposure to clarithromycin, did not demonstrate an increase in or specific pattern of defects, although one study noted an increased risk for spontaneous abortion (*Am J Perinatol* 1998;15(9):523; *Pharmacoepidemiol Drug Saf* 2000;9(7):549)	Not recommended in 1st trimester
Clotrimazole (Canesten®, Lotrimin®, Mycelex®) **FDA pregnancy category: C** (troches)	**Oral thrush:** 10 mg troches 5 x/d **Candida vaginitis:** • 100 mg intravaginal tabs bid x 3 d **or** • qd x 7 d **or** • 1 applicator (5 g) vaginal cream q hs x 7–14d	• GI intolerance: nausea, vomiting • Transaminase elevation • Topical treatment (rare): burning, erythema, pruritus	Embryotoxic in rats and mice. Not teratogenic in mice, rabbits, and rats. No adverse effects or congenital anomalies reported with use of vaginal or topical clotrimazole in pregnancy (*Obstet Gynecol* 1987;69(5):751; *Epidemiology* 1999;10(4):437)	Nystatin is preferred over clotrimazole in management of oral thrush during pregnancy because of minimal systemic absorption Clotrimazole is considered safe for treatment of vaginal candidiasis in pregnancy

Table 13-3 continued

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Cycloserine (Seromycin®) **FDA pregnancy category: C**	**TB:** 10–15 mg/kg/d po (maximum daily dose = 1000 mg, but hard to tolerate) Usual dose 500–750 mg po qd, given in 2 divided doses	• Common CNS side effects: anxiety, confusion, somnolence, disorientation, headache, hallucinations, tremor, hyperreflexia, depression (with suicidal ideation), psychotic disturbances • Occasional seizures • Peripheral neuropathy • Fever • Rash	No data available from animal studies No data on use in human pregnancy	Avoid use in pregnancy unless other options not available
Dapsone (Aczone®) **FDA pregnancy category: C**	**PCP prophylaxis:** 100 mg po qd **Treatment of mild to moderate PCP:** 100 mg po qd + trimethoprim x 3 wk **PCP + toxoplasmosis prophylaxis:** 50 mg po qd or 200 mg q wk + leucovorin and pyrimethamine	• Rash • Blood dyscrasias, including methemoglobinemia, sulfhemoglobinemia, and hemolytic anemia (with or without G6PD deficiency) • Nephrotic syndrome • Fever • Nausea, anorexia • Blurred vision • Photosensitivity • Tinnitus • Insomnia • Irritability • Headache (transient) • Rare sulfone syndrome: fever, exfoliative dermatitis, jaundice, adenopathy, methemoglobinemia, anemia	No animal teratogenicity studies conducted Carcinogenic risk in rats Has been used safely for several decades to treat leprosy, malaria, and various dermatologic conditions during pregnancy (Trop Med Int Health 2003;8(6):488; Drug Saf 2004;27(9):633) Risk of mild maternal hemolysis with long-term therapy and potential risk, though extremely low, of hemolytic anemia in an exposed fetus with G6PD deficiency (South Med J 1989;82(5):668)	Alternative for PCP prophylaxis and treatment of mild–moderate PCP (with TMP); also alternative to toxoplasmosis prophylaxis Screening of mother for G6PD deficiency is recommended before use

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Table 13-3 continued

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Ethambutol (Myambutol®) **FDA pregnancy category: C**	• 15–25 mg/kg po qd (1.6 g max) • 35–50 mg/kg biw (4.0 g max) • 25–30 mg/kg tiw (2.4 g max)	• Optic neuritis: decreased acuity, reduced color discrimination, constricted fields, scotomata (dose related and infrequent with 15 mg/kg) • GI intolerance • Confusion • Precipitation of acute gout	Teratogenic among rodents and rabbits at doses much higher than those used in humans No evidence of teratogenicity in humans	CDC considers ethambutol safe in pregnancy
Ethionamide (Trecator®) **FDA pregnancy category: X**	15–20 mg/kg/d po (max 1 g/d); usually 500–750 mg divided q 24 h, q 12 h, or q 8 h administered w/food or hs	• Common, severe, and dose-dependent GI intolerance: nausea, vomiting, metallic taste, anorexia, abdominal pain • Occasional allergic reaction • Hepatitis • Neurotoxicity • Orthostatic hypotension	Associated with birth defects in multiple animal species No increased risk for defects was noted with doses similar to those used in humans Limited experience in human pregnancy	Avoid use in pregnancy unless other options not available
Famciclovir (Famvir®) **FDA pregnancy category: B**	**Zoster:** 500 mg po q 8 h **Recurrent HSV and HSV suppression:** 125–250 mg po q 12 h	• Headache • Nausea • Fatigue	Carcinogenic but not embryotoxic or teratogenic in animal studies Human data limited	Acyclovir or valacyclovir preferred In pregnancy given limited information on famciclovir

Table 13-3 continued

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Fluconazole (Diflucan®) **FDA pregnancy category: C**	**Candida esophagitis:** 200–800 mg po or IV qd **Candida vaginitis:** 150 mg po x 1; 150 mg po q wk for multiple recurrences **Cryptococcal infection:** • 1200 mg po or IV qd +5FC (alternative induction phase at least 2 wk) • Then 400 mg po qd (consolidation phase x 8 wk); • Then 200 mg po qd (maintenance)	• Dose-related GI intolerance: bloating, nausea, vomiting, pain, anorexia, weight loss (8%–11% with dose <400 mg/d; 30% with dose >400 mg/d) • Reversible alopecia (10%–20% of patients receiving 400 mg/d for 3 mo) • Transaminase elevation to >8 x normal • Rare cases of fetal hepatitis and Stevens–Johnson syndrome	Teratogenic in animal studies, with limb and craniofacial abnormalities reported Craniofacial, limb, and cardiac defects have been reported in 4 infants with 1st-trimester exposure to high-dose fluconazole (*Clin Infect Dis* 1996;22:336; *Am J Med Genet* 1997;72:253) Several cohort studies have shown no increased risk of birth defects with early pregnancy exposure, but most of these involved low doses and short-term exposure (*J Antimicrob Chemother* 2008;62(1):172; *Am J Obstet Gynecol* 1996;75:1645)	Avoid in 1st trimester because of potential for teratogenicity Use topical agents in treatment of candida vaginitis in pregnancy
Flucytosine (Ancobon®) **FDA pregnancy category: C**	25 mg/kg q 6 h (monitor levels; goal = 30–80 mcg/mL at steady state)	• GI intolerance: nausea, vomiting, diarrhea • Marrow suppression with leukopenia or thrombocytopenia (dose related with renal failure, serum concentration >100 mg/mL or concurrent amphotericin) • Confusion • Rash • Hepatitis (dose related) • Enterocolitis • Headache • Photosensitivity reaction • Peripheral neuropathy	Teratogenicity reported in animal studies Data limited to 3 case reports of 2nd and 3rd trimester exposure that resulted in no defects in newborns	4% of administered dose biotransformed to 5FU, which has been associated with congenital malformations Use in pregnancy only if benefits outweigh potential risks

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Table 13-3 continued

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Foscarnet (Foscavir®) **FDA pregnancy category: C**	**CMV retinitis induction:** • 60 mg/kg IV q 8 h **or** • 90 mg/kg IV q 12 h x 14 d **Maintenance:** 90–120 mg/kg IV qd **Acyclovir-resistant HSV or VZV:** • 40 mg/kg IV q 8 h **or** • 60 mg/kg IV q 12 h x 3 wk	• Renal failure: usually reversible; 30% get Cr >2 mg/dL; monitor Cr 1–3 x/wk; d/c if Cr >2.9 mg/dL • Mineral and electrolyte changes: reduced magnesium, phosphorus, ionized calcium, potassium; monitor serum electrolytes 1–2 x/wk and monitor for symptoms of paresthesias • Seizures (10%) • Fever • GI intolerance • Anemia • Genital ulceration • Neuropathy	Skeletal malformation or variation in animal studies No experience with use in early pregnancy A single case report of use in 3rd trimester described normal infant outcome (*Clin Infect Dis* 1999;29(4):937)	Use only if benefits outweigh risks and safer alternatives not available Avoid in 1st trimester if possible Because foscarnet toxicity is primarily renal, monitor amniotic fluid volume by ultrasound weekly after 20 wk gestation to detect oligohydramnios If therapy given near delivery, evaluate electrolyte and renal function in neonate
Fumagillin (Not commercially available in U.S.) **FDA pregnancy category: N/A**	20 mg po tid x 2 wk (not available in U.S.)		Systemic fumagillin associated with increased resorption and growth retardation in rats No data on systemic use in human pregnancy Topical fumagillin has not been associated with embryotoxic or teratogenic effects among pregnant women	Because of antiangiogenic effect of fumagillin, this drug should not be used systemically in pregnant women Topical fumagillin may be considered when therapy with this agent is appropriate (ocular microsporidiosis)

Table 13-3 *continued*

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Furazolidone (No longer available in U.S.) **FDA pregnancy category: C**	100 mg po q 6 h x 7–10 d	• GI intolerance • Yellow to brown discoloration of urine • Allergic reaction • Fever • Hemolysis • Headache	Not teratogenic in animal studies Human data limited to case series that found no association between 1st-trimester use and birth defects	Use in pregnancy only if benefit outweighs potential risk
Ganciclovir (Cytovene®) **FDA pregnancy category: C**	**CMV retinitis induction: 5** mg/kg IV q 12 h x 2 wk, then maintenance: 5 mg/kg IV qd	• Neutropenia (ANC <500 in 15%–20%); usually occurs early in treatment and responds within 3–7 d to drug holiday or to GCSF • Thrombocytopenia (platelet count <20,000 in 10%); reversible; monitor CBC 2–3 x wk and d/c if ANC <500–750 or platelet count <25,000 • Anemia • Fever • Rash • CNS: headache, seizures, confusion, changes in mental status • Abnormal LFTs (2%–3%).	Teratogenic (in concentrations comparable to those achieved in humans) and embryotoxic: cleft palate, anophthalmia, hydrocephalus, aplastic kidney and pancreas (rabbits); growth retardation Safe use in human pregnancy after organ transplantation has been reported (*Transplantation* 1995;60(11):1353). Use in late pregnancy to treat fetal CMV infection in HIV uninfected women has also been reported (*Semin Perinatol* 2007;31(1):10).	For retinal disease, consider intraocular ganciclovir implants or intravitreous injections in 1st trimester to limit fetal exposure to systemically administered drugs Start systemic antiviral therapy after 1st trimester, generally with oral valganciclovir (see below) For patients with colitis or esophagitis, IV ganciclovir is recommended if symptoms are severe enough to interfere with oral absorption Monitor fetus with fetal movement counts in 3rd trimester and after 20 wk gestation with periodic ultrasound for evidence of significant anemia, manifest as hydrops fetalis Evaluate newborn for bone marrow suppression

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Table 13-3 continued

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Interferon (Roferon®, Intron®) **FDA pregnancy category: C**	**Treatment of hepatitis: 3** million units IM or SC tiw + ribavirin Also used at higher doses for treatment of hepatitis B and Kaposi's sarcoma	• Flu-like syndrome • GI intolerance: nausea, vomiting, diarrhea, anorexia • CNS toxicity: delirium; obtundation, depression • Neutropenia • Anemia • Thrombocytopenia • Elevated transaminase • Rash • Alopecia • Proteinuria	Abortifacient in rhesus monkeys when given at 20–500 x human dose Limited case reports of interferon exposure during pregnancy do not suggest an association with birth defects; however, data are too limited to draw conclusions	Not recommended for use in pregnancy because of direct antigrowth and antiproliferative effects (*Neurology* 2005;65(6):807) Because goal of HCV treatment is to prevent long-term sequelae, treatment in pregnancy is rarely indicated
Isoniazid (INH, Tubizid®, Nydrazid®) **FDA pregnancy category: C**	300 mg po qd	• Age-related hepatitis: <20 y (nil); 35 y (6%); 45 y (11%); 55 y (18%); d/c if transaminase levels are >3–5x normal limits • Allergic reactions • Fever • Peripheral neuropathy (especially with preexisting alcoholism, diabetes, pregnancy, malnutrition) • Glossitis	Animal studies show embryocidal effect, but not teratogenic Retrospective analysis of more than 4,900 exposures to INH did not show increased fetal malformations (*Am Rev Respir Dis* 1980;122(1):65)	American Academy of Pediatrics and American Thoracic Society recommend that pregnant women with a positive PPD receive INH if they are HIV infected, have had recent TB contact, or have an X-ray showing old TB, once active disease is ruled out. Start after 1st trimester if possible. Hepatotoxicity caused by INH may occur more frequently in pregnancy and postpartum period; monthly monitoring of liver transaminases is recommended

Table 13-3 continued

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Itraconazole (Sporanox®) **FDA pregnancy category: C**	100–400 mg po qd, depending on specific condition	• Headache • GI intolerance: nausea (10%) and vomiting • Rash (8%) • Hypokalemia reported with high doses (600 mg/d) • Adrenal insufficiency • Impotence • Gynecomastia • Leg edema • Elevated transaminase • Rare cases of fetal hepatitis	Teratogenic in rats and mice (encephaloceles, macroglossia, skeletal malformation) FDA has received 14 case reports of malformations following use of itraconazole; 4 were limb defects. Prospective cohort studies of >300 women with 1st-trimester exposure, however, did not show an increased risk of malformation (*Drug Saf* 2009;32(3):239; *Am J Obstet Gynecol* 2000; 183(3): 617).	In general, avoid azole antifungals in 1st trimester because of potential for teratogenicity
Mefloquine (Lariam®) **FDA pregnancy category: C**	**Uncomplicated malaria treatment:** • 1250 mg po x 1 or • 750 mg 1x, then 500 mg 12 h later **Malaria prophylaxis:** 250 mg po q wk; start 1 wk prior to departure to an endemic area and continue for 4 wk after leaving endemic area	• Common CNS side effects: vertigo, light-headedness, nightmares, headache, decreased fine motor function • Visual disturbances • GI intolerance • Sinus bradycardia	Animal studies suggest potential teratogenicity and/or embryotoxicity, but clinical experience has not shown evidence of such effects in humans No evidence of increase in defects Several other large studies found mefloquine to be safe and effective in pregnancy (*J Travel Med* 1998;5(3):121)	Drug of choice for malaria prophylaxis with travel to chloroquine-resistant regions and for continuing prophylaxis after treatment
Nitazoxanide (Alinia®) **FDA pregnancy category: B**	500 mg po q 6–12 h	Generally well tolerated with occasional GI intolerance and headache	No evidence of teratogenicity in animal studies No data on use in human pregnancy	May be considered in pregnancy after 1st trimester in severely symptomatic women

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Table 13-3 continued

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Nystatin (Bio-Statin®, Mycostatin®, etc.) **FDA pregnancy category: C**	**Oral thrush:** 500,000 units; swish and swallow 5 x/d	GI intolerance: nausea, vomiting, diarrhea	No evidence of congenital defects in animal studies No evidence of congenital defects associated with use in pregnancy	May be used for management of thrush during pregnancy because of low systemic absorption
Paromomycin (Humatin®) **FDA pregnancy category: C**	500–1000 mg po q 6 h	Generally well tolerated with occasional nausea, vomiting, diarrhea, anorexia, cramps, epigastric burning pain	No evidence of teratogenicity in animal studies Limited information in human pregnancy Minimal systemic absorption with oral administration, which may minimize potential risk	May be used in pregnancy after 1st trimester in severely symptomatic women
Peginterferon (PegIntron®) [alfa-2B], Pegasys® [alfa-2A]] **FDA pregnancy category: C**	**PegIntron:** 1 mcg/kg SC q wk + ribavirin; dose reduction to 0.5 mcg/kg recommended for ANC <750 or platelet count <50,000 and d/c if ANC <500 or platelet count <25,000 **Pegasys:** 180 mcg SC q wk + ribavirin; reduce dose with hematologic toxicity Peginterferon alfa-2A or alfa-2B + ribavirin is treatment of choice for HCV	• Common: flu-like symptoms, headache, dizziness, fatigue, fever, rigor, injection-site inflammation, depression (29%), insomnia, alopecia, GI intolerance (abdominal pain, anorexia, nausea, vomiting, diarrhea • Occasional: thrombocytopenia, neutropenia, hypo- and hyperthyroidism, elevated LFTs	Abortifacient in rhesus monkeys when given 20–500 x human dose No studies in human pregnancy	Not recommended for use in pregnancy because of direct antigrowth and antiproliferative effects (Neurology 2005;65(6):807) Because goal of HCV treatment is to prevent long-term sequelae, treatment in pregnancy is rarely indicated

Table 13-3 *continued*

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Pentamidine—aerosolized (NebuPent®) **FDA pregnancy category: C**	**PCP prophylaxis:** 300 mg nebulized q mo	• Asthma reaction (2%– 5%) • Cough (30%)	Systemic pentamidine is embryotoxic but not teratogenic in rats and rabbits Aerosolized pentamidine given to 15 women during the 2nd and 3rd trimesters did not alter pregnancy outcome or cause fetal harm (*Am J Obstet Gynecol* 1992;166:387)	Use for PCP prophylaxis only if alternatives not available. There are concerns about systemic absorption and about adequate drug distribution during pregnancy because of restrictive changes with an enlarged uterus.
Pentamidine—intravenous (Nebupent®, Pentacarinat®, Pentam 300®) **FDA pregnancy category: C**	**PCP treatment:** 3–4 mg/kg IV qd	• Nephrotoxicity (25%), usually reversible with d/c • Hypotension (administer IV over 60 min to decrease risk) • Hypoglycemia (5%– 10%); usually occurs after 5 d of treatment including past treatment and may last days or weeks; may lead to insulin-dependent diabetes • Marrow suppression (leukopenia; thrombocytopenia) • GI intolerance: nausea, vomiting, abdominal pain, anorexia, bad taste • Elevated transaminase • Pancreatitis • Toxic epidermal necrolysis • Fever	Systemic pentamidine is embryotoxic but not teratogenic in rat and rabbit studies; however, it has been shown to be embryocidal Pentamidine is concentrated in placental tissue, but the clinical significance of this is unknown (*Am J Obstet Gynecol* 1989; 160(3): 759-61) No human clinical data on use of IV pentamidine	Use in pregnancy only if benefits outweigh potential risks and recommended alternatives cannot be used

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Table 13-3 *continued*

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Posaconazole (Noxafil®) **FDA pregnancy category: C**	**Treatment of invasive fungal infections:** • 200 mg po q 6 h or • 400 mg po q 12 h • Some experts recommend increasing to 400 mg q 8 h for severe infection, lack of clinical response, and/ or low posaconazole serum concentrations **Oropharyngeal and esophageal candidiasis refractory to itraconazole and/or fluconazole:** 400 mg q 12 h, with duration of therapy based on clinical response	• Generally well tolerated • Occasional nausea, vomiting, diarrhea, abdominal pain; increased LFTs • Rare cases of adrenal insufficiency, hypersensitivity reaction, QTc prolongation	Has been shown to cause skeletal malformations in rats, but not in rabbits, when given at 3–5 x human exposure No adequate controlled studies	Avoid in pregnancy
Primaquine **FDA pregnancy category: C**	**PCP treatment:** 15–30 mg (base) po qd + clindamycin	• Hemolytic anemia (G6PD deficiency) • Methemoglobinemia • GI intolerance • Neutropenia	No animal studies available No human data available	Generally not used in pregnancy because of risk of maternal hemolysis Potential risk of hemolytic anemia in exposed G6PD-deficient fetus; screen mother for G6PD deficiency before use

Table 13-3 *continued*

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Pyrazinamide FDA pregnancy category: C	**Latent TB:** 15 mg/kg/d (2.0 g max) **Active TB:** 20–25 mg/kg/d (2.0 g max) **Intermittent therapy:** 30–50 mg/kg 2–3 x wk (3.0–4.0 g max)	• Nongouty polyarthralgia • Asymptomatic hyperuricemia • Hepatitis (dose related; frequency not increased when given with INH or rifampin; rarely serious) • GI intolerance • Gout	No evidence of increased congenital defects in rodent data Minimal human data available	WHO and International Union Against Tuberculosis and Lung Diseases have recommended routine use of PZA in pregnant women; it has not been recommended for general use during pregnancy in the U.S. because of limited data If PZA not included in initial treatment regimen, minimum duration of TB therapy should be 9 mo Decision to use PZA should take into account gestational age and susceptibility pattern of MTB strain

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Table 13-3 continued

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Pyrimethamine (Daraprim®) **FDA pregnancy category: C**	**Acute treatment of toxoplasmosis:** 100–200 mg loading dose, then 50–75 mg po qd + sulfadiazine 4–6 g po qd in 4 divided doses for at least 6 wk + leucovorin 10–20 mg po qd **Toxoplasmosis maintenance dose:** After acute treatment, pyrimethamine 25–50 mg po qd + sulfadiazine 2–4 g po qd in 4 divided doses + leucovorin 10–25 mg po qd **Toxoplasmosis prophylaxis:** 50–75 mg po q wk + dapsone + leucovorin 25 mg po q wk	• Folic acid deficiency with megaloblastic anemia and pancytopenia (dose-related and reversed with leucovorin) • Allergic reactions • GI intolerance: nausea, vomiting, anorexia	Teratogenic in animal studies Human data have not suggested an increased risk for defects (*Curr Drug Saf* 2006;1(1):1; *Drug Saf* 2007;30(6):481; *Clin Perinatol* 1994;21:675; *Clin Infect Dis* 1994;18:853)	Recommended as part of treatment regimen for toxoplasmic encephalitis and prophylaxis for patients who cannot tolerate TMP-SMX

Table 13-3 *continued*

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Quinine (Qualaquin®) **FDA pregnancy category: C**	**Uncomplicated malaria:** 650 mg q 8 h x 3–7 d, plus: • doxycycline 100 mg bid x 7 d **or** • clindamycin 450 mg q 8 h x 7 d **or** • pyrimethamine/sulfadoxine 3 tabs on last day of quinine	• GI intolerance • Cinchonism (tinnitus, headache, nausea, abdominal pain, visual disturbances) • Hemolytic anemia with G6PD deficiency • QTc prolongation • Thrombocytopenia • Hepatitis	At high doses, associated with increased risk for birth defects (especially deafness) in some animal species At high doses, associated with increased risk for birth defects (especially deafness) in humans	Use of therapeutic doses in pregnancy considered safe Treatment of choice with a diagnosis of chloroquine-resistant *P. vivax*; with uncomplicated chloroquine-resistant *P. falciparum* malaria, prompt treatment with quinine and clindamycin is recommended, particularly in 1st trimester Because of potential for hypoglycemia, monitor glucose levels of pregnant women treated with quinine and their neonates
Ribavirin (Rebetol®) **FDA pregnancy category: X**	**Treatment of hepatitis C:** • **<75 kg:** 400 mg q AM and 600 mg q PM + interferon • **>75 kg:** 600 mg bid + interferon	• Hemolytic anemia (mean Hb decrease 3 g/dL) • Leukopenia • Hyperbilirubinemia • Increased uric acid	Demonstrated to be teratogenic in low doses in multiple animal species (limb abnormalities, craniofacial defects, exencephaly, anophthalmia) No human data available. At this time, inadvertent pregnancy during paternal RBV exposure has not been associated with adverse events (*Am J Gastroenterology* 2001;96:2286).	Use contraindicated during pregnancy and in male partners of pregnant women Women of childbearing potential and men receiving RBV should be counseled about risks and need for consistent contraception during and for 6 mo after use of RBV Pregnancies that occur in women taking RBV should be reported to the Ribavirin Pregnancy Registry (800-593-2214)

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Table 13-3 continued

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Rifabutin (Mycobutin®) **FDA pregnancy category: B**	• 300 mg po qd • **With unboosted PIs** (e.g., IDV, NFV): 150 mg qd or 300 mg tiw • **With boosted PIs** (e.g., LPV/r, DRV/r, SQV/r, ATV/r) or ATV: 150 mg qod • **With EFV:** 450 mg qd or 600 mg tiw • **With NVP:** standard dose or 300 mg tiw Not recommended with DLV Consider therapeutic drug monitoring with PIs and NNRTI co-administration	• Orange discoloration of urine, tears, sweat • Uveitis with eye pain, photophobia, redness, blurred vision; usually seen with high doses (600 mg/d) or concurrent use of fluconazole or clarithromycin • Hepatitis • GI intolerance • Allergic reactions	Animal data show no increase in birth defects No human data available	Limited experience in pregnancy Many drug interactions, for which dose modifications are recommended (see Table 13-8, p. 500 and Table 13-9, p. 505)
Rifampin (Rifadin®) **FDA pregnancy category: C**	**For TB prophylaxis or active TB:** 10 mg/kg/d (600 mg/d max, but up to 600 mg bid with CNS infections) **With DOT:** 600 mg 2–3 x/wk	• Orange discoloration of urine, tears, sweat • Hepatitis (usually cholestatic changes during first month; frequency not increased when given with INH) • Jaundice (usually reversible with dose reduction and/or continued use) • GI intolerance • Hypersensitivity reactions • Flu-like syndrome with intermittent use characterized by dyspnea, wheezing	Some but not all animal studies show increased risk of cleft palate, spina bifida, embryotoxicity No evidence of human teratogenicity	American Thoracic Society recommends rifampin in combination with INH and ethambutol if treatment for drug-sensitive TB is needed during pregnancy Many drug interactions, including with ARVs Administer prophylactic vitamin K 10 mg to neonate because of potential increased risk of hemorrhagic disease

Table 13-3 continued

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Sulfadiazine (Lantrisu®, Neotrizine®, etc.) **FDA pregnancy category: C**	**Acute treatment of toxoplasmosis:** Sulfadiazine 4–6 g/d po in 4 divided doses + pyrimethamine 50–75 mg po qd for at least 6 wk + leucovorin 10–20 mg po qd **Toxoplasmosis maintenance dose:** After acute treatment, sulfadiazine 2–4 g po qd in 4 divided doses + pyrimethamine 25–50 mg po qd + leucovorin 10–25 mg po qd	• Allergic reactions (rash, pruritus) • Crystalluria with renal damage, urolithiasis and oliguria • GI intolerance • Photosensitivity • Hepatitis • Fever • Periarteritis nodosum • Stevens–Johnson syndrome • Serum sickness	At high doses, animals developed cleft palate and bone abnormalities Extensive use in humans without complications except one case of agranulocytosis that was possibly associated (*Drugs in Pregnancy and Lactation*, 7th ed. Baltimore: Williams & Wilkins. 2005)	Theoretical risk of kernicterus in neonate if administered near term
Telaprevir (Incivek®) **FDA pregnancy category: X**	• 750 mg q 8 h • 1125 mg q 8 h (with EFV co-administration) Co-administration recommended only with ATV/r or EFV; not recommended with LPV/r, DRV/r, or FPV/r Must be used in combination with peginterferon and ribavirin	• Rash • Pruritus • Nausea, vomiting • Fever • Anorexia • Dizziness • Anemia • Elevated LFTs	No human data	Not recommended in combination with interferon and ribavirin in pregnancy Because goal of HCV treatment is to prevent long-term sequelae, treatment in pregnancy is rarely indicated
Thalidomide (Thalomid®) **FDA pregnancy category: X**	**Treatment of aphthous ulcers and/or wasting:** 50–200 mg po qd	• Sedation • Rash • Neuropathy • Constipation • Neutropenia (up to 50%)	High potential for birth defects, including absent or abnormal limbs; cleft lip; absent ears; heart, renal, or genital abnormalities Single dose can be associated with teratogenic effects	Contraindicated in pregnancy and in women at risk for pregnancy (not using effective contraception or trying to conceive)

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Table 13-3 continued

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Trimethoprim–sulfamethoxazole (TMP-SMX) (Bactrim®, Septra®, Cotrim®, Sulfatrim®) **FDA pregnancy category: C**	**PCP prophylaxis:** • 1 DS po qd • 1 SS po qd • 1 DS po tiw **PCP treatment:** 5 mg/ kg (based on trimethoprim component) po or IV q 8 h	• Fever • Leukopenia • Rash and/or GI intolerance (25%–50% of patients with HIV); most tolerate readmininistration of lower dose after 2 wk of d/c • Megaloblastic anemia • Neutropenia • Thrombocytopenia • Hematologic toxicity increased with folate depletion and high doses; treat with leucovorin 3–15 mg q d x 3 d • Reversible hyperkalemia (with high doses) • Photosensitivity • Renal failure • Hemolytic anemia with G6PD deficiency • Hepatitis including cholestatic jaundice • Thrush • Erythema multiforme • Stevens–Johnson syndrome	Cleft palate has been observed in some animals In case-control studies, TMP has been associated with an increased risk of neural tube defects and cardiovascular, urinary tract, and multiple anomalies after 1st-trimester exposure, but folic acid supplementation (up to 6 mg) decreased risk of birth defects (N Engl J Med 2000;343(22):1608; Reprod Toxicol 2001;15(6):637) In a surveillance study of Michigan Medicaid recipients, 2,296 exposures to TMP-SMX in 1st trimester resulted in a 5.5% incidence of birth defects. This suggests an association with congenital defects (cardiovascular); however, confounding factors such as maternal disease, concurrent drug use, etc, may be involved (Drugs in Pregnancy and Lactation, 7th ed. Baltimore: Williams & Wilkins. 2005)	Most authorities consider sulfonamides safe in pregnancy. Clinicians may consider use of supplemental folic acid (>0.4-mg/d routinely recommended) in 1st trimester for pregnant women on TMP-SMX, but use should be limited to 1st trimester. Ultrasound at 18–20 wk recommended to assess fetal anatomy after 1st-trimester exposure Theoretical risk of kernicterus in neonate if administered near term TMP-SMX is recommended for treatment and prophylaxis of PCP and prophylaxis of toxoplasmosis in pregnancy Agent of choice for treatment and secondary prophylaxis for isosporiasis in pregnancy

Table 13-3 *continued*

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Valacyclovir (Valtrex®) **FDA pregnancy category: B**	**Treatment of zoster:** 1000 mg po tid **Recurrent HSV:** 1000 mg po bid **HSV suppression:** 500 mg po bid	• GI intolerance: nausea, vomiting, diarrhea • Headache • Constipation	Not teratogenic in animal studies Use during pregnancy appears to be safe and well tolerated, though data are limited (*JAMA* 2010;304:859)	Can be used for treatment and suppression of genital HSV infections and as treatment for uncomplicated chicken pox or shingles in pregnancy Valacyclovir is converted to acyclovir Suppressive therapy with either valacyclovir or acyclovir is recommended starting at 36 wk gestation for pregnant women with recurrences of genital herpes to reduce need for Cesarean delivery (*Obstet Gynecol* 2007;109:1489) No known benefit of suppressive therapy for women who are seropositive for HSV-2 without a history of genital lesions

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Table 13-3 continued

Use of Antimicrobial Agents in Pregnancy

Drug Name	Dosing	Adverse Effects	Animal Data and Human Experience in Pregnancy	Comments
Valganciclovir (Valcyte®) **FDA pregnancy category: C**	**Induction:** 900 mg po bid w/ food x 3 wks **Maintenance:** 900 mg po qd	• Diarrhea • Nausea • Fever • Bone marrow suppression • Elevated LFTs	Embryotoxic in rabbits and mice; teratogenic in rabbits in concentrations comparable to those achieved in humans: cleft palate, anophthalmia, hydrocephalus, aplastic kidney and pancreas (rabbits); growth retardation No experience reported with use in human pregnancy, but concerns are expected to be same as those for ganciclovir	On basis of limited data, toxicity reports and studies, and ease of use of various drugs, valganciclovir is recognized as treatment of choice during pregnancy Monitor fetus with fetal movement counts in 3rd trimester and periodic ultrasounds after 20 wk gestation for evidence of significant anemia, manifest as hydrops fetalis Evaluate newborn for bone marrow suppression
Voriconazole (Vfend®) **FDA pregnancy category: D**	• 6 mg/kg IV q 12 h x 2 doses (load), then 3–4 mg/kg IV q 12 h infused over 1–2h • **>40 kg:** 200 mg po tid x 1 d (load), then 200–300 mg po bid • **<40 kg:** 100 mg po q 12 h; may be increased to 150 mg po q 12 h Administer on an empty stomach; avoid high-fat food	• Common: abnormal vision, described as blurriness, color changes, enhanced vision (20.6%, but <1% required d/c) • Occasional: LFTs (13%), alkaline phosphatase (4%–8% of patients with hepatitis require d/c); hallucination (4.3%); rash (6%); nausea, vomiting	Teratogenic and embryotoxic in animal studies at doses lower than recommended human doses No adequate controlled studies	Avoid in pregnancy Do not use with RTV (400 mg bid) Check for potential drug-drug interactions (see Table 13-9, p. 505 for specific recommendations) Monitor trough concentrations for invasive fungal infections (goal >1–2 mcg/mL)

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Source: *Medical Management of HIV Infection*, 16th ed. 2012. Durham, NC: Knowledge Source Solutions

Notes: 1. At the time of publication of this guide, the FDA was preparing a revision of drug categories for pregnancy and lactation that will likely do away with the current letter categories. 2. Unless otherwise noted, all data are taken from FDA labeling.

Table 13-4

Safety of Commonly Used Antimicrobials

Drug Name	Animal Data	Human Experience in Pregnancy	Comments
Aminoglycosides FDA pregnancy category: D	Fetotoxicity reported in rodent studies	Toxicity to eighth cranial nerve in fetus is well documented with exposure to kanamycin and streptomycin and can potentially occur with other aminoglycosides	If possible, streptomycin should be avoided as part of TB treatment in pregnancy Gentamicin is FDA pregnancy category C, although it has the same potential adverse effects. Use as preferred aminoglycoside if treatment is indicated. Amikacin or capreomycin might be alternatives when an aminoglycoside is required for treatment of MDR TB
Aztreonam FDA pregnancy category: B	Animal studies indicate no harm to fetus	No clinical data in pregnancy	Likely to be safe in pregnancy but, because of lack of data, use only if benefits are thought to outweigh potential risk
Cephalosporins FDA pregnancy category: B	Not teratogenic or fetotoxic	Extensive pregnancy exposure not associated with birth defects	Usually considered safe to use in pregnancy
Chloramphenicol FDA pregnancy category: C	No animal data	A collaborative perinatal project monitored 98 1st- trimester exposures and 348 exposures anytime during pregnancy; no relationship was found between chloramphenicol and congenital malformations (*Drugs in Pregnancy and Lactation*, 7th ed. Baltimore: Williams & Wilkins. 2005)	Although there is no evidence of teratogenicity, chloramphenicol should not be used near term because of potential for development of "gray baby" syndrome and possible infant death due to cardiovascular collapse

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Table 13-4 continued

Safety of Commonly Used Antimicrobials

Drug Name	Animal Data	Human Experience in Pregnancy	Comments
Clindamycin **FDA pregnancy category: B**	No fetal harm demonstrated in rat studies. Cleft palate observed in one mouse strain	In a surveillance study of Michigan Medicaid recipients, 647 1st-trimester exposures to clindamycin resulted in a 4.8% incidence of birth defects. Patterns of anomalies do not support an association between clindamycin and congenital effects (*Drugs in Pregnancy and Lactation*, 7th ed. Baltimore: Williams & Wilkins. 2005).	Usually considered safe to use in pregnancy
Erythromycin **FDA pregnancy category: B**	No teratogenic effect in rat studies	In a surveillance study of Michigan Medicaid recipients, 6972 1st-trimester exposures to erythromycin resulted in a 4.6% incidence of birth defects. Patterns of anomalies do not support an association between erythromycin and congenital malformations (*Drugs in Pregnancy and Lactation*, 7th ed. Baltimore: Williams & Wilkins. 2005).	Avoid estolate salt due to hepatotoxicity in 10% of patients. Other forms of erythromycin are usually considered safe to use in pregnancy.
Fluoroquinolones **FDA pregnancy category: C**	Animal data indicate arthropathy that resulted in erosions in joint cartilage in immature animals	Congenital malformation rate was 4.8% in a prospective follow-up study of 666 cases of fluoroquinolone exposure (most during 1st trimester); this did not exceed previously reported background rate (Eur J Obstet Gynecol Reprod Biol 1996;69:83) A registry study of >1100 quinolone exposures during pregnancy found no increase in rate of birth defects (*Pharmacoepidemiol Drug Saf* 2004;13(S1):S206)	Fluoroquinolones can be used in pregnancy as alternative antibiotics when indicated

Table 13-4 *continued*

Safety of Commonly Used Antimicrobials

Drug Name	Animal Data	Human Experience in Pregnancy	Comments
Imipenem **FDA pregnancy category: C**	No evidence of teratogenicity Increased embryologic loss has been observed in monkeys at 0.6 x maximal recommended human dose Maternal toxicity observed in pregnant rabbits and monkeys—weight loss, nausea, diarrhea, and death in some cases	Limited data in pregnancy have not shown an increased risk of malformations	Because of limited human data, use only for serious infections when potential benefits outweigh risk
Meropenem **FDA pregnancy category: B**	No evidence of teratogenicity	No clinical data in pregnancy	Because of limited human data, use only for serious infections when potential benefits outweigh risk
Metronidazole **FDA pregnancy category: B**	Animal (rodents) data indicate risk of carcinogenicity	In 4 studies (2 meta-analyses, a population-based case-control study, and a prospective controlled cohort study) no increased risk in birth defects was found (*Teratology* 2001;63:186; *Br J Obstet Gynecol* 1998;105:322; *Br J Clin Pharmacol* 1997; 44:179; *Am J Obstet Gynecol* 1995;172:525)	Most authorities consider use of metronidazole safe in 2nd and 3rd trimesters Use with caution in 1st trimester
Nitrofurantoin **FDA pregnancy category: B**	Not teratogenic or fetotoxic in rat and rabbit studies	In a surveillance study of Michigan Medicaid recipients, 1292 exposures to nitrofurantoin resulted in a 4.0% incidence of birth defects. These data did not support an association between nitrofurantoin and congenital defects (*Drugs in Pregnancy and Lactation*, 7th ed. Baltimore: Williams & Wilkins. 2005).	Most authorities consider use of nitrofurantoin safe in pregnancy

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Table 13-4 _continued_

Safety of Commonly Used Antimicrobials

Drug Name	Animal Data	Human Experience in Pregnancy	Comments
Penicillins **FDA pregnancy category: B**	Carcinogenicity demonstrated in rats after prolonged subcutaneous administration of penicillin in peanut oil	Several collaborative perinatal project reports involving >12,000 exposures to penicillin derivatives during 1st trimester indicated no association between penicillin derivative drugs and birth defects (_Drugs in Pregnancy and Lactation_, 7th ed. Baltimore: Williams & Wilkins. 2005).	Usually considered safe to use in pregnancy
Tetracyclines **FDA pregnancy category: D**	Teratogenic in animal studies, resulting in retardation of skeletal development and embryotoxicity	Contraindicated in pregnancy due to retardation of skeletal development and bone growth, enamel hypoplasia, and discoloration of fetal teeth. Maternal liver toxicity also reported (_Drugs in Pregnancy and Lactation_, 7th ed. Baltimore: Williams & Wilkins. 2005).	Contraindicated in pregnancy
Vancomycin **FDA pregnancy category: C**	No animal data	Manufacturer has received reports of use during pregnancy without adverse fetal effects	Consider use only when benefit outweighs risk of drug administration

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix
Source: _Medical Management of HIV Infection_, 16th ed. 2012. Durham, NC: Knowledge Source Solutions

Table 13-5

Drug Choice in Management of Selected Medical Conditions in Pregnancy

Drug, Class, or Indication	Concerns in Pregnancy	Recommendations
ACNE, SEVERE		
Retinoids (isotretinoin, etretinate) **FDA pregnancy category: X**	Isotretinoin is associated with spontaneous abortion (incidence up to 40%; major malformations (up to 15%); defects in multiple organ systems	Contraindicated in women who are pregnant, trying to become pregnant, or not using effective contraception. FDA restricted distribution program requires monthly pregnancy tests and recommends two simultaneous forms of effective contraception.
	Etretinate, which is used for treatment of acne and psoriasis, is stored in adipose tissue and has an extremely long half-life. In 30 cases of pregnancy exposure, 30% had congenital defects (*J Gynecol Obstet Biol Reprod* 1993; 22(1):43).	Patients taking etretinate are advised not to conceive for at least 2 y following cessation of treatment because of the drug's long half-life: etretinate has been detected in serum up to 3 y after cessation of chronic treatment
ASTHMA: It is safer for pregnant women with asthma to be treated than to have asthma symptoms and exacerbations, with possible maternal and fetal hypoxia		
Rescue therapy	Generally considered safe in pregnancy; no evidence of increased defects	Inhaled short-acting beta-2 agonist is therapy of choice; inhaled albuterol is preferred
Long-term control	Theophylline has more side effects, a narrow therapeutic index, and requires serum monitoring	Treatment depends on severity and response to medications; stepwise approach to therapy is recommended
	Few data on use of leukotriene receptor antagonists in pregnancy	In general, inhaled corticosteroids are first-line treatment, with budesonide preferred, followed by increasing doses of steroids and/or addition of long-acting beta-agonist (e.g., salmeterol)
	Low- to moderate-dose inhaled steroids effective and considered safe in pregnancy (inhaled budesonide FDA category B)	Severe asthma may require regular oral corticosteroid use to achieve adequate control
	Systemic steroids may increase risk of cleft palate; may also be associated with increased risk of maternal hypertension, glucose intolerance, and infection	
	Inhaled bronchodilators regarded as relatively safe in pregnancy	

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Table 13-5 continued

Drug Choice in Management of Selected Medical Conditions in Pregnancy

Drug, Class, or Indication	Concerns in Pregnancy	Recommendations
CANCER		
Antimetabolites (e.g., 5-fluorouracil, methotrexate, cytarabine) **FDA pregnancy category: X** (most)	In general, antineoplastic agents given in 1st trimester may have teratogenic effects. In 2nd and 3rd trimesters, they may result in intrauterine growth restriction.	Management of cancer in pregnancy depends on type of malignancy, stage and expected rate of progression, specific treatment needed, and gestational age
Alkylating agents (e.g., busulfan, chlorambucil, cyclophosphamide, mechlorethamine, cisplatin, bleomycin, vinblastine) **FDA pregnancy category: D** (most)	In general, antineoplastic agents given in 1st trimester may have teratogenic effects. In 2nd and 3rd trimesters, they may result in intrauterine growth restriction.	Successful treatment of cancer while continuing with a pregnancy may be possible in individual cases with expert consultation. Other options include deferral of treatment until after delivery (with possible early delivery) and termination of pregnancy.
Tamoxifen **FDA pregnancy category: D**	Little data in human pregnancy; some reports of defects Increased pregnancy loss in some animal studies. Results of animal studies suggest tamoxifen may cause developmental genital-tract abnormalities and that an interval of several years could exist between in utero exposure and clinical manifestations. Similar to DES in structure and activity in experimental systems	Avoid use in pregnancy and in women who are trying to conceive or are not using effective contraception Long-term follow-up recommended for exposed infants for adverse effects, including carcinogenicity

Table 13-5 *continued*

Drug Choice in Management of Selected Medical Conditions in Pregnancy

Drug, Class, or Indication	Concerns in Pregnancy	Recommendations
GLUCOSE INTOLERANCE/DIABETES: Pregnancy increases risk for glucose intolerance. No definite evidence that pregnant women on PIs are at increased risk for diabetes. Poorly controlled pregestational diabetes is associated with significant increased risk of adverse maternal and fetal outcomes, including worsening of end-organ damage, preeclampsia, congenital anomalies, intrauterine fetal death, excessive fetal growth, etc. Gestational diabetes is associated with increased risk for hypertensive disorders, macrosomia, newborn hyperbilirubinemia, shoulder dystocia and birth trauma, and need for cesarean delivery.		
Oral hypoglycemics	Not well studied in pregnancy	Use of all oral agents for control of type 2 diabetes during pregnancy should be limited and individualized
	Glyburide does not cross placenta; no evidence of adverse maternal and neonatal complications with use of this agent	Glyburide may be considered for treatment of gestational and type 2 diabetes mellitus
	Metformin has been used in pregnancy, but long-term effects of in utero exposure are not well studied	
Insulin	Insulin requirements increase throughout pregnancy	Safe to use in pregnancy
HYPERTENSION: Chronic HTN is associated with potentially significant maternal and fetal adverse outcomes: preterm delivery, intrauterine growth restriction, fetal death, placental abruption, as well as, when severe, maternal cardiac decompensation, renal deterioration, and CNS hemorrhage. HTN in pregnancy defined as SBP ≥140 and/or DBP ≥ 90. Pharmacologic treatment is generally indicated with SBP >150–160 and/or DBP >100–110 (treatment of milder HTN not recommended unless underlying cardiac or renal disease is present, due to concerns about interference with placental blood flow /fetal growth). Distinguish HTN from PEC, which typically appears at >20 wk gestation, is associated with proteinuria and, when severe, with seizures and hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). PEC alone is associated with normal BP prior to pregnancy and resolves after delivery; superimposed PEC is more common in setting of chronic HTN.		
Alpha-2 agonist (methyldopa)	Extensive experience in pregnancy and appears safe; limited effects on uteroplacental blood flow	Methyldopa safe to use in pregnancy and generally considered a first-line agent

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Table 13-5 continued

Drug Choice in Management of Selected Medical Conditions in Pregnancy

Drug, Class, or Indication	Concerns in Pregnancy	Recommendations
Alpha and beta blockers **Atenolol – FDA pregnancy category: D** Metoprolol	Beta-blockers associated with small-for-gestational-age infants	Labetalol (alpha and beta blocker) better tolerated and considered an alternative to methyldopa IV labetalol considered safer than IV hydralazine and does not decrease placental perfusion Atenolol not recommended In pregnancy. Data on other beta blockers is limited, but they may be considered if benefit outweighs potential risk. Monitor fetal growth
Calcium channel blockers	Limited experience in pregnancy but no evidence of increase in adverse effects or defects	Use if benefit considered to outweigh potential risk. Nifedipine is preferred agent, with most experience.
Diuretics	Concerns have been raised about effects on normal blood volume expansion in pregnancy, but recent meta-analysis found no increase in adverse perinatal effects (Can Fam Physician 2009;55(1):44)	Considered safe and effective and not contraindicated in pregnancy, except when uteroplacental perfusion is decreased (e.g., PEC, intrauterine growth restriction)
ACE inhibitors (e.g., captopril, enalapril, lisinopril) **FDA pregnancy category:** **C (1st trimester)** **D (2nd and 3rd trimesters)**	Associated with oligohydramnios, pulmonary hypoplasia, skull hypoplasia, fetal and neonatal renal failure and death Use in 1st trimester before development of renal tubular function not associated with defects	Contraindicated in pregnancy, particularly in 2nd and 3rd trimesters If patient becomes pregnant while taking an ACE inhibitor, alternative treatment is recommended; if not possible, fetus should be monitored closely with ultrasound
Angiotensin II receptor blockers **FDA pregnancy category:** **C (1st trimester)** **D (2nd and 3rd trimesters)**	Concerns similar to those for ACE inhibitors	Contraindicated in pregnancy, particularly in 2nd and 3rd trimesters If patient becomes pregnant while taking an ARB, alternative treatment is recommended; if not possible, fetus should be monitored closely with ultrasound

Table 13-5 continued

Drug Choice in Management of Selected Medical Conditions in Pregnancy

Drug, Class, or Indication	Concerns in Pregnancy	Recommendations
LIPID DISORDERS		
HMG-CoA reductase inhibitors (statins)	Possible increased risk for defects, particularly with atorvastatin, lovastatin, simvastatin, cerivastatin; also potential increased risk for other adverse neonatal outcomes	Contraindicated in pregnancy and should not be administered to women who are trying to become pregnant or not using effective contraception
FDA pregnancy category: X (all)		If pregnancy occurs, discontinue statin use. Treatment can resume after delivery; this interruption is not believed to adversely effect overall outcomes.

NAUSEA AND VOMITING: "Morning sickness" is very common, and generally resolves spontaneously toward end of 1st trimester. Hyperemesis gravidarum is at the extreme end of the spectrum and is a common indication for hospital admission during pregnancy; multiple gestation, molar pregnancy are risk factors. N/V first presenting after 9 wk gestation: rule out other conditions (e.g., gastroenteritis, pyelonephritis, hepatitis, pancreatitis, ulcer, drug toxicity/intolerance, acute fatty liver of pregnancy). Hyperemesis has been associated with Wernicke's encephalopathy due to vitamin B1 deficiency, with resultant risk of permanent neurologic disability and low-birth-weight infants. There are concerns about adherence/absorption in women with hyperemesis on ARVs.

Drug, Class, or Indication	Concerns in Pregnancy	Recommendations
Antihistamine H₁ receptor antagonists (Pyridoxine +/-doxylamine)	Good safety data for vitamin B6, doxylamine, phenothiazines, trimethobenzamide; data more limited for other agents but benefits considered to outweigh risk in severe N/V	Treatment of N/V in pregnancy with ginger has shown beneficial effects and may be considered a nonpharmacologic option
Phenothiazines	Droperidol associated with prolonged QT interval and potentially fatal arrhythmia	Step-wise additive management is recommended: vitamin B6 (pyridoxine), doxylamine, promethazine or dimenhydrinate, metoclopramide or trimethobenzamide, methylprednisolone or ondansetron
Benzamides		
Anticholinergics	Association between use of methylprednisolone use in 1st trimester and oral clefts, though risk is small	Use corticosteroids with caution and avoid if possible in 1st trimester
Metoclopramide		
5-hydroxytryptamine-3 inhibitors (ondansetron)		IV hydration as needed to prevent/treat dehydration; include dextrose and vitamins, especially thiamine, with prolonged vomiting
Corticosteroids		For severe and/or refractory hyperemesis, particularly with persistent weight loss, consider enteral or parenteral nutrition; enteral nutrition is preferred and may allow continued administration of ARVs

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Table 13-5 continued

Drug Choice in Management of Selected Medical Conditions in Pregnancy

Drug, Class, or Indication	Concerns in Pregnancy	Recommendations
PAIN		
Acetaminophen	No evidence of association with birth defects	Considered safe for short-term use in all stages of pregnancy Preferred analgesic/antipyretic during pregnancy
Aspirin	High-dose aspirin is FDA pregnancy category D in 3rd trimester; may increase risk for maternal or newborn hemorrhage, particularly at higher doses. Use of aspirin in 3rd trimester may result in premature closure of ductus arteriosus and may prolong gestation and labor.	Use of aspirin, especially of chronic or intermittent high doses, should generally be avoided in pregnancy; however, low-dose aspirin may be used for thromboprophylaxis in pregnancy in some high-risk conditions (e.g., antiphospholipid syndrome)
Nonsteroidal anti-inflammatory drugs **FDA pregnancy category: C→D** ≥30 wk gestation	3rd-trimester concerns include risk of premature closure of ductus arteriosus, oligohydramnios, possible increased risk of necrotizing enterocolitis or intraventricular hemorrhage, persistent pulmonary hypertension in neonate, and prolonged pregnancy	Generally avoid use of NSAIDs in pregnancy
Narcotics		Narcotic analgesics can be used short term in pregnancy. Avoid use of high doses for prolonged periods near term as neonatal respiratory depression and withdrawal can occur.
PSYCHIATRIC ILLNESS: Inadequate treatment may result in adverse maternal and infant outcomes, including nonadherence to care, increased substance use, premature birth, low-birth-weight infants, etc. Multidisciplinary management recommended. A single medication at a higher dose is recommended over multiple medications. Use nonpharmacologic treatment when feasible (e.g., psychotherapy). Electroconvulsive therapy is safe to use in pregnancy if needed for severe depression. When medication is needed, drugs with fewer metabolites, higher protein binding (decreases placental transfer), and fewer drug interactions are preferred. Select drugs based on history of efficacy and available reproductive safety information.		
Benzodiazepines (Clonazepam, lorazepam, alprazolam) **FDA pregnancy category: D**	Possible small increased incidence of cleft lip/palate; possible neonatal withdrawal syndrome	Do not abruptly withdraw in pregnancy. In general, avoid in pregnancy; use based on risk vs benefit considerations.

Table 13-5 continued

Drug Choice in Management of Selected Medical Conditions in Pregnancy

Drug, Class, or Indication	Concerns in Pregnancy	Recommendations
Nonbenzodiazepine anxiolytics and hypnotics (Buspirone, zolpidem)	Data limited in pregnancy but no increase in defects noted	
Antidepressants (SSRIs, SNRIs, tricyclics, etc.) (Fluoxetine, sertraline, citalopram, nortriptyline, bupropion)	No confirmed increased incidence of birth defects, though some conflicting data for SSRIs; some studies have reported increased risk of cardiac defects, specifically with paroxetine, though absolute risk small Decreased serum concentrations in pregnancy; possible neonatal withdrawal syndrome; unconfirmed association reported with SSRIs and newborn persistent pulmonary hypertension Limited data for bupropion but no evidence of increase in defects	Individualize treatment based on risk vs benefits; avoid use of paroxetine if possible but also avoid abrupt discontinuation (associated with withdrawal symptoms) Consider fetal echocardiography with early-pregnancy exposure to paroxetine
Lithium **FDA pregnancy category: D**	Increased incidence of heart defects; decreased serum concentrations in pregnancy; potential increased risk for lithium toxicity in neonate	Use only if benefits thought to outweigh risks If indicated, use sustained-release formulation Monitor lithium levels Consider fetal echocardiography
Antipsychotics	No confirmed increase in birth defects; possible risk for neuroleptic malignant syndrome and intestinal obstruction in neonate	Minimize doses to limit need to utilize medications for extrapyramidal side effects Atypical antipsychotics (e.g., clozapine, olanzapine, quetiapine, risperidone) generally better tolerated and may be more effective, but have very limited safety data in pregnancy; avoid routine use Options for typical antipsychotics include haloperidol, trifluoperazine, perphenazine

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Table 13-5 continued

Drug Choice in Management of Selected Medical Conditions in Pregnancy

Drug, Class, or Indication	Concerns in Pregnancy	Recommendations
SEIZURE DISORDERS		
Phenytoin **Phenobarbital** **Carbamazepine**	Increased incidence in both major and minor malformations associated with all anti-seizure medications; most common major malformations are NTDs, congenital heart and urinary-tract defects, skeletal abnormalities, and cleft palate	Several anticonvulsants also used in treatment of bipolar disorder
Valproate	Valproate associated with higher rates of defects and may have increased placental transfer	If anti-seizure medications cannot be withdrawn in pregnancy, administer most suitable medication for seizure type. No consensus exists as to which medication is most teratogenic; with exception of valproate, most effective agent for individual patient should be given.
Lamotrigine	Lamotrigine may have lower risk of defects	Use lowest effective dose; if possible avoid combination therapy to limit risk of teratogenicity
Topiramate	In-utero exposure to anti-seizure medications may be linked to impaired cognitive outcomes in childhood	Monitor drug levels in plasma throughout pregnancy
All FDA pregnancy category D (except lamotrigine: category C)	Limited human information on fetal risks of newer drugs (gabapentin, felbamate, tiagabine, levetiracetam, pregabalin)	If possible avoid valproate in pregnant women and in women who are trying to conceive or are not using effective contraception
	Decreased serum concentrations in pregnancy	Consider increased preconception folate supplementation (4 mg qd) for women on anti-seizure medications, particularly those on valproate or carbamazepine, to reduce risk of NTDs
	Oral hormonal contraceptive failure before or after pregnancy may be increased due to drug interaction with cytochrome P450-inducing anti-seizure medications (carbamazepine, phenytoin, phenobarbital, felbamate, oxcarbazepine, topiramate), resulting in decreased hormone levels	Oral vitamin K (10mg/d) supplementation in last month of pregnancy recommended in patients on enzyme-inducing anti-epileptic drugs (e.g phenytoin, phenobarbital, carbamazepine)
		Prenatal surveillance for defects with serum alpha-fetoprotein; fetal echocardiography and detailed ultrasound of fetal anatomy

Table 13-5 *continued*

Drug Choice in Management of Selected Medical Conditions in Pregnancy

Drug, Class, or Indication	Concerns in Pregnancy	Recommendations
THYROID DISEASE		
Thioamides (for hyperthyroidism; methimazole, propylthiouracil) **FDA pregnancy category: D**	Untreated hyperthyroidism associated with increased risk for preterm delivery, severe preeclampsia, heart failure, low birth weight, possible fetal loss. Neonates may be at risk of hyper- or hypothyroidism due to transplacental passage of antibodies in Graves disease or autoimmune thyroiditis. Recent data suggest no significant increase in defects with either PTU or methimazole	Either PTU or methimazole can be used to treat pregnant women with hyperthyroidism. Beta blockers may be used during pregnancy to ameliorate symptoms of thyrotoxicosis until thioamides decrease thyroid hormone levels. Iodine 131 contraindicated in pregnant women because of risk of fetal thyroid ablation
Levothyroxine (for hypothyroidism)	Untreated hypothyroidism associated with increased risk of preeclampsia and possible fetal growth restriction	Safe to use in pregnancy Treatment of hypothyroidism using levothyroxine in pregnant women is same as for nonpregnant women
VENOUS THROMBOEMBOLISM (TREATMENT OR PROPHYLAXIS)		
Low-molecular-weight heparin (enoxaparin, dalteparin, tinzaparin) **Unfractionated heparin** **Warfarin – FDA pregnancy category: X**	Warfarin has been associated with fetal hemorrhage and anomalies in all three trimesters	LMWH is preferred UFH is alternative; consider transition to UFH at 36 wk gestation Protamine sulfate can be used if rapid reversal of anticoagulant effect is needed Also consider graduated compression stockings in pregnancy and pneumatic compression boots in intrapartum period Warfarin contraindicated in pregnancy

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix. FDA pregnancy categories noted only for those drugs that are category D or X
Source: ACOG

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Table 13-6

Alternative/Complementary Medication Concerns in Pregnancy

Substance	Animal Data and Human Experience	Use in Pregnancy, Possible Health Hazards, Comments
Comfrey (herb)	No animal data No human experience in pregnancy	Avoid; possible obstruction of blood flow to liver; may lead to death
Chaparral (herb; used in traditional American Indian medicine)	No animal data No human experience in pregnancy	Avoid; liver disease; may be irreversible
Germander (herb)	No animal data No human experience in pregnancy	Avoid; liver disease; may lead to death
Germanium (mineral)	No animal data No human experience in pregnancy	Avoid; kidney damage; possibly death
L-tryptophan (amino acid)	No animal data No human experience in pregnancy	Avoid; eosinophilic myalgia syndrome, a potentially fatal blood dyscrasia FDA has limited import of L-tryptophan into U.S.
Lobelia (herb; Indian tobacco)	No animal data No human experience in pregnancy	Avoid; respiratory distress, tachycardia, hypotension; possibly coma and death at higher doses
Ma-huang (*Ephedra sinica*)	No animal data No human experience in pregnancy	Avoid; FDA warns of possible health hazards, including high BP, irregular heartbeat, nerve damage, injury, insomnia, tremor, headache, seizure, heart attack, stroke, death FDA has received >500 reports of adverse events, including 8 fatalities (MMWR 1996;45:689)
Magnolia-Stephania (herbs)	No animal data No human experience in pregnancy	Avoid; renal failure; possibly irreversible

Table 13-6 *continued*

Alternative/Complementary Medication Concerns in Pregnancy

Substance	Animal Data and Human Experience	Use in Pregnancy, Possible Health Hazards, Comments
Niacin (in doses >500 mg immediate-release or >750 mg sustained-release)	No animal data No human experience in pregnancy	Avoid use of high doses in pregnancy GI symptoms (nausea, vomiting, diarrhea, abdominal cramps); liver disease
St. John's wort (*Hypericum perforatum*)	No animal data No human experience in pregnancy	Meta-analysis suggests St. John's wort more effective than placebo and as effective as low-dose tricyclic antidepressants for short-term management of mild to moderately severe depression (*J Nerv Ment Dis* 1999;187(9):532) Due to lack of data in pregnancy, routine use of St. John's wort cannot be recommended Major drug interaction: indinavir trough concentration decreases by 81% when co-administered with St. John's wort. This interacton applies to all PIs and NNRTIs.
Selenium (in doses >800–1000 mcg/d)	No animal data No human experience in pregnancy	Avoid high doses in pregnancy; possible tissue damage*
Slimming/dieter's tea	No animal data No human experience in pregnancy	Avoid; nausea, diarrhea, vomiting, stomach cramps, chronic constipation, fainting; possibly death

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Table 13-6 continued

Alternative/Complementary Medication Concerns in Pregnancy

Substance	Animal Data and Human Experience	Use in Pregnancy, Possible Health Hazards, Comments
Vitamin A	Animal data: known teratogen at high doses	Until more data are available it is prudent to consume only RDA of 8000 IU, which can be obtained through a balanced diet
	Human data: Double-blinded randomized trial of low-dose supplementation with vitamin A or beta-carotene (7000 mcg retinol equivalent) in malnourished pregnant women reported a 40% decrease in newborn mortality (BMJ 1999;318(7183):570)	
	In a prospective case-controlled study of 423 exposures to 10,000 IU vitamin A during first 9 wk of pregnancy, an increased risk of major malformations was not reported (Teratology 1999;59:7)	
Vitamin B6 (in doses >100 mg/d)	No animal data	Avoid high doses in pregnancy; ataxia, peripheral neuropathy
	No human experience in pregnancy	
Willow bark (herb)	No animal data	Avoid; allergic reaction
	No human experience in pregnancy	Although marketed as aspirin-free, contains a precursor of aspirin, with subsequent conversion to aspirin
Wormwood (herb)	No animal data	Avoid; neurological symptoms, paresthesia, delirium, paralysis
	No human experience in pregnancy	

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix
Source: *Medical Management of HIV Infection*, 16th ed. 2012. Durham, NC: Knowledge Source Solutions

Table 13-7

Table 13-7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency

Antiretrovirals Generic Name (Abbreviation)/Trade Name	Usual Daily Dose	Dosing in Renal Insufficiency (Including with chronic ambulatory peritoneal dialysis and hemodialysis)			Dosing in Hepatic Impairment	

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Stribild should not be initiated in patients with CrCl <70 mL/min. Use of the following fixed-dose combinations is not recommended in patients with CrCl <50 mL/min: Atripla, Combivir, Stribild, Trizivir, or Epzicom. Use of Truvada is not recommended in patients with CrCL <30 mL/min.

Abacavir (ABC)/Ziagen
Usual Daily Dose: 300 mg PO BID
Dosing in Renal Insufficiency: No dosage adjustment necessary
Dosing in Hepatic Impairment:

Child-Pugh Score	Dose
5–6	200 mg PO BID (use oral solution)
>6	Contraindicated

Didanosine EC (ddI)/Videx EC
Usual Daily Dose: Body weight ≥60 kg: 400 mg PO once daily; Body weight <60 kg: 250 mg PO once daily
Dosing in Hepatic Impairment: No dosage adjustment necessary

CrCL (mL/min)	Dose (once daily) ≥60 kg	<60 kg
30–59	200 mg	125 mg
10–29	125 mg	125 mg
<10, HD, CAPD	125 mg	use ddI oral solution

Didanosine oral solution (ddI)/Videx
Usual Daily Dose: Body weight ≥60 kg: 200 mg PO BID or 400 mg PO once daily; Body weight <60 kg: 250 mg PO once daily or 125 mg PO BID
Dosing in Hepatic Impairment: No dosage adjustment necessary

CrCL (mL/min)	Dose (once daily) ≥60 kg	<60 kg
30–59	200 mg	150 mg
10–29	150 mg	100 mg
<10, HD, CAPD	100 mg	75 mg

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Table 13-7 continued

Table 13-7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency

Antiretrovirals Generic Name (Abbreviation)/ Trade Name	Usual Daily Dose	Dosing in Renal Insufficiency (Including with chronic ambulatory peritoneal dialysis and hemodialysis)			Dosing in Hepatic Impairment

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS continued

Emtricitabine (FTC)/Emtriva
200 mg oral capsule once daily **or** 240 mg (24 mL) oral solution once daily

	Dose	
CrCL (mL/min)	Capsule	Solution
30–49	200 mg q48h	120 mg q24h
15–29	200 mg q72h	80 mg q24h
<15 or on HD*	200 mg q96h	60 mg q24h

*On dialysis days, take dose after HD session.

Dosing in Hepatic Impairment: No dosage recommendation

Lamivudine (3TC)/Epivir
300 mg PO once daily **or** 150 mg PO BID

CrCL (mL/min)	Dose
30–49	150 mg q24h
15–29	1 × 150 mg, then 100 mg q24h
5–14	1 × 150 mg, then 50 mg q24h
<5 or on HD*	1 × 50 mg, then 25 mg q24h

*On dialysis days, take dose after HD session.

Dosing in Hepatic Impairment: No dosage adjustment necessary

Table 13-7 *continued*

Table 13-7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency

Antiretrovirals Generic Name (Abbreviation)/Trade Name	Usual Daily Dose	Dosing in Renal Insufficiency (Including with chronic ambulatory peritoneal dialysis and hemodialysis)	Dosing in Hepatic Impairment
NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS continued			
Stavudine (d4T)/Zerit	**Body weight ≥60 kg:** 40 mg PO BID **Body weight <60 kg:** 30 mg PO BID	**Dose** CrCL (mL/min) **≥60 kg** **<60 kg** 26–50 20 mg q12h 15 mg q12h 10–25 or on HD* 20 mg q24h 15 mg q24h *On dialysis days, take dose after HD session.	No dosage recommendation
Tenofovir (TDF)/Viread	300 mg PO once daily	**Dose** CrCL (mL/min) 30–49 300 mg q48h 10–29 300 mg twice weekly (every 72–96 hours) <10 and not on HD Not recommended On HD* 300 mg q7d *On dialysis days, take dose after HD session.	No dosage adjustment necessary
Emtricitabine (FTC) + **Tenofovir** (TDF)/Truvada	1 tablet PO once daily	**Dose** CrCL (mL/min) 30–49 1 tablet q48h <30 or on HD Not recommended	No dosage recommendation

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Table 13-7 continued

Table 13-7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency

Antiretrovirals Generic Name (Abbreviation)/ Trade Name	Usual Daily Dose	Dosing in Renal Insufficiency (Including with chronic ambulatory peritoneal dialysis and hemodialysis)	Dosing in Hepatic Impairment
NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS continued			
Zidovudine (AZT, ZDV)/ Retrovir	300 mg PO BID	CrCl (mL/min): <15 or HD* — Dose: 100 mg TID **or** 300 mg once daily. *On dialysis days, take dose after HD session.	No dosage recommendation
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS			
Delavirdine (DLV)/Rescriptor	400 mg PO TID	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment.
Efavirenz (EFV)/Sustiva	600 mg PO once daily, at or before bedtime	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment.
Efavirenz (EFV) + **Tenofovir** (TDF) + **Emtricitabine** (FTC)/Atripla	1 tablet PO once daily	Not recommended for use in patients with CrCl <50 mL/min. Instead use the individual drugs of the fixed-dose combination and adjust TDF and FTC doses according to CrCl level.	No dosage recommendation; use with caution in patients with hepatic impairment.
Etravirine (ETR)/Intelence	200 mg PO BID	No dosage adjustment necessary	*Child-Pugh Class A or B:* No dosage adjustment. *Child-Pugh Class C:* No dosage recommendation

Table 13-7 continued

Table 13-7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency

Antiretrovirals Generic Name (Abbreviation)/ Trade Name	Usual Daily Dose	Dosing in Renal Insufficiency (Including with chronic ambulatory peritoneal dialysis and hemodialysis)	Dosing in Hepatic Impairment
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS continued			
Nevirapine (NVP)/Viramune or Viramune XR	200 mg PO BID **or** 400 mg PO once daily (using Viramune XR formulation)	*Patients on HD:* limited data; no dosage recommendation	*Child-Pugh Class A:* No dosage adjustment *Child-Pugh Class B or C:* Contraindicated
Rilpivirine (RPV)/Edurant	25 mg PO once daily	No dosage adjustment necessary	*Child-Pugh Class A or B:* No dosage adjustment *Child-Pugh Class C:* No dosage recommendation
Rilpivirine (RPV) + **Tenofovir** (TDF) + **Emtricitabine** (FTC)/Complera	1 tablet PO once daily	Not recommended for use in patients with CrCl <50 mL/min. Instead use the individual drugs of the fixed-dose combination and adjust TDF and FTC doses levels according to CrCl level.	*Child-Pugh Class A or B:* No dosage adjustment *Child-Pugh Class C:* No dosage recommendation
PROTEASE INHIBITORS			
Atazanavir (ATV)/Reyataz	400 mg PO once daily **or** (ATV 300 mg + RTV 100 mg) PO once daily	No dosage adjustment for patients with renal dysfunction not requiring HD *ARV-naïve patients on HD:* (ATV 300 mg + RTV 100 mg) once daily *ARV-experienced patients on HD:* ATV or RTV-boosted ATV not recommended	**Child-Pugh Class** — **Dose** B — 300 mg once daily C — Not recommended RTV boosting is ***not*** recommended in patients with hepatic impairment (Child-Pugh Class B or C).

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Table 13-7 *continued*

Table 13-7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency

Antiretrovirals Generic Name (Abbreviation)/ Trade Name	Usual Daily Dose	Dosing in Renal Insufficiency (Including with chronic ambulatory peritoneal dialysis and hemodialysis)	Dosing in Hepatic Impairment
PROTEASE INHIBITORS continued			
Darunavir (DRV)/Prezista	(DRV 800 mg + RTV 100 mg) PO once daily (ARV-naïve patients only) **or** (DRV 600 mg + RTV 100 mg) PO BID	No dosage adjustment necessary	*Mild-to-moderate hepatic impairment:* No dosage adjustment *Severe hepatic impairment:* Not recommended
Fosamprenavir (FPV)/Lexiva	1400 mg PO BID **or** (FPV 1400 mg + RTV 100–200 mg) PO once daily **or** (FPV 700 mg + RTV 100 mg) PO BID	No dosage adjustment necessary	*PI-naïve patients only:* **Child-Pugh Score** / **Dose** 5–9 / 700 mg BID 10–15 / 350 mg BID *PI-naïve or PI-experienced patients:* **Child-Pugh Score** / **Dose** 5–6 / 700 mg BID + RTV 100 mg once daily 7–9 / 450 mg BID + RTV 100 mg once daily 10–15 / 300 mg BID + RTV 100 mg once daily
Indinavir (IDV)/Crixivan	800 mg PO q8h	No dosage adjustment necessary	*Mild-to-moderate hepatic insufficiency because of cirrhosis:* 600 mg q8h

Table 13-7 *continued*

Table 13-7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency

Antiretrovirals Generic Name (Abbreviation)/ Trade Name	Usual Daily Dose	Dosing in Renal Insufficiency (Including with chronic ambulatory peritoneal dialysis and hemodialysis)	Dosing in Hepatic Impairment
PROTEASE INHIBITORS continued			
Lopinavir/ ritonavir (LPV/r) Kaletra	400/100 mg PO BID **or** 800/200 mg PO once daily	Avoid once-daily dosing in patients on HD	No dosage recommendation; use with caution in patients with hepatic impairment.
Nelfinavir (NFV)/Viracept	1250 mg PO BID	No dosage adjustment necessary	*Mild hepatic impairment:* No dosage adjustment *Moderate-to-severe hepatic impairment:* Do not use
Ritonavir (RTV)/Norvir	*As a PI-boosting agent:* 100–400 mg per day	No dosage adjustment necessary	Refer to recommendations for the primary PI.
Saquinavir (SQV)/Invirase	(SQV 1000 mg + RTV 100 mg) PO BID	No dosage adjustment necessary	*Mild-to-moderate hepatic impairment:* Use with caution *Severe hepatic impairment:* Contraindicated
Tipranavir (TPV)/Aptivus	(TPV 500 mg + RTV 200 mg) PO BID	No dosage adjustment necessary	*Child-Pugh Class A:* Use with caution *Child-Pugh Class B or C:* Contraindicated

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Table 13-7 continued

Table 13-7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency

Antiretrovirals Generic Name (Abbreviation)/ Trade Name	Usual Daily Dose	Dosing in Renal Insufficiency (Including with chronic ambulatory peritoneal dialysis and hemodialysis)	Dosing in Hepatic Impairment
INTEGRASE INHIBITORS			
Raltegravir (RAL)/Isentress	400 mg BID	No dosage adjustment necessary	*Mild-to-moderate hepatic insufficiency:* No dosage adjustment necessary *Severe hepatic insufficiency:* No recommendation
Elvitegravir (EVG)/ **Cobicistat** (COBI)/ **Tenofovir** (TDF)/ **Emtricitabine** (FTC)/Stribild (only available as a co-formulated product)	1 tablet once daily	EVG/COBI/TDF/FTC **should not be initiated** in patients with CrCl <70 mL/min. Discontinue EVG/COBI/TDF/FTC if CrCl declines to <50 mL/min while patient is on therapy.	*Mild-to-moderate hepatic insufficiency:* No dosage adjustment necessary *Severe hepatic insufficiency:* Not recommended
FUSION INHIBITOR			
Enfuvirtide (T20)/Fuzeon	90 mg subcutaneous BID	No dosage adjustment necessary	No dosage adjustment necessary

Table 13-7 *continued*

Table 13-7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency

Antiretrovirals Generic Name (Abbreviation)/ Trade Name	Usual Daily Dose	Dosing in Renal Insufficiency (Including with chronic ambulatory peritoneal dialysis and hemodialysis)	Dosing in Hepatic Impairment
CCR5 ANTAGONIST			
Maraviroc (MVC)/ Selzentry	The recommended dose differs based on concomitant medications and potential for drug-drug interactions.	**CrCl <30 mL/min or on HD** *Without potent CYP3A inhibitors or inducers:* 300 mg BID; reduce to 150 mg BID if postural hypotension occurs *With potent CYP3A inducers or inhibitors:* Not recommended	No dosage recommendations. Concentrations will likely be increased in patients with hepatic impairment.

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

* Approved adult dose, but for most PIs lower doses are usually used with RTV boosting

** Prediction based on PK principles. Drugs likely to be removed have a Vd <0.7 L/kg, protein binding <80%, and size <1500 Dalton

Source: Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

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Table 13-8

Drugs That Should Not Be Used with Antiretroviral Agents

This table only lists drugs that should not be co-administered at any dose and regardless of ritonavir (RTV) boosting.

Anti-retroviral Agents[a,b]	Cardiac Agents	Lipid-Lowering Agents	Antimyco-bacterials	Gastro-intestinal Drugs	Neuro-leptics	Psycho-tropics	Ergot Derivatives (vasoconstrictors)	Herbs	Anti-retroviral Agents	Others
				Drug Categories						
ATV +/– RTV	amiodarone dronedarone	lovastatin simvastatin	rifampin rifapentine[c]	cisapride	pimozide	midazolam[e] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	ETR NVP	alfuzosin irinotecan salmeterol sildenafil for PAH
DRV/r	amiodarone dronedarone	lovastatin simvastatin	rifampin rifapentine[c]	cisapride	pimozide	midazolam[e] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	none	alfuzosin salmeterol sildenafil for PAH
FPV +/– RTV	amiodarone dronedarone flecainide propafenone	lovastatin simvastatin	rifampin rifapentine[c]	cisapride	pimozide	midazolam[e] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	ETR	alfuzosin salmeterol sildenafil for PAH

Table 13-8 *continued*

Drugs That Should Not Be Used with Antiretroviral Agents

This table only lists drugs that should not be co-administered at any dose and regardless of ritonavir (RTV) boosting.

Anti-retroviral Agents[a,b]	Cardiac Agents	Lipid-Lowering Agents	Antimyco-bacterials	Gastro-intestinal Drugs	Neuro-leptics	Psycho-tropics	Ergot Derivatives (vasoconstrictors)	Herbs	Anti-retroviral Agents	Others
				Drug Categories						
LPV/r	amiodarone dronedarone	lovastatin simvastatin	rifampin[d] rifapentine[c]	cisapride	pimozide	midazolam[e] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	none	alfuzosin salmeterol sildenafil for PAH
SQV/r	amiodarone dronedarone dofetilide flecainide lidocaine propafenone quinidine	lovastatin simvastatin	rifampin[d] rifapentine[c]	cisapride	pimozide	midazolam[e] triazolam trazodone	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort garlic supplements	none	alfuzosin salmeterol sildenafil for PAH
TPV/r	amiodarone dronedarone flecainide propafenone quinidine	lovastatin simvastatin	rifampin rifapentine[c]	cisapride	pimozide	midazolam[e] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	ETR	alfuzosin salmeterol sildenafil for PAH

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Table 13-8 *continued*

Drugs That Should Not Be Used with Antiretroviral Agents

This table only lists drugs that should not be co-administered at any dose and regardless of ritonavir (RTV) boosting.

Anti-retroviral Agents[a,b]	Cardiac Agents	Lipid-Lowering Agents	Antimyco-bacterials	Gastro-intestinal Drugs	Neuro-leptics	Psycho-tropics	Ergot Derivatives (vasoconstrictors)	Herbs	Anti-retroviral Agents	Others
				Drug Categories						
EFV	none	none	rifapentine[c]	cisapride	pimozide	midazolam[e] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St John's wort	other NNRTIs	none
ETR	none	none	rifampin rifapentine[c]	none	none	none	none	St John's wort	unboosted PIs ATV/r, FPV/r, or TPV/r other NNRTIs	carbama-zepine pheno-barbital phenytoin clopido-grel
NVP	none	none	rifapentine[c]	none	none	none	none	St. John's wort	ATV +/− RTV other NNRTIs	ketocon-azole

Table 13-8 *continued*

Drugs That Should Not Be Used with Antiretroviral Agents

This table only lists drugs that should not be co-administered at any dose and regardless of ritonavir (RTV) boosting.

Anti-retroviral Agents[a,b]	Cardiac Agents	Lipid-Lowering Agents	Antimyco-bacterials	Gastro-intestinal Drugs	Neuro-leptics	Psycho-tropics	Ergot Derivatives (vasoconstrictors)	Herbs	Anti-retroviral Agents	Others
				Drug Categories						
RPV	none	none	rifabutin rifampin rifapentine[c]	proton pump inhibitors	none	none	none	St. John's wort	other NNRTIs	carbama-zepine oxcarba-zepine pheno-barbital phenytoin
MVC	none	none	rifapentine[c]	none	none	none	none	St. John's wort	none	none

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Table 13-8 continued

Drugs That Should Not Be Used with Antiretroviral Agents

This table only lists drugs that should not be co-administered at any dose and regardless of ritonavir (RTV) boosting.

Anti-retroviral Agents[a,b]	Drug Categories									
	Cardiac Agents	Lipid-Lowering Agents	Antimyco-bacterials	Gastro-intestinal Drugs	Neuro-leptics	Psycho-tropics	Ergot Derivatives (vasoconstrictors)	Herbs	Anti-retroviral Agents	Others
EVG/ COBI/ TDF/FTC	none	lovastatin simvastatin	rifabutin rifampin rifapentine[c]	cisapride	pimozide	midazolam[e] triazolam	dihydroergotamine ergotamine methylergonovine	St. John's wort	All other ARVs	alfuzosin sildenafil for PAH

[a] DLV, IDV, NFV, and RTV (as sole PI) are not included in this table. Refer to the appropriate FDA package insert for information regarding DLV-, IDV-, NFV-, and RTV (as sole PI)-related drug interactions.

[b] Certain listed drugs are contraindicated on the basis of theoretical considerations. Thus, drugs with narrow therapeutic indices and suspected metabolic involvement with CYP450 3A, 2D6, or unknown pathways are included in this table. Actual interactions may or may not occur in patients.

[c] HIV-infected patients treated with rifapentine have a higher rate of tuberculosis (TB) relapse than those treated with other rifamycin-based regimens. Therefore an alternative agent to rifapentine is recommended.

[d] A high rate of Grade 4 serum transaminase elevation was seen when a higher dose of RTV was added to LPV/r or SQV or when double-dose LPV/r was used with rifampin to compensate for rifampin's induction effect and therefore, these dosing strategies should not be used.

[e] Use of oral midazolam is contraindicated. Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation.

Suggested alternatives to:

- **Lovastatin, simvastatin:** Fluvastatin, pitavastatin, and pravastatin (except for pravastatin with DRV/r) have the least potential for drug-drug interactions (see Table 15a). Use atorvastatin and rosuvastatin with caution; start with the lowest possible dose and titrate based on tolerance and lipid-lowering efficacy.

- **Rifampin:** Rifabutin (with dosage adjustment, see Tables 15a and 15b)

- **Midazolam, triazolam:** temazepam, lorazepam, oxazepam

Source: *Medical Management of HIV Infection*, 16th ed., 2012. Durham, NC: Knowledge Source Solutions

Table 13-9

Recommended Dose Modifications with Boosted Protease Inhibitors, Non-Nucleoside Reverse Transcriptase Inhibitors, Integrase Inhibitors, and CCR5 Antagonists

Class	Agent	ART/Modification
Antifungal agents	Itraconazole	• All PIs: Monitor for toxicities • Itraconazole ≤200 mg/d • EFV, NVP, ETR: ↓ itraconazole possible dose adjustments may be needed • EVG: ↑ itraconazole: itraconazole ≤200 mg/d • MVC: 150 mg bid • MVC: 150 mg bid
	Ketoconazole	• LPV/r, TPV/r, FPV/r, DRV/r, RTV: ketoconazole ≤200 mg/d • FPV: ≤400 mg/d • NVP: Consider fluconazole as an alternative • RPV AUC ↑ 49%; ketoconazole AUC ↓ 24%; monitor for breakthrough fungal infection
	Voriconazole	• EFV: contraindicated at standard doses • NPV: ↓ voriconazole possible, ↑ NVP possible: monitor for toxicity and antifungal response • All boosted PIs: significant ↓ in voriconazole levels: do not co-administer unless benefit outweighs risk • EVG: ↑ voriconazole: consider drug levels and adjust dose as needed • MVC: 150 mg bid
	Fluconazole	• ETR: AUC ↑ 86%; use with caution • NVP: AUC ↑; monitor for ADR or use alternative • PI/r; EFV, RAL, MVC: Use standard dose • With TPV/r co-administration, do not exceed fluconazole 200 mg/d

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Table 13-9 continued

Recommended Dose Modifications with Boosted Protease Inhibitors, Non-Nucleoside Reverse Transcriptase Inhibitors, Integrase Inhibitors, and CCR5 Antagonists

Class	Agent	ART/Modification
Antifungal agents (continued)	Posaconazole	• ATV: concentrations may be increased; monitor for adverse effects • Do not co-administer with unboosted FPV • EFV: ↓ posaconazole level: avoid co-administration unless benefits outweigh risk • EVG: ↑ posaconazole: monitor posaconazole drug levels if co-administered
Anticonvulsants	Phenobarbital Phenytoin Carbamazepine	• Phenobarbital may decrease concentrations of all PIs: consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response • Carbamazepine: may decrease PI levels significantly (except for DRV): consider alternate anticonvulsant or monitor drug levels of both drugs and assess virologic response; DRV: monitor anticonvulsant level and adjust dose as needed • MVC: 600 mg bid if used without strong CYP3A inhibitor • Phenobarbital, carbamazepine, phenytoin: do not co-administer with ETR, RPV; NVP or EFV: ↓ anticonvulsant and ARV: monitor drug levels of both drugs, monitor virologic response and consider alternative anticonvulsant • EVG: ↑ carbamazepine possible: consider alternate anticonvulsant • Phenytoin: all boosted PIs ↓ phenytoin; ↓ ARV level with ATV/r, DRV/r, SQV/r, TPV/r, LPV/r: consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response
	Valproic acid	• LPV/r: AUC ↑ 75%; monitor valproic acid levels and virologic response; monitor for LPV-related toxicity
	Lamotrigine	• LPV/r: lamotrigine AUC ↓ 50%; dose increase of lamotrigine may be needed

Table 13-9 *continued*

Recommended Dose Modifications with Boosted Protease Inhibitors, Non-Nucleoside Reverse Transcriptase Inhibitors, Integrase Inhibitors, and CCR5 Antagonists

Class	Agent	ART/Modification
Narcotics/Treatment for Opioid Dependence	Methadone	• NVP, EFV: May significantly decrease methadone concentrations. Monitor for withdrawal symptoms. ↑ methadone dose often needed • RPV: Methadone ↓ 26%: monitor for withdrawal symptoms • TPV/r, LPV/r, SQV/r, DRV/r, ATV/r, SQV/r: May decrease methadone levels and require monitoring for withdrawal symptoms, but clinical significance is unclear
	Oxycodone	• LPV/r: ↑ oxycodone AUC 2.6 fold: monitor for opioid-related adverse effects. Oxycodone dose reduction may be necessary
	Buprenorphine	• ATV/r: ↑ buprenorphine 66%: monitor for sedation. Buprenorphine dose reduction may be necessary • TPV/r: ↓ TPV: consider monitoring TPV level

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Table 13-9 *continued*

Recommended Dose Modifications with Boosted Protease Inhibitors, Non-Nucleoside Reverse Transcriptase Inhibitors, Integrase Inhibitors, and CCR5 Antagonists

Class	Agent	ART/Modification
Antimycobacterial agents	Rifabutin‡	• All PIs with RTV boosting: standard PI dose; Rifabutin dose 150 mg/dg or 300 mg 3x/wk. consider TDM • EFV: RBT 450–600 mg/d or 600 mg 3x/wk • MVC: 300 mg bid; 150 mg bid with PI co-administration • EVG: ↓ EVG: do not co-administer • ETR: rifabutin 300 mg qd, ETR SD; if ETR used with PI/r, rifabutin should not be co-administered • RPV: Contraindicated; do not co-administer
	Rifampin	• All PIs and NNRTIs contraindicated except EFV (600 mg/d) using SDs of rifampin. Monitor virologic response • MVC: co-administration not recommended • RAL: Avoid or use RAL 800 mg bid; monitor virologic response • EVG: ↓ EVG: do not co-administer

Table 13-9 *continued*

Recommended Dose Modifications with Boosted Protease Inhibitors, Non-Nucleoside Reverse Transcriptase Inhibitors, Integrase Inhibitors, and CCR5 Antagonists

Class	Agent	ART/Modification
	Simvastatin	• EVG: do not co-administer
	Lovastatin	• All boosted PIs: Contraindicated • EFV, NVP, ETR: ↓ statin: adjust statin dose according to lipid response
	Atorvastatin	• All PIs may substantially increase levels. Use lowest possible dose of atorvastatin. • TPV/r: do not co-administer • EFV, ETR: May reduce atorvastatin levels; adjust atorvastatin dose according to lipid responses • EVG: titrate statin dose slowly and use lowest dose possible
Lipid-lowering agents	Pravastatin	• No dose change with most agents • DRV/r: May ↑ statin AUC 81%: use lowest possible starting dose of pravastatin with careful monitoring • EFV: ↓ statin level: Adjust statin dose according to lipid response
	Rosuvastatin	• ATV/r, LPV/r, DRV/r, SQV/r: titrate rosuvastatin dose carefully and use lowest necessary dose; monitor for toxicities • EVG: ↑ rosuvastatin level: titrate statin dose slowly and use lowest dose possible • RAL, MVC: Interaction unlikely
Calcium channel blockers (CCBs)		• All PIs: ↑ CCB level: Use with caution, titrate CCB dose and monitor closely; ECG monitoring recommended when CCB used with ATV • EFV, NVP: ↓ CCB level possible: titrate CCB dose based on clinical response • EVG: ↑ CCB level possible: co-administer with caution. Monitor for CCB efficacy and toxicity

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Table 13-9 continued

Recommended Dose Modifications with Boosted Protease Inhibitors, Non-Nucleoside Reverse Transcriptase Inhibitors, Integrase Inhibitors, and CCR5 Antagonists

Class	Agent	ART/Modification
Contraceptives (See table 7-4)		
	Budesonide (systemic)	• All PIs: ↓ PI levels, ↑ glucocorticoids: do not co-administer unless benefits outweigh risks: co-administration can result in adrenal insufficiency, including Cushing's syndrome
	Budesonide (inhaled or intranasal)	• All PI/r: ↑ glucocorticoids (see above recommendation)
Corticosteroids	Dexamethasone	• All PIs: ↓ PI levels: use systemic dexamethasone with caution or consider alternative corticosteroid for long-term use • EFV, NVP, ETR: ↓ ARV levels: consider alternate corticosteroid for long-term use. If dexamethasone used, monitor virologic response • RPV: ↓ significant RPV: contraindicated with >1 dose dexamethasone • EVG: ↓ EVG possible: co-administer with caution, monitor HIV virologic response
	Fluticasone (inhaled or intranasal)	• All PI/r: significant ↑ steroid level; do not co-administer unless benefits outweigh risks of systemic corticosteroid adverse effects • EVG: possible ↑ fluticasone: use alternative inhaled steroid especially for long-term use
	Prednisone	• LPV/r: ↑ prednisone ↓ LPV; Monitor virologic response. Do not co-administer unless benefits outweigh risks of systemic corticosteroid adverse effects

Table 13-9 *continued*

Recommended Dose Modifications with Boosted Protease Inhibitors, Non-Nucleoside Reverse Transcriptase Inhibitors, Integrase Inhibitors, and CCR5 Antagonists

Class	Agent	ART/Modification
Antidepressants	TCAs	• Boosted PI, EVG may ↑ TCA concentrations; use lowest possible TCA dose and titrate based on clinical assessment and/or drug levels
	Bupropion	• LPV/r, TPV/r: ↓ bupropion: titrate dose based on clinical response • EFV: ↓ bupropion: titrate dose based on clinical response
	Trazodone	• ATV/r, LPV/r, DRV/r, TPV/r, FPV/r: use lowest dose of trazodone and monitor for CNS and cardiovascular adverse effects • EVG: possible ↑ trazodone: initiate with lowest dose and titrate carefully • SQV/r: Contraindicated
	Sertraline	• DRV/r, EFV: ↓ sertraline: titrate dose based on clinical response • EVG: ↑ SSRI possible: initiate with lowest dose and titrate based on clinical response

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Table 13-9 continued

Recommended Dose Modifications with Boosted Protease Inhibitors, Non-Nucleoside Reverse Transcriptase Inhibitors, Integrase Inhibitors, and CCR5 Antagonists

Class	Agent	ART/Modification
	H_2 blockers	• ATV/r: H_2 blocker dose should not exceed a dose equivalent to famotidine 40 mg bid in ART-naive or 20 mg bid in ART-experienced • Administer ATV/r 400/100 if used with H_2 blocker and TDF • RPV: Administer H_2 blocker 12 h before or 4 h after RPV
	Clopidogrel	• ETR: May decrease efficacy of clopidogrel; avoid co-administration, if possible
	Warfarin	• Monitor INR closely if given with any PI or NNRTI (or EVG); adjust warfarin dose as needed • PI/r and RTV may ↓ INR at steady state
Miscellaneous	Antacid	• RPV: ↓ RPV when given simultaneously; give antacids at least 2 hr. before or at least 4 hr. after RPV • ATV/r, TPV/r: give ARV at least 2 hr. before or 1 hr. after antacids or buffered medications • EVG: separate EVG and antacid administration by more than 2 hr.
	Proton Pump Inhibitors (PPIs)	• ATV/r: PPIs should not exceed a dose equivalent to omeprazole 20 mg/d in PI-naïve patients. PPIs should be administered at least 12 hrs. before ATV/r; PPIs are not recommended in PI-experienced patients • DRV/r, TPV/r: ↓ omeprazole; may need to ↑ omeprazole dose • SQV/r: ↑ SQV: monitor for toxicity • RPV: ↓ RPV: contraindicated, do not co-administer

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

* RTV 100–200 mg/d may be given with voriconazole. May ↓ voriconazole concentrations. Monitor voriconazole levels.

† Do not coadminister ETR with DRV/r or SQV/r when combined with rifabutin

‡ For treatment of TB, most experts recommend rifabutin 150 mg qd with PI/r. Consider rifabutin therapeutic dose management.

§ Bepridil contraindicated with EFV; clinical significance unknown

Source: *Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents* (http://aidsinfo.nih.gov). Accessed 5/22/2013

Table 13-10

Clinically Pertinent Food-Drug Recommendations

Atazanavir	Take with food or within 2 h of a meal
Clarithromycin XL	
Darunavir	
Etravirine	
Itraconazole capsule	
Ribavirin	
Rifapentine	
Ritonavir	
Tipranavir	
Valganciclovir	
AZT	Can be taken with food to decrease GI side effects
Atovaquone	Take with high-fat meal
Nelfinavir	
Rilpivirine	
Efavirenz	Manufacturer recommends taking on empty stomach. Take on empty stomach to minimize risk of CNS side effects.
Didanosine* Indinavir (unboosted)† Isoniazid	Take on empty stomach (1 h before or 2 h after a meal)
Itraconazole solution Voriconazole	
Grapefruit juice	Increases saquinavir levels 40%–100%, but decreases indinavir AUC by 26%. Unlikely to be clinically significant with boosted PIs.

* No food restriction when ddI is co-administered with TDF, but this combination is generally not recommended due to potential for increased ddI toxicity and higher rates of virologic failure

† No food restriction when IDV is co-administered with RTV

Source: *Medical Management of HIV Infection,* 16th ed., 2012. Durham, NC: Knowledge Source Solutions

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Chapter 14:

Quality Management

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Chapter 14: Quality Management

Chapter 14 at a Glance

Quality Management

Improved Patient Care

A structured approach: Improved patient outcomes are a goal toward which all clinicians strive. Without a formal process to measure and evaluate the effectiveness of care, however, a clinician cannot be certain that a goal is being met. *Quality management (QM)* is a process designed to identify meaningful goals, establish and implement a plan for achieving them, measure outcomes and, in the clinical setting, realize improved patient outcomes. For the purposes of this guide, QM refers to an overarching strategy encompassing quality improvement (QI) activities and a formalized structure for assessing the quality of care in any setting and with any patient population. Table 14-1 provides a brief glossary of terms essential to any discussion of QM.

Table 14-1

Brief Glossary of Quality Management Terms

Term	Definition
Indicator also known as process indicator, performance measure, or outcome measure	An operational definition of a specific quality characteristic that can be measured. Indicators typically conform to widely accepted guidelines or standards of care. Of note, "outcome" refers more specifically to benefits or results for patients that accrue as a result of QI activity. Results may be positive or negative, and outcome may be measured on the patient or system level. Regardless of the term used, all refer to a measureable indication of an organization's performance in relation to a specified QI process.
Quality assurance	QA refers to a formal set of activities to review and safeguard the quality of services provided. QA includes quality assessment and implementation of corrective actions to address deficiencies. It is focused on ensuring that standards are adhered to, problems are identified, and discrete quality issues are resolved. Resolution focuses most often on a responsible individual. QA is more commonly used in a regulatory environment.
Quality improvement also known as continuous quality improvement or performance improvement	QI is an organizational approach to improving quality of care and services that relies on established principles and methodologies. To be successful, QI requires committed leadership; resources; staff involvement; stakeholder involvement; and a patient-oriented, cross-functional team approach. QI is a continual process of improvement activities and performance measurements.
Quality management	QM refers to an overarching strategy that encompasses both QI activities and a formalized structure for assessing quality of care in any setting or with any patient population.

Table 14-1 continues on the next page

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Table 14-1	continued

Brief Glossary of Quality Management Terms

Term	Definition
Root cause analysis	Root cause analysis is the first step toward developing permanent solutions to problems. It first entails identifying all the contributing or underlying causes of a problem; results of this analysis are often organized into a "fishbone diagram." The results provide a way to approach solutions in the different domains identified.
Total quality management	TQM is a strategic approach to management that aims to embed awareness of quality in all organizational processes. TQM encompasses all QI activities as well as management of systems that foster QI, including communications, education, and resource allocation.

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

QM can be applied to accomplish a wide variety of goals, such as enhancing clinical care for a specific population, assessing population-specific needs, understanding and correcting system inefficiencies, measuring outcomes, and identifying lessons learned. This chapter focuses on ways in which care of women with HIV can be improved in the face of everyday challenges confronting them and their HIV care providers.

Elements of a Quality Management Program

A QM program comprises all program-specific quality activities. To be successful, a QM program should have three key elements: (1) a quality infrastructure, (2) performance measurement, and (3) QI activities.

Infrastructure

The QM infrastructure, which provides the foundation and support for a QM program, has five essential components: (1) vision and planning, (2) oversight, (3) formalized structure, (4) resources, and (5) evaluation. These components are described in Table 14-2.

Table 14-2	
Components of Quality Management Infrastructure	
Component	**Key Tasks**
Vision and planning	• Quality vision is established and articulated. • Annual planning process is implemented. • Written QM plan is developed that includes defined responsibilities, accountability, performance measures, QI activities, and timetable.
Oversight	• Performance data, findings, and accomplishments are shared frequently, both internally and externally. • Progress on QM plan is reviewed routinely. • QM infrastructure and planned activities are actively supported by senior leaders.
Formalized structure	• QM committee with appropriate membership is established. • Senior leaders, key providers, and stakeholders are actively involved in QM committee. • Priorities are established, and recommendations for current and future QM activities are solicited by QM committee. • Meetings are held regularly; reporting mechanisms are defined, and meeting minutes are maintained. • Mechanisms for interface with QI project teams are clearly defined. • Membership is reviewed and updated annually.
Resources	• Key staff with QM activities are identified. • Dedicated time is allocated for QM activities. • Meeting space, training, materials, and other resources are provided. • Mechanisms to collect, aggregate and synthesize data.
Evaluation	• QM program effectiveness in meeting organizational needs is assessed annually. • Stakeholders inform all intended results. • Accomplishments are recognized. • Areas for continued improvement are identified using performance data.

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Performance Measurement

Formalized performance measures are used to assess quality of care, determine progress over time, and confirm that changes made through the QI process actually have improved patient outcomes. Perceptions of care providers may be helpful in identifying areas for QI focus, but individual assumptions and perceptions may not align with documented clinical measures and trend data. Figure 14-1 illustrates such a discrepancy between a care provider's assumption—that patients in her clinical practice were receiving regular Pap smears—and the reality made clear by clinical documentation.

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As part of QM activities, goals for each element of care should be established so that care providers are able to assess their performance. If the goals are not met in certain areas, these areas may be enhanced through a QI project. Regular review of data is critical, and additional analysis may be required for data that may indicate the existence of problems.

Figure 14-1
Provider Perception Versus Documented Reality

Assumption
Provider A believes that at least 75% of women in her clinical practice received a Pap smear within the past 12 months.

Reality
Electronic medical records indicate that only 42% of patients received a Pap smear in the past year.
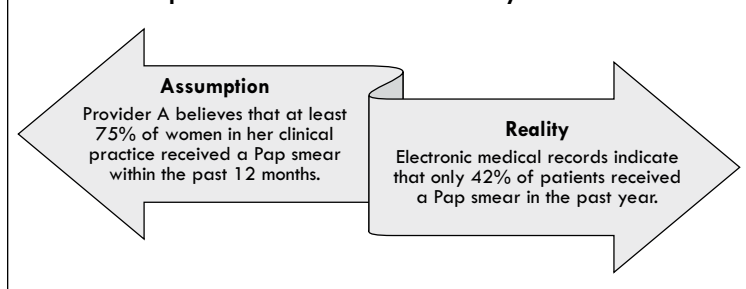
Creating a performance measurement plan: Establishing a performance measurement plan entails defining and selecting performance measures that are relevant to a specific program or population and then identifying appropriate data sources. The data that are collected must reflect the services and quality of care being provided. Finally, data must be collected at regular, defined intervals.

Standardized HIV care performance measures: Standardized performance measures for HIV care, including performance measures specific to OB-GYN care, have been established by several national entities: The Health Resources and Services Administration HIV/AIDS Bureau (HAB), the National Quality Forum (NQF), and the New York State Department of Health AIDS Institute National Quality Center (NQC) in partnership with HRSA HAB. The HAB performance measures have been developed specifically for use by programs funded by the Ryan White HIV/AIDS Treatment Extension Act of 2009. The performance measures endorsed by the NQF can be used across all service delivery systems, including private practices and large HMOs. Performance measures developed by the NQC were derived from established HIV clinical guideline panels to reflect the comprehensive package of services important to provide the best possible care to patients with HIV. The NQC performance measures include several specific to OB-GYN care.

Table 14-3 includes performance measures specific to care of women with HIV, sampled from the three resources noted in the previous paragraph. The measures are expressed in a standard format (i.e., a specific aspect of patient care accompanied by a quantitative measure designed to assess the quality of that care). Table 14-4 categorizes the same measures into three target groups: (1) pregnant women; (2) nonpregnant, sexually active women who want conception; and (3) all sexually active women.

Table 14-3

Performance Measures Specific to Care of Women with HIV

Source	Performance Measure	Numerator	Denominator
HRSA/HAB	% of women with HIV who have a Pap smear in MY	No. of HIV infected female patients who had Pap smear results documented in MY	No. of HIV-infected female patients who were >18 yr old in MY or reported history of sexual activity and had a medical visit with a provider at least 1x in MY
			Exclusions: Patients who (1) were <18 yr old and denied history of sexual activity or (2) had hysterectomy for nondysplasia or nonmalignant indications
HRSA/HAB	% of pregnant women with HIV infection prescribed ART	No. of HIV infected pregnant women who were prescribed ART during 2nd and 3rd trimester	No. of HIV infected pregnant women who had a medical visit with a provider with prescribing privileges at least once in MY
			Exclusions: (1) Patients with terminated pregnancy; (2) pregnant patients in 1st trimester and newly enrolled in care during last 3 mo of MY
HRSA	% of pregnant women who were screened for HIV infection during the 1st or 2nd prenatal care visit	No. of pregnant women who were screened for HIV infection during the 1st or 2nd prenatal care visit	No. of pregnant women seen for 2 prenatal visits during MY
NQC	% of women with HIV who receive preconception care and counseling	No. of HIV infected women who received counseling about importance and use of male or female condoms	No. of sexually active HIV infected women
NQC	% of women with HIV contemplating pregnancy who receive preconception care and counseling	No. of HIV infected women receiving preconception counseling	No. of sexually active HIV infected women contemplating pregnancy
NQC	% of pregnant women with HIV who received CD4+ count and viral load each trimester of pregnancy	No. of HIV infected patients for whom CD4+ count and viral load were measured each trimester of pregnancy	No. of HIV infected pregnant women

Table 14-1 continues on the next page

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Table 14-3　*continued*

Performance Measures Specific to Care of Women with HIV

Source	Performance Measure	Numerator	Denominator
NQC	% of pregnant women with HIV who had HIV RNA measured at 34–36 wk gestation	No. of patients who had HIV RNA measured at 34–36 wk for mode of delivery assessment	No. of HIV infected patients for whom CD4+ count and viral load were measured each trimester of pregnancy
NQC	% of pregnant women with HIV who received counseling to avoid breastfeeding	No. of HIV infected pregnant women who received counseling to avoid breastfeeding	No. of HIV infected pregnant women who delivered a live-born infant within the time period of study
NQC	% of pregnant women with HIV who received intrapartum zidovudine	No. of HIV infected pregnant women who received administration of IV zidovudine during labor or prior to scheduled cesarean delivery alone or in combination with other ARV drugs	No. of HIV infected pregnant women within the time period of study who have delivered a live-born infant
NQC	% of postpartum women who received maternal postpartum follow-up	No. of HIV infected women who received documented maternal postpartum follow-up including monitoring of HIV infection with CD4+ counts and viral load tests	No. of HIV infected postpartum women

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Performance measures are subject to ongoing change and revision. Readers are directed to the URLs below for the most up-to-date versions. Additional performance measures targeted for HIV infected patients, regardless of gender, can also be found at the following websites:

HRSA/HAB measures: http://hab.hrsa.gov/deliverhivaidscare/habperformmeasures.html

HRSA measures: http://www.hrsa.gov/healthit/coremeasures.html

NQC measures: http://www.nationalqualitycenter.org/index.cfm/5659

NQF measures: http://www.qualityforum.org

Table 14-4			
Performance Measure by Target Population			
Measure	**Population**		
	Pregnant Women	Nonpregnant, Sexually Active, Wants Conception	All Sexually Active Women
Pap smear	X	X	X
Preconception counseling		X	
HIV screening	X	X	X
Prescribed ART	X		
CD4+ and viral load each trimester	X		
HIV RNA @ 34–36 wk	X		
Breastfeeding counseling	X		
Intrapartum zidovudine	X		
Maternal follow-up	X		

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Use of measures: Performance measurement data can be used to identify potential problems and areas in need of improvement; these areas can be examined further through the implementation of QI projects. Note that performance measurement is just one component of a QM strategy and is not an end in itself. Data analysis and subanalysis can be conducted to determine differences in clinical outcomes on the basis of any number of factors (e.g., gender, race, location, language, socioeconomic status, presence of children). Table 14-5 illustrates the results of subanalysis performed to determine gender differences in provision of CD4+ cell counts. In this example, 85.5% of all clients with HIV infection had 2 or more CD4+ cell counts performed during the measurement year. However, subpopulation analysis revealed that this level was reached for a lower percentage of female patients (71.4%), and further analysis revealed that among female patients, the standard was achieved most often for Latina patients and least often for African-American patients. Had this information been aggregated, resources used to address the actual observed disparity may not have had an appreciable impact because the largest gain would have been realized by focusing on the African-American women. When presenting data, program staff should keep in mind that data, charts, graphs, and other visual depictions of results can often relay messages or emphasize key points or trends more effectively than words.

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Table 14-5

Sample Performance Measure Subanalysis: Percentage of Patients with HIV Infection Who Had ≥2 CD4+ Cell Counts Performed in Measurement Year

Eligible Population	Numerator	Denominator	Percentage
Patients With HIV Infection	*No. Who Had ≥2 CD4+ Cell Counts Performed*	*No. Who Had ≥1 Medical Visit*	*Numerator ÷ Denominator x 100*
All patients (N = 425)	342	400	85.5
Male (n = 295)	257	281	91.5
Female (n = 130)	85	119	71.4
African-American female (n = 78)	44	70	62.9
Latina female (n = 14)	11	12	91.7
Caucasian female (n = 38)	30	37	81.1

Quality Improvement

Well-selected performance data can provide information about how well a system or program is functioning and identify potential problems. Table 14-6 provides an example. Analysis of performance measure data indicate that Agency A appears to be doing well with ART for pregnant women, medical visits, and *Pneumocystis carinii* pneumonia (PCP) prophylaxis. For each measure, baseline rates have been maintained or have improved over time. Although hepatitis B (HBV) vaccination and cervical cancer screening rates remain low, notable improvement has been made in comparison to baseline data. However, rates of TB screening and CD4+ cell counts have declined. Of particular interest is the difference in rates of CD4+ cell count monitoring and medical visits: Although the majority of patients (94%) had ≥1 medical visit during the measurement period, only 76% had ≥2 CD4+ cell counts during the same time frame.

Table 14-6					
Example of Annual Quality Review Results (Agency A)					
Indicator	**Performance (%)**		**Indicator**	**Performance (%)**	
	Baseline	Current		Baseline	Current
Medical visits	91	94	Cervical cancer screening	53	68
ART	78	82	Adherence counseling	73	78
CD4+ cell count	84	76	TB screening	66	62
PCP prophylaxis (if indicated)	90	91	Syphilis screening	59	77
ART for pregnant women	95	98	HBV vaccine completed	45	54

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Goals: Goals for each indicator should be set based on best practices. Any downward trend or measure that did not meet a defined goal can be further explored as a QI project. Once a process or issue is identified, a QI team should be convened. A QI team is a working group constituted to address one specific opportunity for improvement. The team should consist of the people who have regular involvement in the process and should have a leader, facilitator, or both. In this example, given the data presented above, the QI project could examine the rate of CD4+ cell count testing (Figure 14-2).

Figure 14-2
Quality Improvement Problem and Goal

Problem	**Goal**
In 2010, the percentage of CD4+ cell counts conducted at least every 6 months decreased to 76%.	Increase the percentage of CD4+ cell counts completed at least every 6 months for HIV infected patients to 90%.
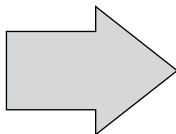
For each QI project, the specific problem should be identified, baseline data should be collected, and a clearly defined goal should be established. Various strategies can be used to understand the issue at hand and identify potential change strategies that can be implemented to reach the goal. In these processes, such tools as fishbone diagrams, flowcharts, and force field analysis can be useful.

Another useful tool is the Model for Improvement (Figure 14-3), which poses three questions to help guide a QI project: (1) What are we trying accomplish? (2) How will we know that a change is an improvement? (3) What changes can we make that will result in improvement?

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Figure 14-3
Model for Improvement
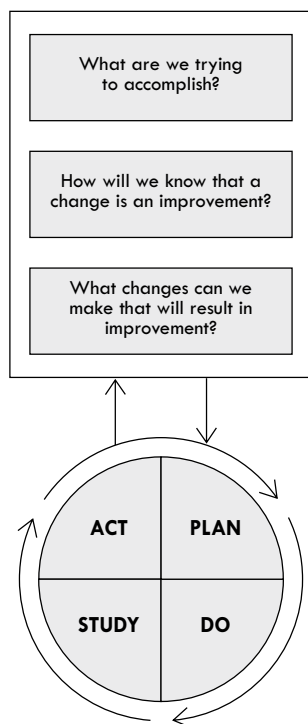
Source: © *The Improvement Guide: A Practical Approach to Enhancing Organizational Performance,* 2nd ed. 2009. San Francisco, CA: Jossey-Bass. Reproduced with permission of John Wiley & Sons, Inc.

Plan–Do–Study–Act: By understanding a problem and implementing tests of change, performance rates can improve. However, not all change results in an improvement. To ensure that positive change is being made, performance must be measured. Plan–Do–Study–Act (PDSA) cycles (Figure 14-4) prompt a QI team to engage in continuous efforts to make change and measure its effect on patient outcomes. Multiple PDSA cycles are required to implement change that is sustainable over time. The most effective QI teams regularly communicate their progress with a QM committee. Senior leadership can be used to minimize or remove barriers, allocate resources, and provide guidance and support.

Figure 14-4
Elements of Plan–Do–Study–Act Cycle

PLAN
- State cycle objectives
- Make predictions
- Strategize: who, what, where, when

DO
- Carry out test
- Document problems and unexpected observations
- Begin data analysis

STUDY
- Complete data analysis
- Compare data and predictions
- Summarize lessons learned

ACT
- What changes are to be made?
- What is to be the next cycle?
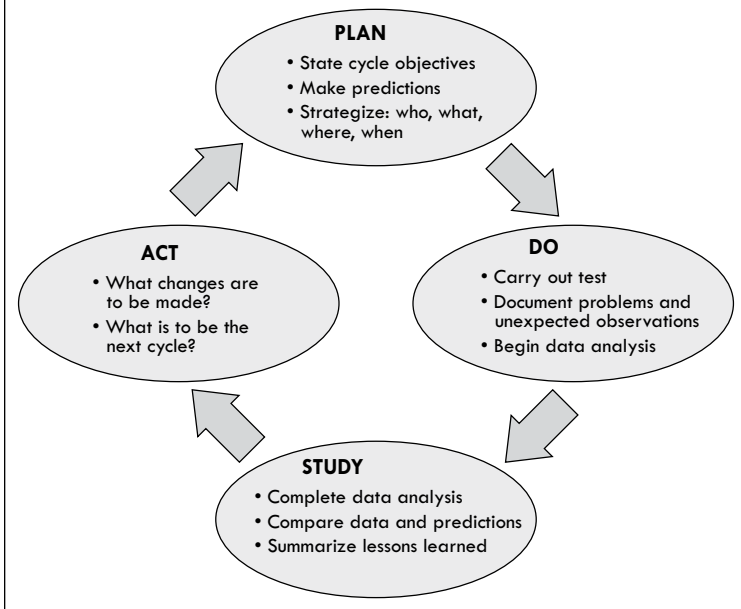
Case Study: Quality Improvement In Action

The case study that follows illustrates components of QM program as implemented in an urban, hospital-based HIV clinic.

Quality Management Infrastructure

The HIV program's QM committee was established to support and guide all quality-related initiatives for the HIV program. The QM Committee, which met monthly, included the following members: medical director, nurse practitioner from each site, program director, site managers, QA manager, policy and procedure manager, pharmacist, and peer educator.

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Performance Measurement

The QM Committee was charged with identifying and monitoring performance measures that addressed a range of clinical issues. When the committee examined the measures, it was clear that systems needed to be enhanced to improve the clinic's Pap smear rate. Patient data indicated the following information, which prompted initiation of a QI project:

- Visit adherence: 75%

- Patients on ART: 88%

- Viral load <48 c/mL: 57%

- Annual Rapid Plasma Reagin (RPR): 94%

- Women with annual Pap: 13%

Problem identified: Pap smear completion rate varied across clinic sites. Key baseline data indicated the following:

- 13% of women referred for routine OB-GYN care kept their appointments and had documented results.

- 35% of tests returned abnormal results.

- 100% of women with abnormal results were scheduled for further evaluation, but only 25% kept their appointments.

Goal: Within 12 months, improve the annual Pap smear rate for women infected with HIV to 75%. The overarching goal was for 100% of women to receive an annual Pap smear and 90% of the women with abnormal results to receive appropriate treatment.

Understanding the problem: Data indicated that, despite a clinician's vigilance in making referrals, female patients in the HIV clinics were not keeping appointments for yearly OB-GYN exams. In response, the team implemented a series of change strategies.

Quality Management Phase 1

Strategies: A series of change ideas were implemented to increase the Pap smear completion rate:

- Phone calls to remind HIV clinic patients of scheduled appointments in the OB-GYN clinic

- Assignment of HIV clinic staff members to meet patients in the OB-GYN clinic to help ease the transition to a new setting and new care providers and to address fears

- Provision of child care for patients who kept their OB-GYN clinic appointments

- Designation of the HIV clinic nurse as a single point of contact and the person with responsibility for scheduling appointments and making follow-up phone calls.

Results: The rate of completion rose to only 42%. Of those patients with abnormal Pap smear results, only 36% received appropriate follow-up. Patient satisfaction surveys and information relayed from peer educators and the Patient Advisory Group indicated that the best way to meet this growing need was to provide onsite Pap smears during clinic visits and to build a women's clinic nested within the HIV clinic.

Quality Management Phase 2

Strategies: On the basis of data collected after the first phase, several additional change ideas were tested:

- Patients were routed to a female nurse practitioner, who conducted Pap smears as part of routine HIV care.

- Reminder tags were placed on charts to indicate when patients were due for OB-GYN care.

- Performance data were reviewed more closely to ensure that every patient was assessed to identify need for OB-GYN care.

Results: Data monitoring provided evidence that the nested approach yielded a higher percentage (60%) of completed Pap smears. To build on these results, several additional services were established:

- On-site follow-up for women with abnormal Pap smear results

- On-site colposcopy, cervical biopsies, and loop electrosurgical excision procedure (LEEP), using equipment obtained from the women's health clinic

- Training and certification in colposcopy for nurse practitioners in the HIV clinic

- One morning per week designated specifically for follow-up visits for women with abnormal results, with a primary care nurse assigned to coordinate appointments

End Results

The QI project was successful in providing patients with easy access to comprehensive care and follow-up. As a result, 57% of women had annual Pap (up from 13%), 84% of all abnormal Pap smears were followed up appropriately, and 100% of all pregnant women received ART prophylaxis for prevention of mother-to-child transmission. Another success was a reduction in missed appointments for onsite OB-GYN care, such that 88% of women adhered to scheduled appointments following completion of the QI initiative.

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Sustaining Change and Spreading Ideas

No Improvement Without Change

Clinicians and staff who initiate change must look at who and what the change will affect and select the changes that will bring about the best clinical outcomes for patients. Often, a needed change is obvious, but the resources or conditions are not readily available to support the effort needed to make change happen.

A dynamic process: Once changes have been made, progress must be monitored over time to ensure that improvements are sustained. Successful change ideas can be spread to other clinical sites and practices. Through the use of repeated PDSA cycles, ideas for change can be tested in new settings and modified as needed. As part of the change strategy, policies and procedures may have to be revised, and staff may have to be retrained or cross-trained to be able to implement new policies and practices.

Not all change = improvement: Improvement requires change, but not every change is an improvement. Purposeful change will alter an existing system in a positive way or create something new that is also improved. Only upon analysis of data and outcomes can it be determined whether a specific change led to a desired improvement.

Keys to QI success: The most important step in any QI project may be simply to get started (i.e., "just do it"; Figure 14-5). Also crucial is the selection of project: It's best to begin with a project that has a good chance of success and that will interest and engage others. Start small and aim for incremental improvement in outcomes by making and testing small changes over short periods of time. Identify and engage or involve a champion for change early on to initiate rapid PDSA cycles that will produce data demonstrating early successes. Include all levels of the system to elicit diverse ideas and buy-in for improvement. Finally, ensure effective leadership, which is essential to the success of any QM program.

Figure 14-5
Secrets of Quality Improvement Success

"Just do it" → Choice of project → Incremental change → Champion for change → Leadership
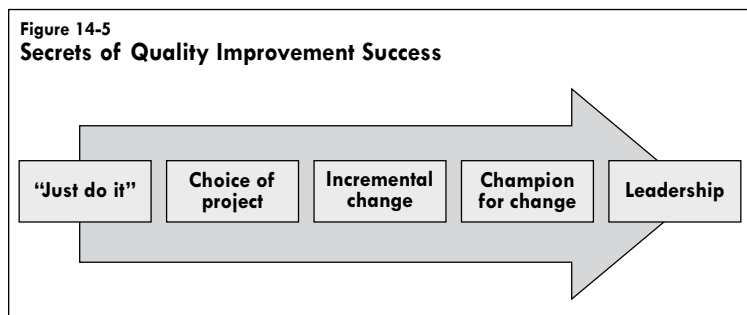
Chapter 15:

Resources

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The authors declare no conflicts of interest

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Chapter 15: Resources

Chapter 15 at a Glance

How to Use this Chapter

A chapter devoted to additional resources is an essential part of this guide. First, HIV clinical care evolves so rapidly that some information in the guide will soon be out of date. Second, a wealth of information that supplements these chapters in specialized areas of care is available. We have included some of the most important resources for clinical care of women with HIV, but the list is by no means exhaustive. Readers can explore the websites for which we have provided URLs to find many other informative sites.

In this electronic information age, the term *resources* includes Internet sites and electronic documents as well as organizations and published documents, so the chapter includes a range of mechanisms for obtaining more information. We consider the Web-based resources to be primary because they are available from anywhere in the world and are usually updated on a periodic basis. Phone contact information is provided where available, so that readers without access to the Internet can still obtain information.

The resources are listed alphabetically in a grid that identifies major topics addressed by each resource as well as the type of information available. There is a brief description of the resource and website and phone contact information. The phone numbers with 800, 888, 877, and 866 prefixes are only toll-free in the United States.

Regarding special populations, many of the resources contain some information (e.g., fact sheets) about or for groups of people with special needs, such as people who are homeless, incarcerated, or transgender. Information for special populations is usually just one component of a resource, which makes the search function on most websites a useful tool for locating information on specific topics or special populations. In addition, providers caring for lesbians with HIV can find relevant information by searching The Body (www.thebody.com) and the website of the American Psychological Association Office on AIDS (www. apa.org/pi/aids/index.aspx).

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Table 15-1

Resources for Healthcare Professionals

Name	URL and/or Telephone Number	Source	Types of Resources Available	Topics Covered
AIDS Clinical Trials Group (ACTG)*	https://actgnetwork.org/	NIH-funded AIDS Clinical Trial Groups	• Website • Print materials • Tel/e-mail/Web consultation	• Research and clinical trials
AIDS Alliance for Children, Youth & Families (formerly the AIDS Policy Center for Children, Youth and Families)	www.aids-alliance.org Tel: 202-785-3564 888-917-2437	Policy center that promotes advocacy, education, and support for children and families affected by HIV/AIDS	• Website • Print materials • Tel/e-mail/Web consultation • Meetings and conferences • Patient education	• Treatment • Peds/adolescents • Psychosocial support and quality of life • Research and clinical trials
AIDS Education Global Information System (AEGIS)	www.aegis.com Tel: 949-495-1952	Nonprofit group that assembles and archives information and resources from the mainstream press, professional journals, and legal and legislative sources	• Website • Tel/e-mail/Web consultation • Meetings and conferences • Patient education	• Prevention • Occupational exposure
AIDS Education and Training Centers (AETCs)	www.aidsetc.org	Network of regional centers that provide HIV training and education for healthcare providers	• Website • Guidelines • Print materials • Tel/e-mail/Web consultation	• Epidemiology • Treatment • Prevention • Peds/adolescents • OB-GYN • Adherence • Psychosocial support and quality of life • Substance abuse • Research and clinical trials • Occupational exposure • Quality improvement • Palliative care

Table 15-1 *continued*				
Resources for Healthcare Professionals				
Name	**URL and/or Telephone Number**	**Source**	**Types of Resources Available**	**Topics Covered**
AIDSInfo* (*AIDS Clinical Trials Information Services and AIDS Treatment Information Services have been integrated into AIDSInfo*)	www.aidsinfo.nih.gov Tel: 301-519-0459 800-HIV-0440 TTY: 888-480-3739 Spanish speakers available M–F, 12 pm–5 pm, EST	HHS project that offers the latest federally approved information on HIV/AIDS clinical research, treatment, prevention, and medical practice guidelines	• Website • Guidelines • Print materials • Tel/e-mail/Web consultation • Meetings and conferences	• Treatment • Prevention • Peds/adolescents • OB-GYN • Nutrition • Occupational exposure
American Academy of HIV Medicine (AAHIVM)*	www.aahivm.org Tel: 202-659-0699	Professional association for HIV specialists; promotes excellence in HIV/AIDS care and offers HIV credentialing for physicians, nurse practitioners, and physician assistants	• Website • Meetings and conferences	• Treatment
American Congress of Obstetricians and Gynecologists (ACOG)*	www.acog.org Tel: 202-638-5577	Professional association for specialists in OB-GYN; provides guidelines and information on reproductive care of women	• Website • Meetings and conferences	• OB-GYN
Association of Nurses in AIDS Care (ANAC)*	www.anacnet.org Tel: 800-260-6780	Professional association for nurses; provides information and advises members about clinical and policy issues related to nursing and HIV care; offers the ACRN credential	• Website • Print materials • Meetings and conferences	• Epidemiology • Nursing standards of practice • Nutrition • Adherence • Treatment • Psychosocial support

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Table 15-1 *continued*

Resources for Healthcare Professionals

Name	URL and/or Telephone Number	Source	Types of Resources Available	Topics Covered
AIDSVU	www.aidsvu.org	Interactive online map of HIV prevalence in U.S. with national, state, and local map views	• Website	• Epidemiology • HIV testing center locations • HIV treatment locations • NIH-funded HIV Prevention and Vaccine Trials Sites
The Body Pro*	www.thebodypro.com	HIV resource for healthcare professionals; goal is to use the Internet to "lower barriers between healthcare professionals and their HIV-infected patients"	• Website • Guidelines • Tel/e-mail/Web consultation • Meetings and conferences	• Epidemiology • Prevention • OB-GYN • Psychosocial support and quality of life • Research and clinical trials • Palliative care
CDC Division of HIV/AIDS Prevention (DHAP)	www.cdc.gov/hiv/resources/guidelines/index.htm Tel: 800-232-4636 TTY: 800-232-6348	Government site that details clinical guidelines and information on prevention of HIV and hepatitis	• Website • Guidelines	• Epidemiology • Prevention • Occupational Exposure • Research and clinical trials
CDC National Prevention Information Network (CDC NPIN)	www.cdcnpin.org Tel: 404-679-3860, 800-458-5231 M–F, 9 am–6 pm, EST	Government site that provides comprehensive reference, referral, and distribution service for information on HIV/AIDS, STIs, and TB; information specialists can assist in identifying appropriate resource materials	• Website • Guidelines • Print materials • Tel/e-mail/Web consultation • Patient education	• Prevention • STIs and TB • Patient education

Table 15-1 *continued*

Resources for Healthcare Professionals

Name	URL and/or Telephone Number	Source	Types of Resources Available	Topics Covered
CDC Prevention with Positives (PWP)	www.cdc.gov/hiv/pwp/index.htm	Government site that provides basic information about scope of PWP and PWP recommendations	• Website • Guidelines • Implementation resources	• Prevention with positives • Reproductive and pregnancy issues
Community Programs for Clinical Research on AIDS (CPCRA)*	http://cpcra.s-3.com	Network of research sites comprising community-based healthcare providers who offer their patients the opportunity to participate in research where they receive their health care	• Website	• Research and clinical trials
HIV and Hepatitis	www.hivandhepatitis.com	Nonprofit agency that provides clinical information and resources on hepatitis and HIV	• Website • Tel/e-mail/Web consultation • Meetings and conferences • Patient education	• Treatment
HIVdent	www.hivdent.org	Nonprofit coalition focused on providing information on dental manifestations of HIV/AIDS	• Website • Guidelines • Meetings and conferences • Articles • Patient education	• Oral health • Treatment • Research and clinical trials
HIV InSite	hivinsite.ucsf.edu	Information on medical treatment, prevention, and policy from the University of California at San Francisco (UCSF)	• Website • Patient education	• Epidemiology • Treatment • Prevention • Peds/adolescents • Psychosocial support and quality of life • Nutrition • Palliative care

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Table 15-1 *continued*

Resources for Healthcare Professionals

Name	URL and/or Telephone Number	Source	Types of Resources Available	Topics Covered
HIV Medication Guide	www.hivmedicationguide.com	Pharma-sponsored website that provides drug information and software to assess for potential drug interactions	• Website • Patient education	• Treatment
HIV Medicine Association (HIVMA)*	www.hivma.org	Professional association within the IDSA; guidelines and information on HIV treatment and care	• Website • Guidelines • Print • Meetings and conferences	• Treatment • Quality improvement • Care in resource-poor settings
HRSA HIV/AIDS Bureau (HAB)	hab.hrsa.gov	Federal agency that administers Ryan White HIV/AIDS Program; provides information supporting care of people with HIV; HRSA/HAB's Special Projects of National Significance grant program tests innovative approaches to the care of people with HIV/AIDS	• Website • Print • Meetings and conferences	• Epidemiology • Treatment • Prevention • Peds/adolescents • OB-GYN • Adherence • Nutrition • Quality improvement • Palliative care • Care in resource-poor settings
Institute of Medicine (IOM)	www.iom.edu	Nonprofit independent organization that works outside of government to provide unbiased and authoritative advice to decision makers and the public	• Reports	• Broad range of topics related to health and health care

Table 15-1 *continued*

Resources for Healthcare Professionals

Name	URL and/or Telephone Number	Source	Types of Resources Available	Topics Covered
International HIV/AIDS Alliance	www.aidsalliance.org	Nonprofit organization that helps communities in developing countries play an effective role in the global response to AIDS	• Website • Print materials	• Prevention • Care in resource-poor settings • Youth • Stigma
Johns Hopkins University AIDS Service	www.hopkins-aids.edu http://www.hopkinsmedicine.org/gim/fellowship/moore_clinic.html	Detailed information on medical treatment and prevention from Johns Hopkins University AIDS Service	• Website • Print • Tel/e-mail/Web consultation • Meetings and conferences	• Treatment • Adherence • Research and clinical trials
National Alliance of State and Territorial AIDS Directors (NASTAD)	www.nastad.org/default.aspx	Represents chief state health agency staff who have programmatic responsibility for administering HIV/AIDS and viral hepatitis healthcare, prevention, education, and supportive service programs funded by state and federal governments	• Website • Policies • Technical assistance • Print	• Policy and advocacy • Health care access • Prevention • Viral hepatitis • HIV counseling and testing
National HIV/AIDS Clinicians' Consultation Center	www.nccc.ucsf.edu/home/ Warmline: 800-933-3413 M–F, 6 am–5 pm, PST PEPline: 888-448-4911 (24/7) Perinatal HIV Hotline: 888-448-8765	National toll-free hotline to counsel healthcare workers with job-related exposure to HIV, hepatitis, and other bloodborne pathogens; offers treating clinicians up-to-the-minute advice on managing occupational exposures and answers other questions on topics related to HIV care	• Website • Guidelines • Tel/e-mail/Web consultation • Meetings and conferences	• Treatment • Peds/adolescents • Occupational exposure

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Table 15-1 *continued*

Resources for Healthcare Professionals

Name	URL and/or Telephone Number	Source	Types of Resources Available	Topics Covered
NIAID Database for Anti-HIV Compounds	www.niaid.nih.gov/daids/dtpdb Tel: 301-496-5717 866-284-4107 TDD: 800-877-8339 M–F, 8:30 am–5 pm, EST	Government site housing computerized databases of chemical structures and biologic data on ARVs	• Website • Tel/e-mail/Web consultation	• Epidemiology • Treatment • Prevention • Research and clinical trials
Caring Connections	www.caringinfo.org/ Tel: 800-658-8898 Multilingual Line: 877-658-8896	Program of the National Hospice and Palliative Care Organization that provides resources, education, advocacy, and a hotline on palliative care and end-of-life issues such as living wills	• Website • Print materials • Tel/e-mail/Web consultation • Patient education	• Peds/adolescents • Psychosocial support and quality of life • Palliative care
PEPFAR	www.pepfar.gov	Government site for the U.S. President's Emergency Plan for AIDS Relief which provides global support to limited-resource countries for HIV prevention, care, and treatment	• Website • Guidance	• Country operational plans • PEPFAR reports
Population Council	www.popcouncil.org Tel: 212-339-0500 877-339-0500	International organization; research and policy on reproductive health and family planning	• Website • Guidelines • Print materials	• Treatment • Peds/adolescents • Research and clinical trials • Care in resource-poor settings

Table 15-1 *continued*

Resources for Healthcare Professionals

Name	URL and/or Telephone Number	Source	Types of Resources Available	Topics Covered
Reproductive Health Online (Reproline)	www.reproline.jhu.edu	Information and training tools on reproductive health in resource-poor settings provided by Johns Hopkins Program for International Education in Gynecology and Obstretrics; information available in Spanish, French, Portuguese, and Russian	• Website • Guidelines • Print materials • Tel/e-mail/Web consultation • Meetings and conferences	• Prevention • OB-GYN • Psychosocial support and quality of life
Resource Center for Prevention with Persons Living with HIV	http://hivpwp.org/	Government initiative focused on persons living with HIV/AIDS to improve their individual health and reduce risk of transmission to others	• Website • Podcasts • Slides • Online training • Webinars	• Linkage to care • Retention • Risk screening and reduction • Partner services • ART as prevention • Adherence • STDs • Reproductive health care • PMTCT
UNAIDS: Joint United Nations Programme on HIV/AIDS	www.unaids.org Tel:+41 22 791 36 66 (Switzerland)	International program; provides technical assistance and HIV/AIDS information to countries and communities	• Website • Guidelines • Print • Patient education	• Epidemiology • Treatment • Psychosocial support and quality of life • Substance abuse • Nutrition • TB

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Table 15-1 *continued*				
Resources for Healthcare Professionals				
Name	**URL and/or Telephone Number**	**Source**	**Types of Resources Available**	**Topics Covered**
The Well Project	www.thewellproject.com Tel: 888-616-9355	Nonprofit organization developed and administered by HIV-positive women; Web portal for women living with HIV; treatment information, groups, organizational tools, slide sets, searchable clinical trials listings, and resource information	• Website • Guidelines • Print • Tel/e-mail/Web consultation • Meetings and conferences • Patient education	• Treatment • Prevention • Peds/adolescents • OB-GYN • Adherence • Substance abuse • Nutrition • Care in resource-poor settings
Women, Children, and HIV	www.womenchildrenhiv.org	Project of UCSF Center for HIV Infection; Information on HIV and pregnancy, prevention of perinatal HIV transmission, and pediatric care; global focus	• Website • Guidelines • Print materials	• Treatment • Prevention • Peds/adolescents • OB-GYN • Psychosocial support and quality of life • Nutrition • Palliative care
WHO HIV/AIDS Department	www.who.int/hiv/en	Technical support for HIV/AIDS treatment and prevention	• Website • Guidelines • Print materials • Tel/e-mail/Web consultation	• Epidemiology • Treatment • Peds/adolescents • OB-GYN • Nutrition

Notes: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix. All URLs were active as of September 2012.

*Must be member to access select information

Table 15-2

Resources for Patients

Name	URL and/or Telephone Number	Brief Description	Resources	Topics Covered
American Social Health Association	www.ashastd.org/ Tel: 919-361-8400 STI Resource Center Hotline: 919-361-8488, M–F, 8 am–6 pm EST	Answers to confidential inquiries about HIV/AIDS prevention, risks, testing, treatment, and other concerns; referrals provided	• Website • Print materials • Tel/e-mail/Web consultation • Meetings and conferences	• Prevention • General HIV information • Common illnesses associated with HIV • Risk reduction
AVERTing HIV and AIDS	www.avert.org/women-hiv-aids.htm	An international HIV and AIDS charity based in the United Kingdom that works to avert HIV/AIDS through education, treatment, and care	• Website • Tel/e-mail/Web consultation	• Epidemiology • Treatment • Prevention • Peds/adolescents • OB-GYN • Adherence • Psychosocial support and quality of life • Nutrition • Occupational exposure • Palliative care
The Body	www.thebody.com	Comprehensive HIV information and resources	• Website • Tel/e-mail/Web consultation	• Epidemiology • Treatment • Prevention • Psychosocial support and quality of life • Nutrition • Palliative care

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Table 15-2 continued

Resources for Patients

Name	URL and/or Telephone Number	Brief Description	Resources	Topics Covered
Canadian AIDS Treatment Information Exchange (CATIE)	www.catie.ca Tel: 416-203-7122 800-263-1638	Comprehensive HIV information and resources on drugs, other medical treatments, and complementary therapies, among other topics; available in English and French.	• Website • Print materials • Tel/e-mail/Web consultation • Meetings and conferences	• Epidemiology • Treatment • Prevention • Adherence
Gay Men's Health Crisis Women and Family Services (New York, NY)	www.gmhc.org Tel: 800-243-7692	Information and services for people with HIV/AIDS, including the Lesbian AIDS Project	• Website • Print materials	• Psychosocial support and quality of life • Nutrition
Healthy Women	www.healthywomen.org/condition/hivaids Tel: 877-986-9472	Health information to educate, inform, and empower women to make smart health choices	• Website • Tel/e-mail/Web consultation	• Treatment • Prevention
National Association of People With AIDS (NAPWA)	www.napwa.org Tel: 240-247-0880 866-846-9366	Advocacy, information, and support for people living with HIV/AIDS	• Website • Print materials • Meetings and conferences	• Treatment • Prevention
New Mexico AIDS Infonet	www.aidsinfonet.org	Nontechnical fact sheets on treatment	• Website • Print materials	• Treatment • Prevention • Peds/adolescents • OB-GYN • Nutrition

Table 15-2 *continued*

Resources for Patients

Name	URL and/or Telephone Number	Brief Description	Resources	Topics Covered
The Office on Women's Health	http://womenshealth.gov/hiv-aids/ Tel: 202-690-7650	Aims to improve the health and sense of well-being of all U.S. women and girls through innovative programs that focus on health and education	• Website • Tel/e-mail/Web consultation	• Treatment • Prevention • Adherence • Psychosocial support and quality of life • Care in resource-poor settings
Project Inform	www.projectinform.org Treatment hotline: 415-558-9051 800-822-7422 M–F, 9 am–5 pm; Sat 10 am–4 pm, PST	Treatment Information and tools for living with HIV, including confidential treatment information by phone and Project Wise, a program focused on HIV/AIDS treatment information and advocacy for women	• Website • Print materials • Tel/e-mail/Web consultation • Meetings and conferences	• Treatment • Prevention • OB-GYN • Adherence • Nutrition • Care in resource-poor settings
San Francisco AIDS Foundation	www.sfaf.org Tel: 415-487-3000 866-245-3424	Information about prevention, care, and experimental treatments	• Website • Print materials	• Epidemiology • Treatment • Prevention • Psychosocial support and quality of life
Women Alive	www.women-alive.org Tel: 323-965-1564	Organization by and for women living with HIV that offers local services in Los Angeles as well as Internet services	• Website • Guidelines • Print materials • Tel/e-mail/Web consultation • Meetings	• Peds/adolescents • Psychosocial support and quality of life • Research and clinical trials • Care in resource-poor settings

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Table 15-2

Resources for Patients

Name	URL and/or Telephone Number	Brief Description	Resources	Topics Covered
Women Organized to Respond to Life-threatening Disease (WORLD)	www.womenhiv.org Tel: 510-986-0340 M–F, 10 am–6 pm, PST	Organization in Oakland, CA, for women with HIV that provides peer advocacy, treatment education training, and retreats	• Website • Tel/e-mail/Web consultation • Meetings	• Adherence • Care in resource-poor settings

Notes: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix. All URLs were active as of September 2012.

Chapter 16:

International Perspectives

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Chapter 16 International Perspectives

Chapter 16 at a Glance

International Perspectives

The primary focus of this guide is to provide a resource for HIV providers in the United States and other high-resource settings. At the same time, though, the global perspective should be considered, because the overwhelming majority of women with HIV live in low- and middle-income countries (LMICs). *LMIC* is a World Bank classification for countries with gross national income (GNI) less than $12,196 per capita in 2009; it excludes the 69 high-income countries with per capita GNI above this level.

Three-quarters of women and girls living with HIV are in sub-Saharan Africa, and half of them live in countries of southern Africa specifically. HIV prevalence among young women aged 15–24 years in sub-Saharan Africa (3.4%) is more than 5 times higher than the global average (0.6%) and more than 30 times higher than that of Western Europe (0.1%) (UNAIDS, *Report on the Global AIDS Epidemic* 2010, CDC, *HIV/AIDS Surveillance Report* 2009;19). Figure 16-1 illustrates the proportion of people living with HIV who are female and aged >15 years.

This chapter explores some of the factors unique to lower-resource settings and the consequent differences in the approach to HIV prevention, care, and treatment, many of which are driven by access or lack of access to human and financial resources.

Figure 16-1
Estimated Proportion of Women and Girls (>15 Years of Age) Living with HIV by Region

Legend:
- Sub-Saharan Africa
- East Asia
- Oceania
- South and South-East Asia
- Eastern Europe and Central Asia
- Western and Central Europe
- Middle East and North Africa
- Caribbean
- Central and South America
- North America

Pie chart values: 1.3%, 3.1%, 1.5%, 0.8%, 2.5%, 4.3%, 0.2%, 1.4%, 8.8%, 76.2%
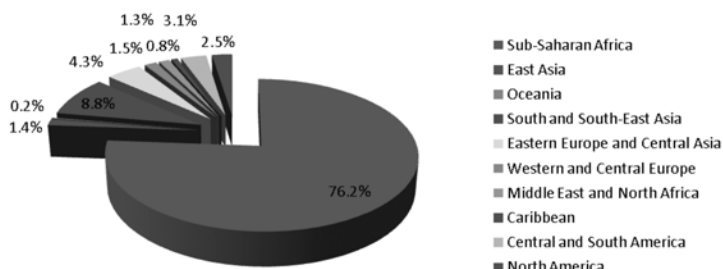
Source: Data from UNAIDS, *Report on the Global AIDS Epidemic* 2010. Available at http://www.unaids.org/globalreport/global_report.htm. Accessed 9/9/2012.

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Factors That Influence Approaches to HIV Care in Low- to Middle-Income Countries

Factors that affect HIV care in a given country include the burden of disease, barriers to care, and prevalence and type of comorbidities.

Burden of Disease

HIV is a leading cause of death worldwide and the number one cause of death in Africa. The highest adult HIV prevalence worldwide is in Swaziland, where 1 in 4 people between ages 15 and 49—and 42% of pregnant women—are living with HIV (UNAIDS, *Report on the Global AIDS Epidemic* 2010, p. 28). This extent of infection is in stark contrast to the United States, which has an estimated 0.6% adult prevalence. The global average prevalence is 0.8%, and many LMICs, including Indonesia, India, and Ecuador, have prevalence less than 0.5%. Even in sub-Saharan Africa, where the regional adult prevalence averages 5.0%, there is great variability among countries: Madagascar, Niger, and Senegal have rates similar to that of the United States, whereas Angola, Ghana, and Ethiopia have rates below 5%. Southern Africa is hardest hit by the epidemic: National adult prevalence rates there range from 12% to 26% (UNAIDS, *Report on the Global AIDS Epidemic* 2010).

Figure 16-2
Global Prevalence of HIV, 2009

No data   < .1%   .1% – < .5%   .5% – < 1%   1% – < 5%   5% – < 15%   > 15% – 28%
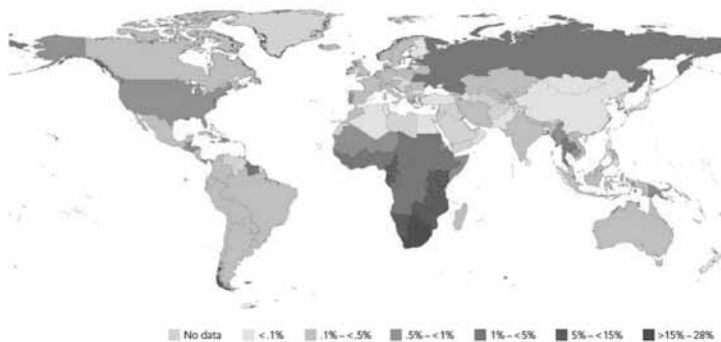
Source: Data from UNAIDS, *Report on the Global AIDS Epidemic* 2010

Although most countries are on track to meet the 2015 UN Millennium Development Goal 5 target of reducing the maternal mortality ratio, defined as maternal death (the death of a woman while pregnant within 42 days of termination of pregnancy) per 100,000 live births, by 75% , five countries in southern Africa—where HIV prevalence is highest—have had increases in maternal deaths since 1990, largely attributable to HIV: Botswana (133%), Zimbabwe (102%), South Africa (80%), Swaziland (62%), and Lesotho (44%) (World Health Organization [WHO], *Trends in Maternal Mortality* 2010; *Lancet*

2007;370:1311). Two countries, Botswana and South Africa, are upper/middle income countries, which mean they are in the same economic category as Brazil and the Russian Federation.

Epidemiology of transmission: The differences in HIV prevalence among countries and regions of the world reflect the differences in epidemiology of HIV transmission in those areas and the degree to which the epidemic is generalized or concentrated. In *generalized epidemics*, transmission is widespread in the heterosexual population, whereas in *concentrated epidemics*, transmission is confined mainly to people who engage in high-risk behaviors and general population prevalence is less than 1%. These differences in epidemiology have implications for prevention, care, and treatment interventions. Table 16-1 characterizes regional epidemics worldwide.

Table 16-1

Characteristics of Regional Epidemics

Region	Description of Epidemic	% of People With HIV >15 Years of Age Who Are Women
Asia	• No country has a generalized epidemic. • HIV is concentrated among IDUs (16% are living with HIV), sex workers and their partners, and MSM.	34
Caribbean	• Unprotected sex, especially paid sex, between men and women is driving transmission.	55
Central and South America	• Main routes of transmission in this region are concentrated among MSM and IDUs. • Brazil accounts for one-third of those infected.	35
Eastern Europe and Central Asia	• Epidemics continue to rise in this region, concentrated mainly among IDUs (25% are living with HIV) and sex workers and their partners.	49
Oceania	• Papua New Guinea has the only generalized epidemic in the region. • Unprotected sex is driving transmission.	46
Sub-Saharan Africa	• The epidemic is stable or decreasing in most countries. • The majority of transmission is due to unprotected heterosexual intercourse. • Mother-to-child transmission during pregnancy, labor, or breastfeeding is also a major source of transmission.	60
Western and Central Europe and North America	• Unprotected sex between men and IDUs continues to dominate patterns of HIV transmission. • Discrete geographic areas are affected, particularly urban coastal settings.	27

Note: All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix

Sources: Adapted from UNAIDS, *Report on the Global AIDS Epidemic* 2010; CDC, *HIV/AIDS Surveillance Report* 2009;19; and *UN Millennium Development Goals Report* 2010

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Barriers to Care

System factors: In many countries of the world, particularly LMICs, healthcare services are provided primarily by Ministries of Health or faith-based (mission) hospitals rather than by private-sector hospitals and clinicians (as in the United States). In those countries, various health system factors contribute to patients' inability to access care:

- *Political factors*, which may include lack of government financial commitment to health, inadequate health facility coverage for the population, competing health priorities, and lack of universal health coverage or individual or group insurance schemes.

- *Economic factors*, such as poor or absent facility and transportation infrastructure, inadequate human resources, and poor pay for healthcare providers. In sub-Saharan Africa, healthcare workers must care for 2 of every 3 people living with HIV globally, yet they represent only 3% of the world's human resources for health (WHO, *Global Tuberculosis Control* 2010). Many healthcare workers in this region are themselves living with HIV, and most are in some way affected by the virus and have responsibilities to orphaned or ill family members.

- *Geographic factors*, such as physical barriers (e.g., impassable roads during rainy season).

- *Organizational factors*, such as lack of interpreters, negative attitudes among staff, inadequate staffing, and vertical and nonintegrated programs.

Patient factors: In countries that have functioning healthcare systems, access to services may be limited by patient factors that serve as barriers to care:

- *Socioeconomic factors*, such as extreme poverty with inability to pay for diagnostic tests, therapeutic interventions, or travel to clinic or hospital; and poor education and health literacy.

- *Cultural factors*, such as traditional practices, cultural and religious beliefs that influence health-seeking behavior, gender disparities, gender-based violence, and stigma related to HIV.

In adopting the 2001 *Declaration of Commitment on HIV/AIDS* (UN General Assembly Resolution S-26/2, 27 June 2001), UN member states agreed to systematically review and regularly report on their progress in realizing universal access to HIV prevention, treatment, care, and support by 2010. When widespread access to antiretroviral therapy (ART) began in 2004 (UNAIDS, *Report on the Global AIDS Epidemic* 2010), it was considered a significant achievement given the health system challenges known to exist in most LMICs.

Comorbidities

Comorbidities commonly associated with or affected by HIV in lower resource countries are often not the same as those seen in the United States, or they may have more significant implications for health because of inadequate resources for screening and treatment. In low-resource settings, common HIV co-infections include infections of significant public health consequence in the general population. This overlap may create competing health priorities and insufficiently coordinated resources where programs are not integrated. In the setting of HIV, increased rates of TB can result in greater risk of TB transmission to people who are not HIV infected. Where HPV infection is endemic, a lack of effective cervical cancer screening programs leads to increased risk of cervical cancer that may not be offset by adequate ART. Malaria and HIV have important interactions in both pregnant and nonpregnant women. All of these co-infections have significant implications for HIV prevention and care needs.

Tuberculosis: An estimated 380,000 HIV infected people died from TB in 2009. Among people living with HIV globally, TB is the leading cause of death. It is the third leading cause of death for HIV infected women of reproductive age. TB is the most common presenting opportunistic infection in the world, and it is the point of entry into HIV care for many patients, particularly in sub-Saharan Africa. South Africa alone accounts for 25% of all HIV-related TB infections globally (UNAIDS, *Report on the Global AIDS Epidemic* 2010; WHO/UNAIDS/UNICEF, *Towards Universal Access Progress Report* 2010).

HIV infection is the single greatest risk factor for the reactivation of latent mycobacterial infection (*Tubercle Lung Dis* 1992;73:311, *Int J Tuberc Lung Dis* 2000;4(2):9). Because of this relationship, there has been a dramatic increase in the incidence of TB in countries with a high prevalence of both TB and HIV (*AIDS* 1995;9:665). In the setting of HIV, TB is more likely to be smear negative or extrapulmonary, making diagnosis more challenging. HIV progression also appears to be increased in the setting of TB (*J Acquir Immune Defic Syndr Hum Retrovirol* 1998;19:361, AIDS 2001;15:143).

The rate of TB is approximately 10-fold higher in HIV infected pregnant women than in pregnant women who are not HIV infected, and TB–HIV co-infection increases maternal mortality. In some tertiary hospitals in South Africa, HIV–TB coinfection accounts for approximately 14% of all maternal mortality (*AIDS* 2001;15:1857). Results of a study from India indicate that HIV–TB coinfection in the mother was associated with a 3.4 increased probability of infant death with maternal HIV infection alone (*Clin Infect Dis* 2007;45:241).

Malaria: Malaria is a leading global cause of death and disability. Eighty-five percent of the 250 million cases and 91% of the 800,000 annual malaria deaths occur in Africa in areas where HIV prevalence is also elevated (Roll Back Malaria, *Key facts*, http://www.rollbackmalaria.org/keyfacts.html; Wellcome Trust, *Illustrated History of Tropical Diseases* 1996;231). Moreover, the interaction of the two diseases may affect transmission, clinical manifestations, and treatment outcomes of both diseases. HIV impairs acquired immunity to malaria, and like other concomitant infections, malaria

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can cause a transient increase in HIV viral load (*Lancet* 2000;356:1051, *J Infect Dis* 2005;192:984, *Lancet* 2005;365:233). In pregnancy, HIV infection increases malaria susceptibility and adverse outcomes; placental malaria is associated with increased risk of mother-to-child transmission of HIV (*AIDS* 2003;17:2539).

Human papillomavirus: HPV is the most common sexually transmitted pathogen worldwide and is the major etiologic agent of cervical cancer. In women in most developing countries, cervical cancer is the most common cancer and the most common cause of cancer death (Cervical Cancer Action, *Progress in Cervical Cancer Prevention: The CCA Report Card* 2011); it kills nearly 250,000 women per year. HIV is associated with higher incidence and prevalence and longer persistence of HPV; with a greater likelihood of oncogenic HPV subtypes; and with increased frequency and severity of cervical dysplasia, a precancerous condition. Invasive cervical cancer is an AIDS-defining illness, and rates of cervical cancer may be increased in the setting of HIV, especially if screening is not adequate.

Different Interventions for Different Settings

Public Health Approach

A public health approach to HIV prevention, care, and treatment is essential in LMICs, where financial constraints, competing health priorities, and shortages of healthcare providers are common. This requirement is particularly true for areas with generalized epidemics. In countries with concentrated epidemics, targeted approaches are essential for efficient use of scarce resources.

Decentralized services for universal access: The Declaration of Alma-Ata, accepted by WHO member countries, emphasizes the importance of primary healthcare for equitable access to health (*Declaration of Alma-Ata* 1978). Universal access to HIV services requires decentralized services at the primary care and community levels. Essential to expansion of services for HIV prevention, care, and treatment in many LMICs is the allocation of clinical tasks to cadres of healthcare workers, who may include the following:

- Lay workers who are trained to provide HIV counseling and testing

- HIV infected women who have gone through prevention of mother-to-child transmission (PMTCT) programs themselves and are then trained to provide peer counseling to other HIV infected pregnant women

- Nurses and clinical officers who are trained to initiate and manage ART

- Nurses who perform voluntary medical male circumcision

- High school graduates who are trained to perform smear microscopy to diagnose TB.

In LMICs, nongovernmental organizations (NGOs) are intimately involved in the provision of HIV prevention, care, and treatment services. By contrast, in well-resourced countries, HIV infected women receive care in a formal public or private healthcare system.

The United States is the largest donor to global AIDS response efforts. Through the President's Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund to Fight AIDS, Tuberculosis and Malaria (in partnership with other high-income countries), the United States provides national governments and NGOs in LMICs with support to expand access to services, without which HIV incidence and mortality would continue to increase in many regions.

Different Prevention Interventions

For every two people who start ART each year, five are newly infected with HIV. In 2008, 72% of all new HIV infections occurred in sub-Saharan Africa (WHO, *Guidance on provider-initiated HIV testing and counselling in health facilities* 2007). Of the 1.4 million pregnant women in need of HIV care, treatment, and support, including options for PMTCT, 91% are in sub-Saharan Africa (WHO/UNAIDS/UNICEF, *Towards Universal Access Progress Report* 2010).

Targeted prevention: HIV prevention efforts should be evidence based and target the common drivers of transmission in different epidemic settings. In the words of UNAIDS, "know your epidemic and respond accordingly." Knowing one's epidemic often means knowing where the last 1,000 new HIV infections occurred, because the next 1,000 infections are likely to occur in similar populations. In concentrated epidemic settings, new HIV infections disproportionately affect "most-at-risk" populations, including sex workers, MSM, and IDUs. In hyperendemic settings such as southern Africa, the majority of new infections occur within the general population, often within stable partnerships (UNAIDS, *HIV Prevention Toolkit*, http://hivpreventiontoolkit.unaids.org/Knowledge_Epidemic.aspx). In several African countries, 50% or more of HIV infected people may be in serodiscordant relationships (*Reprod Health Matters* 2008;16:151, *Lancet Infect Dis* 2010;10:770).

Combination prevention: Combination prevention uses a mixture of behavioral, biomedical, and structural interventions and targets the prevention needs of different populations on the basis of epidemiologic and demographic data (*MMWR* 2006;55 RR14:1). Successful prevention efforts effect change on multiple levels—individual, organizational, and societal—and provide mutually reinforcing messages and interventions (USAID/AIDSTAR-One, *Combination Approaches: An Overview of Combination Prevention*, http://www.aidstar-one.com/focus_areas/prevention/pkb/combination_approaches/overview_combination_prevention).

Behavioral prevention: Behavioral prevention includes the ABC approach—**A**bstinence, **B**e faithful (partner reduction), and **C**ondom use (and promotion). One challenge with behavioral approaches is that many women in LMICs find these prevention strategies difficult to use. For instance, in settings where a woman's status in the family and the community is determined by the number

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of children she bears, condom use may be prohibited because it prevents pregnancy. And in many cases, women have little or no control over the conduct of sexual relationships, particularly in the context of stable partnerships.

Biomedical prevention: Biomedical prevention includes medical approaches to block infection, decrease infectiousness, or reduce risk of infection. One such approach is voluntary male circumcision. Following issuance of WHO and UNAIDS recommendations, this approach is now being scaled up widely in Southern and Eastern Africa , where it has the potential to avert 4.1 million new HIV infections by 2025 if coverage rapidly reaches 80% (USAID Health Policy Initiative, *Potential Cost and Impact of Expanding Male Circumcision in 14 African Countries* 2009). As described in Chapter 3, *Prevention,* ARV-based vaginal microbicides are showing promise as a woman-directed method of prevention (*Science* 2010; 329 :1168). Data from HPTN 052, a randomized clinical trial designed to evaluate ART for prevention of sexual transmission among serodiscordant couples, indicates that earlier initiation of ART (at CD4+ cell counts of 350–550/mm^3) reduced HIV transmission to the uninfected partner by 96% as compared with people who initiated ART at lower CD4+ cell counts (*N Engl J Med* 2011; 365:493).

Results of several PrEP clinical trials using either daily TDF or TDF/FTC in at risk HIV-uninfected individuals are now available and show mixed results (see Chapter 3: *Prevention of HIV Infection*). It is likely that adherence was a key factor in the discrepant results of these studies (*AIDS* 2012;26(7):F13). In July 2012 the FDA approved a label indication for TDF/FTC for reduction of risk for sexual acquisition of HIV infection among adults, including heterosexual women. In August 2012 the CDC issued interim guidance for clinicians considering the use of PrEP for HIV prevention in heterosexually active adults, particularly those with known HIV-infected partners (*MMWR* 2012; 61(31):586):1).

These studies and the HPTN 052 results have major implications for the use of antiretroviral agents for prevention, particularly among serodiscordant couples, and especially for those who wish to conceive or are unable or unwilling to use safer sexual practices. These results may also have implications for prevention in the setting of generalized epidemics or among high-risk groups in concentrated epidemic settings.

Structural prevention: Structural prevention takes into account social, political, and economic factors that contribute to individual risk and vulnerability. A recent study from Malawi found that paying school fees for adolescent girls and providing the girls and their families with a small amount of discretionary income (as little as $4 USD per month) reduced HIV acquisition by 50% and herpes simplex virus-2 (HSV-2) acquisition by 75% among schoolgoing adolescent girls, who were less likely to engage in transactional sex (World Bank, *A cash transfer program reduces HIV infections among adolescent girls,* http://siteresources.worldbank.org/DEC/Resources/HIVExeSummary(Malawi).pdf).

Testing and HIV Diagnosis

Provider-initiated testing and counseling for HIV, also known as *opt-out screening*, in which a patient is notified that testing will be performed unless he or she declines, has been recommended by WHO since 2007 for countries with generalized epidemics (WHO, *Guidance on Provider-Initiated HIV Testing and Counselling in Health Facilities* 2007). However, implementation has been less than ideal in most settings. For example, in 2008, only 22% of TB patients globally knew their HIV status, despite the clear indication for HIV testing that TB provides in most settings, given high co-infection rates (WHO, *Towards Universal Access Progress Report* 2010).

Rapid tests: The use of rapid diagnostic tests for HIV, through either parallel or serial testing, is the mainstay of laboratory diagnosis of HIV in most resource-limited settings, given limited laboratory capacity. Selection of tests in any setting depends on available resources and prevalence of HIV types 1 and 2, which will have an effect on negative and positive predictive values. In addition to the FDA-approved rapid tests described in Chapter 3, several other rapid tests are available internationally.

Diagnosis in infants: With regard to diagnosis of HIV in infants, DNA PCR is used in resource-limited settings if laboratory capacity is sufficient. Where climate, transport of specimens, and laboratory capacity are especially challenging, dry blood spot samples are collected. Because breastfeeding is the primary infant feeding choice of women in most LMICs, HIV testing is conducted again 6 weeks after cessation of breastfeeding to avoid the risk of breast milk transmission.

HIV Care and Treatment in Lower-Resource Settings

The approach to HIV care and treatment in resource-limited settings is substantially different from the approach in the United States, which emphasizes use of state-of-the-art medications and laboratory testing. Care and treatment in lower resource settings, however, emphasize PMTCT and treatment of co-occurring infections such as malaria, TB, and cervical cancer (HPV). Availability of other types of care, including ART, varies from country to country. Laboratory tests for CD4+, viral load, and viral resistance often are not an option.

Prevention of Mother-to-Child Transmission

The international community has set a goal of virtual elimination of mother-to-child transmission of HIV by 2015. However, in 2009, only half of HIV infected pregnant women in LMICs received any antiretrovirals (ARVs) for PMTCT (53%). One country, Nigeria, accounts for one-third of this gap between women in need of ARVs for PMTCT and those who actually receive any intervention, whether single-dose nevirapine, AZT + single dose nevirapine, or HAART. (UNAIDS, *Report on the Global AIDS Epidemic* 2010; WHO, *Towards Universal Access Progress Report* 2010; UN, *Millennium Development Goals Report* 2010).

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It is estimated that half of HIV infected pregnant women have CD4+ cell counts <350/mm³ and require ARVs for their own health. Yet, in 59 LMICs that reported in 2009, only 15% of women who received any ARVs received highly active antiretroviral therapy (HAART) as treatment (UNAIDS, *Report on the Global AIDS Epidemic* 2010; WHO, *Towards Universal Access Progress Report* 2010, *AIDS* 2010;24: 1374; *J Acquir Immune Defic Syndr* 2010;55:404; *WHO Guidelines on HIV and Infant Feeding* 2010).

Care and treatment of HIV infected women, irrespective of pregnancy status, must take priority if universal access to care and treatment is to be achieved. Although 80% of UN member states reported the percentage of adults and children receiving ART and 70% reported on percentage of HIV infected pregnant women who received ARVs to reduce the risk of mother-to-child transmission in 2009, few were able to report on whether pregnant women were receiving ARVs for treatment rather than prevention. Even fewer were able to report on the impact of PMTCT interventions.

In April 2012, WHO endorsed a new option for PMTCT known as Option B+. This involves use of a single universal regimen to both treat HIV-infected pregnant women and for PMTCT and to continue this therapy for life, regardless of CD4+ cell count. The strategic advantages of this approach include further simplification of regimen and service delivery and harmonization with ART programs; protection against MTCT in future pregnancies; prevention against sexual transmission to HIV serodiscordant partners; and avoidance of treatment interruption between pregnancies. Numerous countries are now adopting this approach, although systems and support requirements need careful assessment and outcomes after program implementation need evaluation. (WHO, Programmatic Update-Use of antiretroviral drugs for treating pregnant women and preventing HIV infection in infants. April 2012 (http://www.who.int/hiv/PMTCT_update.pdf)

With regard to choices for infant feeding, although replacement feeding undoubtedly prevents postnatal transmission, in LMICs it has been associated with increased risk of death from other causes. Therefore, in 2010, WHO infant feeding recommendations changed to include the key principle that infant feeding choices for HIV prevention must be balanced with protection from other causes of child mortality (*WHO, Guidelines on HIV and Infant Feeding* 2010). In most low-resource settings, breastfeeding has significant benefits that outweigh risk of HIV transmission: It provides ideal infant nutrition in the first 6 months of life; reduces infant morbidity and mortality; delays return of fertility with exclusive breastfeeding, promoting child spacing and maternal recovery from blood loss; and is low cost and culturally acceptable (*Lancet* 2000;355:451).

Comprehensive Care

Care and treatment of people living with HIV should address the needs of the patient as an individual and as a member of a family; however, the approach to care and treatment in resource-limited settings is substantially different from the approach in the U.S. Comprehensive packages of HIV care vary across countries and depend on resources available and prevalent diseases.

For example, in Africa, the package of care may include insecticide-treated nets for the prevention of transmission of malaria by mosquito vectors and safe water vessels and chlorine for the prevention of water-borne diseases, in addition to condoms and cotrimoxazole.

Tuberculosis: The dual epidemics of TB and HIV require specific interventions to reduce transmission of the bacilli and prevent progression from TB infection to disease. This approach is particularly the case in sub-Saharan Africa, where up to 80% of patients diagnosed with TB are co-infected with HIV. Essential components of care for people living with HIV in such areas include a high index of suspicion combined with isoniazid preventive therapy, respiratory infection prevention and control, and prompt diagnosis and treatment of TB (intensified case finding). TB symptom screening at each patient visit is becoming common in settings of co-epidemics, a situation not applicable to the United States, where incidence of TB is significantly lower.

Malaria: HIV infected people are at increased risk of severe or complicated malaria, depending on the malaria transmission setting, and therefore have an even greater need for malaria prevention and control measures. Insecticide-treated bed nets, confirmed diagnosis (particularly as rapid diagnostic tests are more readily available), and appropriate treatment should be afforded to everyone, regardless of HIV status, but are particularly important for those who are HIV infected. The recommended intermittent preventive therapy for malaria (i.e., 2 to 3 doses of sulfadoxine–pyrimethamine during pregnancy for women in malaria-endemic areas) is not given to HIV infected women taking cotrimoxazole, given the similar effects of the two sulfa drugs (WHO, *Malaria and HIV Interactions and Their Implications for Public Health Policy* 2004).

Cervical cancer: The most effective approach for cervical cancer control is cervical screening. Pap smear with adjunctive high-risk HPV testing is the standard of care in the United States and other high-income countries, but in LMICs, lack of adequate financing, healthcare infrastructure, human resources, and capacity to follow up often make such screening unavailable. Visual inspection with acetic acid (VIA) is considered safe and acceptable, is inexpensive, and provides results immediately, thereby allowing for prompt treatment with cryotherapy or loop electrosurgical excisional procedure (LEEP) or referral for more suspicious lesions. Implementation of this low-tech screening procedure is expanding across many LMICs in HIV care settings. Compared with Pap smear, VIA generally has higher sensitivity but lower specificity, and it has high negative predictive value but low positive predictive value (*Gynecol Oncol* 2010;1793, *J Obstet Gynaecol* 2008;28:638). Results of a cluster randomized trial in India comprising approximately 31,000 women receiving VIA and a similar number of controls indicated the following: VIA+ women received cryotherapy at the same visit, and VIA was associated with a 24% reduction in Stage 2 or higher invasive cervical cancer and a 35% reduction in cervical cancer mortality (*Lancet* 2007;370:398).

In general, HPV DNA testing appears to be more objective and reproducible and has higher sensitivity than VIA. In another cluster randomized trial in India, HPV testing was compared with VIA, cytology, and standard of care (no screening) in >31,000 women in each arm and with 8 years follow-up. HPV testing was associated with 50% reduction in detection of advanced cervical

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cancer and cervical cancer deaths compared with women with no screening. No significant differences were found between women screened with VIA or cytology and standard-of-care participants (*New Engl J Med* 2009;360:1385).

More recently, an HPV DNA test has been adapted for low-resource settings and is being field tested; it can detect 14 high-risk HPV types, and results are available within 2 hours using basic laboratory facilities. However, cost may be a significant barrier. It is likely that more effective screening strategies will utilize both HPV testing and VIA, possibly using one technique as an initial screen with triage of positive results to the second technique. PEPFAR is providing funding to implement use of non-cytology-based screening techniques in HIV programs.

Antiretroviral Treatment

Unmet goals: The international community target of achieving at least 80% ART coverage for treatment-eligible patients by 2010 has not been met, and it is not likely to be met by the renewed goal of 2015. By 2009, of the people who needed HIV treatment, only 19% in Eastern Asia , 25% in Western and Central Africa, 41% in Eastern and Southern Africa, and 57% in Southeast Asia and Oceania had access to ART. However, these percentages represent significant progress, because only 2% of all eligible people were receiving therapy in 2002. Eight LMICs—Botswana, Cambodia, Croatia, Cuba, Guyana, Oman, Romania, and Rwanda—achieved universal access by December 2009, and currently, more than 5 million people are receiving these life-saving drugs (*UNAIDS Global Report* 2010, *WHO Towards Universal Access Progress Report* 2010, *UN Millennium Development Goals Report* 2010).

Eligibility: In 2010, the WHO HIV treatment guidelines were changed to recommend earlier initiation of ART (from CD4+ cell count <200/mm^3 to CD4+ cell count <350/mm^3) irrespective of clinical symptoms and WHO Clinical Stage 3 and 4, including TB, irrespective of CD4+ cell count. This change increases the estimated number of patients eligible for ART from 10 million to 15 million (UNAIDS, *Report on the Global AIDS Epidemic* 2010; WHO, *Towards Universal Access Progress Report* 2010).

Challenges: Although six classes of drugs and more than 20 FDA-approved ARVs are available for use in the United States, only three classes of drugs are widely available for use in the developing world, and choices within those classes are limited, largely related to cost. Standardized first-line and second-line treatment regimens are generally recommended. Common challenges of ARV provision in many countries include the following:

- Limited availability or accessibility of drug alternatives when drug toxicity or failure occurs

- Refrigeration requirement for some formulations where electricity and refrigeration are not widely available

- Co-treatment with TB and the challenge of drug interactions between rifampicin and nevirapine and protease inhibitors

- Limited ability to evaluate and manage adverse effects related to treatment (e.g., hyperlactatemia, lactic acidosis related to d4T)

- Stock-outs: More than one-third (38%) of countries reported at least one stock-out of ARVs (i.e., drug not available at the service delivery point) procured centrally in health facilities in 2009 (WHO, *Towards Universal Access Progress Report* 2010)

- Adherence concerns related to several factors:
  - Stigma of HIV diagnosis, which is often greater in these settings and may affect willingness to take drugs on a regular schedule

  - Sharing of drugs with other infected family members

  - Improvement in symptoms, weight gain, etc., which may be interpreted as a signal that treatment is no longer needed

- Limited number of healthcare providers in general and, in particular, few who are able to prescribe ART

- Inadequate training and mentorship in prescribing ART

- Inadequate availability of referral and consultative services.

Cost: The cost of ART has dropped substantially in the past 10 years, in large part because of pressure from international groups and greater availability of generic formulations, including fixed-dose combinations.

WHO guidelines reserve protease inhibitors for second-line treatment, because of cost as well as other considerations (e.g., storage requirements, more extensive drug interactions). The weighted median costs of second-line regimens that include protease inhibitors are 10- to 40-fold greater than the least expensive first-line regimen, d4T/3TC/NVP (WHO/UNAIDS/UNICEF, *Towards Universal Access Progress Report* 2010).

In 2004, d4T was changed from a preferred to an alternative drug for treatment of HIV-1 by the U.S. Department of Health and Human Services (HHS) because of increasing reports of associated toxicities (HHS, *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*, 2004), yet in LMICs, it has been the backbone of ART in combination with 3TC since the introduction of ARVs. The most common first-line regimen in the 59 LMIC countries evaluated in 2009 (excluding the Americas region) were d4T/3TC/NVP (38.1%), d4T/3TC/EFV (21.5%), AZT/3TC/NVP (18.9%) and AZT/3TC/EFV (12.6%). However, as of 2010, WHO no longer recommends d4T in the first-line regimen as a result of drug toxicity (hyperlactatemia affects up to 5% of those taking d4T), and many governments are currently phasing out the use of the drug entirely (WHO, *Antiretroviral Therapy for HIV Infection in Adults and Adolescents* 2010). Table 2 presents a comparison of HIV prevention, care, and treatment in the United States and LMICs.

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Table 16-2

Comparison of Recommended HIV Prevention, Care, and Treatment in the United States and in Low- and Middle-Income Countries

Intervention	United States	International (LMICs)
Primary HIV prevention	• Condoms (male and female) • Reduced number of partners • STI prevention/screening/ treatment • Harm reduction for IDUs • Drug abuse treatment • PEP • ART as prevention	• Condoms (male and female) • Voluntary male medical circumcision • Reduced number of partners • STI prevention/screening/ treatment • PEP • ART as prevention
HIV testing	• Opt-out testing recommended • Reactive rapid or conventional screening test, with confirmation by supplemental antibody test (e.g., Western blot)	• Opt-out testing recommended in regions with generalized epidemics • Serial or parallel rapid tests for screening and confirmation
STI screening in pregnancy	• HIV, syphilis, HbsAg, C. trachomatis, N. gonorrhoea, and trichomoniasis • HCV in high-risk women	• HIV and syphilis
Cervical cancer screening and prevention	• Year 1, cytology x2; annually thereafter if normal • Colposcopy if any abnormal Pap smear • Excisional treatment with LEEP or cervical conization for high-grade lesions • HPV vaccine recommended for primary prevention	• Pap smear where available, but access is extremely limited Alternatives include VIA; cryotherapy or LEEP can be performed at same visit if VIA is abnormal • HPV testing an option if rapid test available and affordable • HPV vaccine largely unavailable due to cost
Vaccinations for primary prevention	• HPV recommended for children and adolescents irrespective of HIV status • HBV, HAV, pneumococcal, and influenza vaccines recommended	• HBV recommended if serological testing is available • Influenza vaccination where available and feasible
Other prevention	• Primary prevention of several opportunistic infections, on the basis of CD4+ cell count: - PCP (CD4+ cell count <200/mm^3): TMP–SMX - Toxoplasmosis (CD4+ cell count <100/mm^3):TMP–SMX - Disseminated MAC disease (CD4+ cell count<50/mm^3): azithromycin - TB (test for (+) latent TB and/or close contact with active TB, if active TB ruled out): isoniazid + pyridoxine	• TMP–SMX decreases clinical malaria in areas of stable malaria transmission • Isoniazid for HIV-infected persons with unknown or (+) TB skin test, once active TB excluded • Sulfadoxine–pyrimethamine during pregnancy for women in malaria-endemic areas (this is not needed of woman already on cotrimoxazole)

Table 16-2   *continued*

Comparison of Recommended HIV Prevention, Care, and Treatment in the United States and in Low- and Middle-Income Countries

Intervention	United States	International (LMICs)
STI screening and treatment	• Annual screening for HIV, syphilis, chlamydia, gonorrhea, and trichomoniasis • Treatment widely available and based on etiologic diagnosis	• Passive case finding, with syndromic management. • Antivirals for HSV not widely available
HIV assessment at diagnosis	• CDC clinical staging • CD4+ cell count • HIV viral load • HIV drug-resistance testing	• WHO clinical staging • CD4+ cell count if available

Initiation of ART	• ART recommended for all with HIV
	  - Strong recommendation: CD4+ cell count <200–500 cells/μl
	  - Moderate recommendation: CD4+ cell count >500 cells/μl
	• ARV resistance testing prior to initiation
	• Screen for HLA-B5701 before starting ABC
	• Co-receptor tropism assay before starting CCR5 inhibitor
		• CD4+ cell count <350/mm^3
		• WHO Clinical Stage 3 or 4 irrespective of CD4+ cell count

PMTCT: maternal interventions	• HAART for all, irrespective of CD4+ cell count or signs/symptoms
	• Cesarean delivery if viral load >1,000 c/mL at 36 weeks
	• Monitor viral load and CD4+ cell count in pregnancy
		• HAART if CD4+ cell count ≤350/mm^3 or WHO Clinical Stage 3 or 4
		• If CD4+ cell count >350/mm^3, then choose option A or B:
		  - **Option A:** AZT beginning at 14 weeks + single dose NVP at onset of labor + AZT/3TC in labor and for 7 days postpartum **or**
		  - **Option B:** triple ARV prophylaxis with AZT/3TC/LPV/r or AZT/3TC/ABC or AZT/3TC/EFV or TDF/3TC(FTC)/EFV beginning at 14 weeks and continuing until delivery or, if breastfeeding, until 1 week after complete cessation
		  - **Option B+:** triple ARVs with TDF/3TC/FTC/EFV, starting as soon as diagnosed and continued for life

PMTCT: ART preferred/ alternative drugs/ regimen	• **NRTIs:** AZT, 3TC, ABC, FTC, TDF • **NNRTIs:** NVP; EFV • **PIs:** LPV/r, ATV, SQV/r; DRV/r • **INSTI:** RAL	• AZT/3TC/NVP or AZT/3TC/EFV or TDF/3TC(FTC)/NVP or TDF/3TC(FTC)/EFV

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Table 16-2 *continued*

Comparison of Recommended HIV Prevention, Care, and Treatment in the United States and in Low- and Middle-Income Countries

Intervention	United States	International (LMICs)
PMTCT: infant interventions	• Avoid breastfeeding • Infant prophylaxis with AZT for 6 weeks • When the mother has not received antepartum ARV drugs: add 3 doses of NVP in the first week of life • DNA–PCR or RNA assay at 14–21 days, 2–3 months and 4–6 months; confirm positive test on separate sample to diagnose HIV	• Exclusive breastfeeding for 6 months • Infant prophylaxis if mother is on HAART: AZT or NVP for 4-6 weeks • If mother is on ARV prophylaxis only: *Option A:* - **Breastfeeding:** daily NVP until 1 week after all exposure to breast milk (minimum 4–6 weeks if breastfeeding stops before 6 weeks) - **Nonbreastfeeding:** daily NVP or sd-NVP at birth and twice daily AZT for 4–6 weeks • Mother on ARV prophylaxis only: *Maternal Option B:* breastfeeding or replacement feeding: - Daily NVP *or* twice-daily AZT for 4–6 weeks • DNA–PCR at 6 weeks (if available); otherwise, antibody testing at 18 months
Preferred first-line ART regimens	• EFV/TDF/FTC or ATV/r/TDF/FTC or DRV/r/TDF/FTC or RAL/TDF/FTC	• AZT or TDF +3TC (or FTC) + EFV or NVP • Move toward AZT or TDF-based regimens from d4T, when d4T regimens have been used as principal option
TB/HIV co-infection	• Preferred: rifampin plus EFV-based ART • Rifabutin is preferred rifamycin in PI-based regimen needed, dose reduction of rifabutin indicated	• EFV-based regimen (alternatives if EFV not tolerated: NVP or triple NRTI) • Rifampicin is in first-line TB regimen: co-administration with PI-based regimen not recommended because of drug interactions

Notes: If an intervention is included in the U.S. column but not in the international guidelines column, then that intervention is not recommended by WHO. All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix.

Sources: WHO, *Antiretroviral Therapy for HIV Infection in Adults and Adolescents* 2010; ACOG, *Practice Bulletin: Clinical Management Guidelines for Obstetrician–Gynecologists* 2010;117; MMWR 2010;59 RR12 ;1; WHO, *Guidelines for the Management of Sexually Transmitted Infections* 2003; WHO, *Essential Prevention and Care Interventions for Adults and Adolescents Living With HIV in Resource-Limited Settings* 2008; WHO, *Antiretroviral Drugs for Treating Pregnant Women and Preventing HIV Infection in Infants* 2010; WHO, *Cervical Cancer Screening in Developing Countries* 2002

Targeted Laboratory Testing

Country-level guidelines: In most LMICs, the WHO guidelines are adapted at the country level to guide provision of HIV services; in the United States and other high-resource countries, guidelines for care are developed nationally and updated regularly. Guidelines vary from country to country, largely as a result of differential resources. Access to resistance testing in LMICs is virtually nonexistent, in stark contrast to the United States, where HIV resistance testing is widely available and implemented at patient entry into care and with treatment failure. Even viral load testing is not widely available in LMICs, where one test may cost more than the country's per capita health expenditure (WHO, *Patterns of Global Health Expenditures: Results for 191 Countries* 2002).

Efficient use of resources: In the United States, laboratory tests are considered essential elements of HIV care because they assist clinicians in determining the optimal treatment regimen. However, in LMICs, considerations of cost, efficient use of resources, and inadequate laboratory infrastructure have precluded their widespread use. In addition to a country-level HIV drug resistance and assessment strategy, WHO recommends targeted use of viral load testing to reduce the risk of resistance (WHO, *Antiretroviral Therapy for HIV Infection in Adults and Adolescents* 2010)

It has been established that routine laboratory monitoring for toxic effects, such as hematology and liver function tests, are not necessary for safe delivery of ART; however, CD4+ cell count monitoring is important in determining eligibility for treatment and deciding when a switch to second-line treatment might be necessary (*Lancet* 2010; 375: 123). Now that eligibility includes anyone with CD4+ cell count <350/mm^3, a lack of access to CD4+ testing will exclude many patients who may need HAART but do not have WHO Clinical Stage 3 or 4 disease.

Managing ART: The WHO guiding principles for ART management include the following:

- Laboratory monitoring is not a prerequisite for initiation of ART.

- CD4+ cell count and viral load testing are not essential for monitoring.

- Laboratory monitoring should be symptom directed.

- If resources allow, viral load should be used to confirm treatment failure suspected on the basis of immunological or clinical criteria.

- If resources allow, viral load should be measured every 6 months to detect failure earlier (WHO, *Antiretroviral Therapy for HIV Infection in Adults and Adolescents* 2010).

Table 16-3 shows the divergence between U.S. and WHO recommendations for laboratory monitoring. In many LMICs, even CD4+ cell count, the only recommended test (all others are considered desirable), is not widely available.

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Table 16-3

Minimum Recommended Laboratory Monitoring Schedules

Time	U.S. Guidelines: HHS 2011	International Guidelines: WHO 2010
At diagnosis or entry into care	• CD4+ cell count • HIV viral load • Resistance testing • HBV and HCV serology • Basic chemistry • ALT, AST, total and direct bilirubin • CBC with differential • Fasting lipid profile • Fasting glucose or hemoglobin A1C • Urinalysis	• CD4+ cell count • *HBsAg*
Routine care when not on ART	• CD4+ cell count every 3–6 mo. • HIV viral load every 3–6 mo. • Basic chemistry every 6–12 mo. • ALT, AST, total and total bilirubin every 6–12 mo. • CBC with differential every 3–6 mo. • Fasting lipid profile v 12 mo. • Fasting glucose or hemoglobin A1C every 12 mo.	• CD4+ cell count every 6 months
At initiation of ART or switch	• CD4+ cell count • HIV viral load • Resistance testing • HLA–B*5701 testing if considering ABC • Tropism testing if considering CCR5 antagonist • HBV serology repeated if not immune at baseline • Basic chemistry • ALT, AST, total and total bilirubin • CBC with differential • Fasting lipid profile • Fasting glucose or hemoglobin A1C • Urinalysis • Pregnancy test if starting EFV	• CD4+ cell count • *Creatinine clearance if starting TDF and high risk[1]* • *ALT if starting NVP and high risk[2]* • *Hb if starting AZT and low CD4+ cell count or BMI*
2-8 weeks after ART initiation or switch	• HIV viral load • Basic chemistry • ALT, AST, total and direct bilirubin • CBC with differential if on AZT • Fasting lipid profile	• *ALT and AST at 2 and 4 weeks for women with CD4+ cell count >250/mm^{3} and NVP* • *ALT and AST at 4 weeks if HCV or HBV co-infection* • *Hb if on AZT at 4 weeks and low CD4+ cell count or BMI*

| Table 16-3 | *continued* |

Minimum Recommended Laboratory Monitoring Schedules

Time	U.S. Guidelines: DHHS 2	International Guidelines: WHO 2010
Every 3-6 months after ART initiation or switch	• CD4+ cell count • HIV viral load • Basic chemistry • ALT, AST, total and direct bilirubin • CBC with differential • Fasting glucose or hemoglobin A1C, if abnormal at last measurement	• *ALT and AST at 12 weeks for women with CD4+ cell count >250/mm³ and NVP* • *Hb if on AZT and low CD4+ or BMI*
Every 6 months after ART initiation or switch	• Fasting glucose • Urinalysis if on TDF • Fasting lipid profile if abnormal at last measurement	• CD4+ cell count • *Creatinine clearance if on TDF*
At 12 months after ART initiation or switch	• Fasting lipid profile • Urinalysis • CD4+ cell count (in clinically stable patients with suppressed viral load, monitor every 6–12 mo.)	
Treatment failure[3]	• CD4+ cell count • HIV viral load • Resistance testing • Tropism testing if considering a CCR5 antagonist	• CD4+ cell count • *HIV viral load to confirm treatment failure* • HIV viral load if immunological failure

Notes: "Desirable" tests are in *italics*. All abbreviations are defined in the list of Abbreviations and Acronyms, p. ix.

[1] Defined as underlying renal disease, older age group, low BMI, diabetes, hypertension, and concomitant use of boosted PI or nephrotoxic drugs.

[2] Defined as ART-naïve HIV infected women with CD4+ cell count >250/mm³ or HCV coinfection.

[3] Treatment failure in resource-limited settings is diagnosed differently from in the United States, because viral load monitoring is not readily available. If it is available, virological failure is only diagnosed when the viral load remains >5,000 copies/mL. Alternatively, clinical failure is the diagnosis of new or recurrent WHO Stage 4 condition on HAART (not immune reconstitution and inflammatory syndrome), and immunological failure is a fall of CD4+ cell count to below baseline, 50% from peak value, or failure to rise above 100/mm³.

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Conclusion

Scientific knowledge and advances, translated into effective clinical interventions, are the fundamental underpinnings of HIV prevention, care, and treatment; however, for most of the world, social and economic factors are the prime determinants of the approach to HIV/AIDS care. Healthcare structure and social support systems must be strengthened if global HIV control is to be achieved. Gender equity in society, including reproductive choice, economic independence, and freedom from gender-based violence, is essential for optimal HIV prevention and care in women.

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