Beth Israel Deaconess Medical Center
Healthcare Associates HIV Manual

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The recommendations contained in this monograph are based upon published guidelines for HIV-infected adults. Because the field of HIV disease is constantly advancing and standards of practice continue to evolve, clinicians should be familiar with the current medical literature and request consultations as necessary.

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Comments are welcome and can be e-mailed to the author at hlibman@bidmc.harvard.edu.

Overview

The care of HIV-infected patients has undergone dramatic changes over the past two decades with the advent of combination antiretroviral therapy and the introduction of viral load testing and resistance testing in clinical practice. Patients are hospitalized less frequently with opportunistic infections and are living longer. However, with this encouraging news have come important challenges. For patients, they include long-term adherence to a medical regimen and dealing with its toxicities. For health care practitioners, they include keeping up with a rapidly changing but incomplete knowledge base and addressing the needs of complicated outpatients within time constraints.

The management of HIV disease lends itself to a primary care approach. Most successful models are multidisciplinary. In addition to history and physical examination, the initial evaluation of HIV-infected patients should include assessment of their knowledge of the disease and emotional state. Baseline laboratory studies are performed to screen for occult disease and guide drug usage, to determine HIV disease status, and to look for evidence of concurrent infections. The CD4 cell count and viral load are essential for staging and guiding therapeutic decisions. The diagnosis and management of chronic hepatitis and tuberculosis remain significant challenges in patients with HIV disease.

Antiretroviral therapy is recommended in all HIV-infected patients regardless of their clinical status or CD4 cell count. There are both individual (decreased morbidity and mortality) and public health (decreased sexual transmission) benefits of treatment. The strength of antiretroviral therapy recommendations and evidence supporting them are greater in patients with lower CD4 counts.

The recommended initial regimen is a nucleoside reverse transcriptase inhibitor (NRTI) x 2 *plus* a non-nucleoside reverse transcriptase inhibitor (NNRTI), boosted protease inhibitor (PI), or integrase inhibitor (II). Drug combinations over the past several years have consisted of a decreased number of pills that are dosed less frequently and associated with fewer side effects. Factors that may have a negative impact on adherence should be reviewed and addressed prior to initiation of therapy. About three-quarters of patients will achieve maximal viral suppression with their initial regimen, and the majority of these will continue to have undetectable virus on a long-term basis. The success rate diminishes progressively with subsequent regimens. All HIV-infected patients, regardless of whether they are receiving antiretroviral therapy, should be monitored with laboratory tests. HIV resistance testing is indicated when the viral load is not maximally suppressed on antiretroviral therapy.

Complications have been associated with the long-term treatment of HIV infection. These include: 1) lipodystrophy syndrome (body fat maldistribution, hyperlipidemia, glucose intolerance); 2) coronary artery disease; 3) premature bone loss; 4) avascular necrosis of hips; 5) lactic acidemia/acidosis; and 6) peripheral neuropathy.

Opportunistic infection (OI) prophylaxis for PCP is indicated if CD4 count < 200/mm^3; TMP-SMX is the drug of choice. Prophylaxis for toxoplasmosis is indicated in patients with positive toxoplasmosis serology if CD4 count < 100/mm^3. Prophylaxis for MAC infection is indicated if CD4 count < 50/mm^3; azithromycin is the drug of choice. OI prophylaxis can often be safely discontinued for these infections following immune reconstitution with antiretroviral therapy.

Routine health care maintenance issues in HIV-infected patients include immunizations (e.g., pneumococcal, hepatitis B, hepatitis A, and influenza vaccines), periodic screening for concurrent infections (e.g., syphilis, other STDs, and tuberculosis), regular Pap smears in women (and perhaps anal Pap smears in at-risk populations), and other age- and sex-appropriate interventions.

Chapter 1. HIV Testing and Counseling

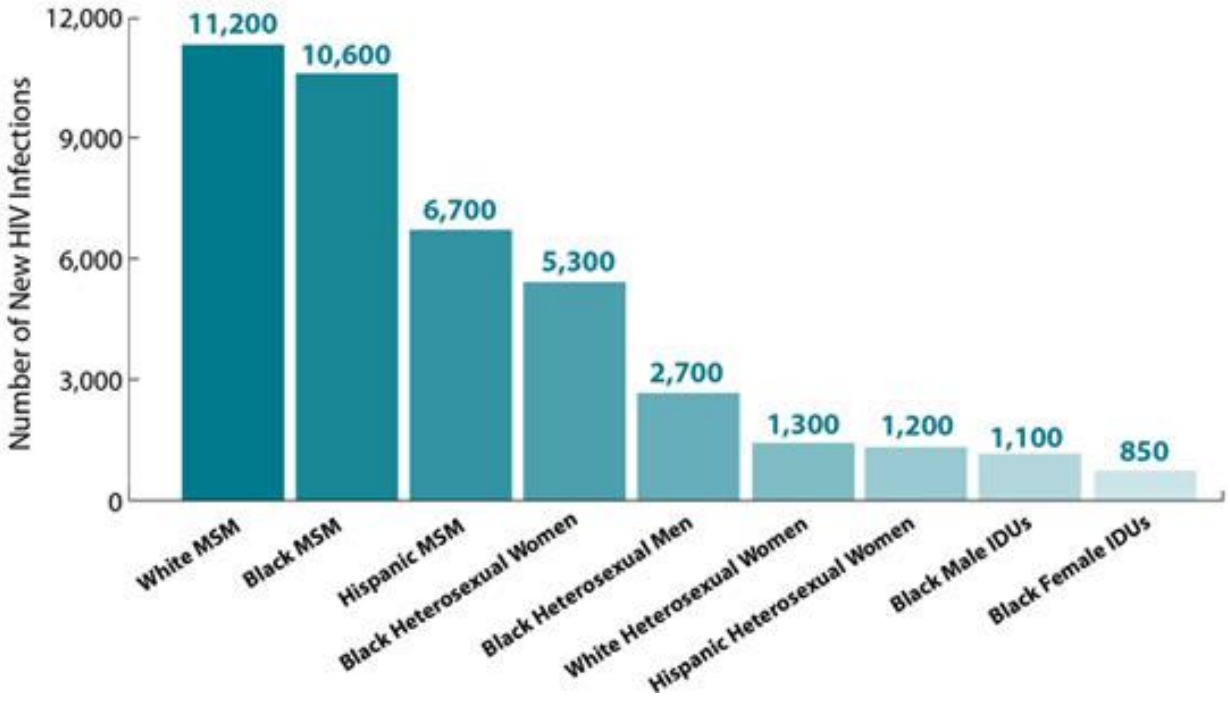
Background

Health care personnel in Massachusetts are required by statute to obtain verbal informed consent from the patient or his/her health care proxy prior to HIV antibody testing. An HIV antibody test can be ordered by a treating physician or authorized HIV counselor. Pretest and post-test counseling, while often useful, should not be construed by practitioners as a barrier to testing. All newly diagnosed cases of HIV infection are reportable to the Massachusetts Department of Public Health.

Epidemiology of HIV/AIDS and Risk of HIV Transmission

Despite advances in treatment, HIV infection remains a leading cause of morbidity and mortality. There are an estimated 1,148,200 HIV-infected persons in the United States and approximately 50,000 new cases per year. Sixty-two percent of new cases are transmitted by male-to-male sexual contact, 27% by heterosexual contact, 7% by injection drug use, 3% by male-to-male sexual contact and injection drug use, and 1% by other means. Thirty-six percent of new cases are in persons age 13-29 years, 23% age 30-39 years, 23% age 40-49 years, and 17% age 50 years or older. Forty-seven percent of new cases are in African Americans, 28% in whites, 21% in Hispanics, and 4% in others.

Figure 1: Estimated New HIV Infections in the United States, 2010, for the Most Affected Subpopulations



Estimated HIV Transmission Rate Per Event by Exposure Route

- Transfusion of contaminated blood 90%
- Needle-sharing injection drug use 0.7%
- Unprotected receptive anal intercourse 1.0%
- Occupational needle-stick exposure 0.3%
- Unprotected receptive vaginal intercourse 0.2%
- Unprotected insertive vaginal intercourse 0.03%
- Unprotected insertive anal intercourse 0.07%
- Unprotected receptive oral intercourse 0.06%
- Unprotected insertive oral intercourse 0.005%

It is important to note that these figures are approximate and may vary depending on the viral load of the source, the presence of other sexually transmitted diseases in both persons, male circumcision (for insertive vaginal intercourse), and other factors.

Guidelines

In late 2006, the Centers for Disease Control and Prevention (CDC) recommended inclusion of HIV antibody testing as part of the routine health care of healthy adults and adolescents after determining that about one-quarter of HIV-infected persons were unaware of their serostatus. The key points of these guidelines follow:

- All healthy adolescent and adult patients should be screened at least once during their lives after notification that an HIV test will be performed unless they decline ("opt-out" testing)
- Specific informed consent is unnecessary
- Persons at high risk for HIV infection should be screened at least annually
- Prevention counseling should be not required as part of routine HIV testing, but it is strongly encouraged for persons at high risk

HIV antibody testing should be never be construed by patients as coercive. As these federal recommendations are implemented over time, the hope is that a higher percentage of HIV-infected persons will become aware of their serostatus and that decreased HIV transmission will result through a reduction in risk behaviors and the institution of antiretroviral therapy.

Traditional Indications

Historical

- Men who have sex with men
- Persons with multiple sexual partners
- Current or past injection-drug users (IDUs)
- Recipients of blood products between 1978 and 1985
- Persons with current or past sexually transmitted diseases
- Commercial sex workers and their sexual contacts
- Persons who have been sexually assaulted
- Persons who have had occupational exposures
- Pregnant women and women of childbearing age
- Children born to HIV-infected mothers
- Sexual partners of those at risk for HIV infection
- Persons who consider themselves at risk or request testing

Clinical

- Tuberculosis
- Syphilis
- Recurrent shingles
- Unexplained chronic constitutional symptoms
- Unexplained generalized adenopathy
- Unexplained chronic diarrhea or wasting
- Unexplained encephalopathy
- Unexplained thrombocytopenia
- Thrush or chronic/recurrent vaginal candidiasis
- HIV-associated opportunistic diseases (e.g., *Pneumocystis* pneumonia, Kaposi's sarcoma)
- Suspected primary HIV syndrome

Primary HIV infection is a nonspecific viral illness that occurs on average two weeks after exposure and is characterized by fever, adenopathy, pharyngitis, rash, and myalgia/arthalgia. It should be considered in the patient with a prolonged or atypical viral illness or with Epstein-Barr virus (monospot)-negative mononucleosis-like syndrome. In the patient with suspected primary HIV infection or recently acquired HIV infection (less than three months prior), both an HIV antibody test and viral load are necessary for diagnosis. A negative or indeterminate antibody test in conjunction with a very high viral load (often millions of copies/ml) is characteristic of primary HIV infection. Low titer false-positive HIV viral load assays have been reported in persons with acute non-HIV-related illness, so caution is advised in their interpretation in this setting.

Contraindications

- Inability of patient to understand implications of test result
- Acute psychosis
- Major depression or suicidality
- Lack of adequate personal support system

Potential Benefits and Risks

- Individual health benefits include antiretroviral therapy, prophylaxis for opportunistic infections, screening and prophylaxis for tuberculosis, screening for and treatment of syphilis and other sexually transmitted diseases, administration of appropriate vaccinations, and institution of other health care maintenance measures
- Public health benefits include decrease in HIV transmission through identification of primary HIV infection, reduction of high-risk behaviors and lowering of viral loads, and monitoring of HIV infection epidemiology
- Risks include false-positive test result, false-negative test result, adverse psychological reactions, breach of confidentiality, and social discrimination

Pretest Counseling

Pretest counseling often includes the following:

- Distinguishing between anonymous and confidential testing and discussing the availability of home-testing kit
- Reviewing natural history of HIV infection
- Reviewing reasons for testing and expectations
- Reviewing individual risk behaviors and risk-reduction measures
- Discussing meaning of positive and negative results
- Assessing personal and social supports

Conventional Testing Procedure

- HIV antibody testing is performed by using an enzyme-linked immunosorbent assay (ELISA), which is a highly sensitive test
- If this result is negative, the HIV antibody test is reported as negative
- If this result is positive, the ELISA is generally repeated
- If the repeat test is positive, a Western blot (WB) assay, which is more specific, is performed for confirmation
- If WB assay result is positive (2 or 3 out of 3 characteristic bands present), the HIV antibody test is reported as positive

- WB results are occasionally described as indeterminate (1 of 3 characteristic bands present); in these instances, supplemental testing (e.g., HIV viral load) is recommended
- An indeterminate WB may indicate the presence of recent HIV-1 infection or of HIV-2 infection, which is endemic in West Africa
- A low CD4 cell count is not diagnostic of HIV disease and should never be used in lieu of HIV antibody testing

Rapid immunoassay tests (e.g., OraQuick) that detect HIV antibody in blood or oral fluid within 20 minutes have been developed. These enable clinicians to provide definitive negative and preliminary positive results immediately. A positive rapid HIV antibody test should be confirmed with the more specific WB.

Newer HIV diagnostic modalities (e.g., fourth-generation combination of antibody and p24 antigen assays) may change the testing paradigm in the future.

Post-test Counseling

Post-test counseling often includes the following:

- Reviewing meaning of test results and implications
- If test result is positive:
  Assessing patient's reaction and ability to cope
  Anticipating need for immediate support and follow-up plan for medical evaluation
- If test result is negative:
  Restating possibility of acquiring HIV infection if patient is involved in high-risk activities
  Dispelling any false beliefs regarding invulnerability or immunity to HIV infection

Risk Reduction Counseling

Risk reduction counseling is an important component of both pretest and post-test counseling. It should include the following advice:

- Reduce or limit the number of sexual partners
- Use latex condoms with water-based lubricant for all sexual activity
- Detoxification or methadone maintenance program for IDUs
- Use sterile needles; however, if equipment is shared, make sure it is cleaned with bleach as recommended
- Do not share personal items such as razors and toothbrushes

Chapter 2. Initial Evaluation of Patients

History

In addition to reviewing the past medical and family medical histories, medications (prescription, OTC, and complementary drugs), and allergies of the patient with newly diagnosed HIV infection, the following issues should be addressed:

- HIV risk behaviors (sexual and drug use)
- Knowledge of HIV infection
- Emotional response to diagnosis
- Family and social situation
- Employment and insurance status
- Travel history
- Exposure to tuberculosis, syphilis, other sexually transmitted diseases, and viral hepatitis (A, B, and C)
- Status of immunizations

In the patient with established HIV infection followed previously by another practitioner, knowledge of prior opportunistic diseases, CD4 cell counts (nadir and recent) and HIV viral load results (highest and recent), and antiretroviral therapy chronology, including drugs used and reasons their discontinuation, are also important.

Review of Systems and Physical Examination

Attention should focus on the following organ system symptoms and signs and on screening for HIV-related conditions:

- Constitutional symptoms: fever, chills, night sweats, weight loss
- Integument: seborrhea, psoriasis, onychomycosis, herpes simplex virus, varicella-zoster virus, Kaposi's sarcoma, generalized adenopathy
- HEENT: altered vision, dysphagia, cytomegalovirus (CMV) retinitis, thrush, oral hairy leukoplakia, periodontal disease
- Pulmonary: cough, dyspnea, evidence of pneumonia
- Gastrointestinal: odynophagia, diarrhea, organomegaly, anal dysplasia/ carcinoma
- Genitourinary: vaginitis, pelvic inflammatory disease, genital warts, cervical dysplasia/carcinoma
- Neurological: headache, problems with memory, change in behavior or personality, focal abnormalities

Laboratory Studies

Baseline laboratory evaluation is performed to assess for organ system dysfunction, to stage and monitor HIV disease, and to screen for other important disorders. Recommended studies include the following:

- Complete blood and differential counts
- Glucose, BUN/creatinine, liver function tests
- HgbA1c and fasting lipid profile
- Urinalysis
- CD4 cell count (see below)
- HIV viral load (see below)
- HIV genotype test
- RPR or VDRL
- Anti-HAV
- HBsAg, HBcAb (HBsAb if prior immunization)
- Anti-HCV
- Toxoplasmosis (IgG) serology
- PPD or gamma-interferon release assay
- Pap smear in women
- *Chlamydia* and GC assays in persons at risk
- Consider anal Pap smear in persons at risk

A G6PD qualitative screening test (if *Pneumocystis jiroveci* (*carinii*) pneumonia [PCP] prophylaxis with dapsone is contemplated) and CMV IgG antibody test (if blood transfusions are anticipated) are also appropriate. In addition, it may be reasonable to perform a chest x-ray in some clinical circumstances (e.g., history of injection drug use).

The following tests are important for the staging and monitoring of HIV disease:

CD4 Cell Count

- Main surrogate marker for HIV disease progression
- Normal range is 350 to 1100/mm^3; there is average decline of 75-100/mm^3 per year without treatment but variability between patients and in a given patient over time
- Intercurrent illnesses may transiently affect value
- Some inter- and intra-laboratory variability, so use caution in interpreting widely disparate values
- Clinical uses are to determine need for antimicrobial prophylaxis and to assess prognosis

HIV Viral Load

- Measurement of viral RNA in plasma by polymerase chain reaction (PCR)
- Lower limit of detection of ultrasensitive PCR assay is < 20 copies/ml
- High level correlates with CD4 cell count decline and clinical disease progression
- Normal variability of 0.3 log (three- to five-fold)
- Intercurrent illnesses and immunizations may transiently affect value
- Clinical uses are to monitor antiretroviral therapy

Spectrum of HIV Disease

Patients are at risk for the following medical conditions at listed CD4 cell count thresholds:

CD4 Cell Count > 500/mm^3

- Most patients asymptomatic
- Bacterial infections (pneumococcus, staphylococcus), pulmonary tuberculosis, shingles, other dermatologic conditions

CD4 Cell Count 500-200/mm^3

- Many patients asymptomatic
- Generalized adenopathy, thrush, Kaposi's sarcoma

CD4 Cell Count < 200/mm^3

- PCP, toxoplasmosis, cryptococcosis

CD4 Cell Count < 50/mm^3

- CMV and *Mycobacterium avium* complex infections
- Increased risk of lymphoma
- Mortality highest

It is important to note that the risk for a specific opportunistic disease increases the longer the CD4 cell count is below threshold and the more it drops below that level. For instance, the risk of a patient developing PCP is far greater if his CD4 cell count is 20/mm^3 for three months than it is if his CD4 cell count is 200/mm^3 for one week.

The CD4 percentage (CD4 count/total lymphocyte count) may be useful adjunctively in clinical settings in which the CD4 cell count may not accurately reflect the patient's immune status (e.g., anatomic or functional asplenism).

Chapter 3. Antiretroviral Therapy

Background

The past two decades have shown great advances in the management of HIV disease. Most patients with HIV infection, including those with very advanced disease, benefit from antiretroviral therapy. The following recommendations are based on our current understanding of the pathophysiology of HIV disease and the results of clinical trials. They reflect updated guidelines of US Department of Health and Human Services. *Because of the changing nature of clinical practice in this area, expert consultation should be sought when initiating or changing drug regimens.*

Pathophysiology of HIV Infection

Viral replication occurs throughout the course of HIV infection at very high rates. It is estimated that 10^{10} viral particles are produced each day. The patient's immune system keeps pace with this activity during the clinical latency period. However, in the absence of effective antiretroviral treatment, the immune system ultimately reaches a "point of exhaustion," at which viral replication exceeds its ability to produce CD4 cells. This leads to a decline in immunologic function and the development of clinical manifestations including opportunistic infections and neoplasms.

The rate of viral replication is thought to stabilize after primary infection at a particular level or "set point." This level may be maintained within a ten-fold range over months and possibly years. The viral load is highly correlated with the rate of disease progression and mortality.

General Guidelines

The primary goal of antiretroviral therapy is "to keep the viral load as low as possible for as long as possible." Maximal suppression of the virus makes it more difficult for resistance to develop. Partial suppression results in the emergence of resistant mutant strains in the viral population. These are present because of the rapid turnover of HIV and the many random errors made during replication. They predominate in the context of ineffective treatment because of a competitive advantage over pansensitive (“wild type”) virus.

Approximately three-quarters of patients on combination antiretroviral therapy will achieve maximal viral suppression, and this effect is durable in the majority. Medication adherence is essential. Subsequent attempts at viral suppression may be increasingly less successful. Current antiretroviral regimens are not curative probably because of persistence of HIV in quiescent CD4 lymphocytes and because of "sanctuary sites," which are regions of the body, such as the central nervous system and gonads, in which some drugs do not penetrate well.

Combination antiretroviral therapy is the standard of care for HIV infection. Monotherapy and less potent combination regimens lead to the development of viral resistance within weeks to months. There are currently twenty-five antiretroviral agents and seven fixed-dose drug combinations available. Antiretroviral drugs are classified by their mode of action against the virus as follows: 1) nucleoside reverse transcriptase inhibitors (NRTIs); 2) non-nucleoside reverse transcriptase inhibitors (NNRTIs); 3) protease inhibitors (PIs); 4) entry inhibitors (EIs); and 5) integrase inhibitors (IIs).

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Generic Name	Abbreviation	Brand Name
zidovudine	ZDV, AZT	Retrovir
didanosine	ddI	Videx
stavudine	d4T	Zerit
lamivudine	3TC	Epivir
abacavir	ABC	Ziagen
emtricitabine	FTC	Emtriva
tenofovir (nucleotide)	TDF	Viread
zidovudine/lamivudine	ZDV/3TC	Combivir
zidovudine/lamivudine/abacavir	ZDV/3TC/ABC	Trizivir
abacavir/lamivudine	ABC/3TC	Epivir
tenofovir/emtricitabine	TDF/FTC	Truvada

Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Generic Name	Abbreviation	Brand Name
nevirapine	NVP	Viramune
delavirdine	DLV	Rescriptor
efavirenz	EFV	Sustiva
etravirine	ETR	Intelence
rilpivirine	RPV	Edurant

Protease Inhibitors (PIs)

Generic Name	Abbreviation	Brand Name
saquinavir	SQV	Invirase
ritonavir	RTV	Norvir
indinavir	IDV	Crixivan
nelfinavir	NFV	Viracept
lopinavir/ritonavir	LPV/RTV	Kaletra
atazanavir	ATV	Reyataz
fosamprenavir	FPV	Lexiva
tipranavir	TPV	Aptivus
darunavir	DRV	Prezista

Entry Inhibitors (EIs)

Generic Name	Brand Name
Enfuvirtide (fusion inhibitor)	Fuzeon
Maraviroc (CCR5 antagonist)	Selzentry

Integrase Inhibitors (IIs)

Generic Name	Brand Name
Raltegravir	Isentress
Dolutegravir	Tivicay

Multi-class combination preparations include TDF/FTC/EFV (Atripla), TDF/FTC/RPV (Complera), and TDF/FTC/elvitegravir/cobicistat (Stribild).

Dosing, toxicity, and other information for individual agents are described in the drug glossary. Antiretroviral agents vary considerably in their dosing and frequency, how they should be administered (with food or when fasting), their side effect profiles, and their potential interactions with other drugs.

Specific Guidelines

When should antiretroviral therapy be initiated?

Antiretroviral therapy is recommended in all HIV-infected patients regardless of their clinical status or CD4 cell count. There are both individual (decreased morbidity and mortality) and public health (decreased sexual transmission) benefits of treatment. The strength of antiretroviral therapy recommendations and evidence supporting them are greater in patients with lower CD4 counts.

- CD4 cell count < 350/mm^3 (AI)
- CD4 cell count 350 to 500/mm^3 (AII)
- CD4 cell count > 500/mm^3 (BIII)

Regardless of CD4 count, initiation of antiretroviral therapy is strongly recommended in HIV-infected patients with the following conditions:

- Pregnancy
- History of an AIDS-defining condition (Table 3-1)
- HIV-associated nephropathy
- HIV/hepatitis B coinfection

Rating of Recommendations: A=Strong; B=Moderate; C=Optional.
Rating of Evidence: I=Data from randomized controlled trials; II=Data from well-designed nonrandomized trials or observational cohorts studies with long-term clinical outcomes; III=Expert opinion.

Antiretroviral therapy has been shown to prevent transmission of HIV from an infected person to his/her sexual partner. This public health benefit may be important to consider when advising patients, especially those in a serodiscordant relationship.

Patients starting antiretroviral therapy should understand its potential benefits and risks and the importance of medication adherence, and they should be willing to commit to taking it on a long-term basis. Baseline laboratory testing, including CD4 cell count and viral load measurement, should be performed before initiating therapy (see Chapter 2).

What agents should be used?

Combination therapy using three drugs is recommended as initial therapy in the absence of virologic resistance. Recommended combinations include TDF/FTC given in conjunction with EFV *or* a RTV-boosted PI (ATV or DRV) *or* an II (Table 3-2).

Patient adherence to medical therapy is essential. Frequently missed doses will render a drug regimen ineffective and lead to the development of resistance. Missing as few as 5 to 10 percent of doses will decrease the likelihood of achieving viral suppression with older PI-based regimens; NNRTI and boosted PI regimens appear somewhat more forgiving. Every effort should be made to address factors, such as active substance abuse or significant psychological problems, in advance which may interfere with medication adherence (Tables 3-3 and 3-4).

NNRTIs and PIs have many potential drug interactions. Some agents are contraindicated for co-administration, and others may require dosage adjustment. More detailed information is available in the guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents at www.aidsinfo.nih.gov.

How should antiretroviral therapy be monitored?

Patients started on antiretroviral therapy should return in four weeks to assess toxicity of the regimen and to repeat safety studies (CBC, glucose, renal and hepatic function tests, lipid profile), CD4 cell count, and viral load. The viral load should decrease at least three-fold over this period of time. The CD4 count and viral load should be repeated monthly until virologic suppression is achieved. Once this task has been accomplished, follow-up laboratory studies should be performed every three to six months.

Except for short-term interruption because of toxicity or an acute illness that precludes oral therapy, antiretroviral drugs should be continued indefinitely. The safety

and effectiveness of treatment interruption strategies have not been demonstrated. Patients interested in this approach to management should be encouraged to participate in a clinical trial.

When should an antiretroviral drug regimen be modified?

Indications for modification of a drug regimen include inadequate viral load suppression, a rising viral load after suppression has been achieved, or the inability to tolerate medication(s). Inadequate viral load suppression or a rising viral load is the first evidence of resistance. This finding should prompt inquiry into the patient's medication adherence. If it has been compromised, every effort should be made to address the factors involved, and the viral load should be repeated one month later before considering modification of the regimen.

If a modified regimen is necessary, how should new drugs be selected?

If the regimen is being changed because of development of viral resistance, an entirely new combination that does not share cross-resistance with current drugs is recommended. A careful prior antiretroviral drug history and HIV resistance testing (see below) are important in selecting new agents. *Interpretation of resistance testing is a complicated and evolving field, and expert consultation is strongly recommended for practitioners with limited clinical experience.*

HIV Resistance Testing

The HIV genotype test provides a genetic "blueprint" of the predominant viral strain. It determines the presence of specific mutations in the HIV genome that correlate with clinical resistance to individual antiretroviral drugs. Results are generally interpreted using rules-based algorithms. The phenotype test provides a drug-sensitivity profile. It measures the inhibitory concentration (50% or 90%) of drugs and compares them to values seen with a pansensitive ("wild type") strain. Changes of greater than 2.5- to 4-fold are reliably detected. Results are generally categorized as sensitive, resistant, or intermediate. Resistance testing for IIs is available but generally not included in conventional genotypes.

HIV genotype testing is more readily available and less costly than phenotype testing but provides an indirect measure of susceptibility. Phenotype testing is generally preferred when multiple complex resistance mutations are anticipated. Both tests examine only the predominant virus isolated and may miss resistant background strains. Because of this characteristic, they are better at identifying drugs to which the virus is resistant than in predicting which ones will be effective.

Long-Term Treatment Complications

Significant complications have been associated with HIV infection and its treatment. These include: 1) lipodystrophy syndrome (body fat maldistribution, hyperlipidemia, glucose intolerance); 2) coronary artery disease; 3) premature bone loss; 4) avascular necrosis of hips; 5) lactic acidemia/acidosis; and 6) peripheral neuropathy.

Lipodystrophy syndrome has been reported in HIV-infected patients on combination antiretroviral therapy, especially regimens containing d4T and/or PIs. This syndrome consists of body morphology changes (deposition of fat in abdomen, breasts, and neck; loss of fat in face and extremities), metabolic complications (hyperlipidemia, glucose intolerance/diabetes mellitus), or both. The pathogenesis of lipodystrophy syndrome is not fully understood, and its management is syndromic (Figure 3-1).

The incidence of coronary artery disease in HIV-infected patients is higher than that in seronegative patients matched for age and gender. Studies have demonstrated an increase in subclinical atherosclerosis (e.g., carotid intima media thickness) and clinical endpoints (e.g., acute myocardial infarction). HIV infection is associated with increased soluble and cellular markers of inflammation, endothelial dysfunction, and altered coagulation, all of which have been shown to contribute to cardiovascular disease. The degree to which HIV infection itself, antiretroviral therapy, and traditional risk factors contribute to increased risk in this population is unknown. The PI class appears to be associated with higher risk of coronary artery disease. Abacavir has also been identified in some studies as a risk factor, although the data are inconsistent.

Premature bone loss (osteopenia/osteoporosis) has been reported in HIV-infected patients on long-term antiretroviral therapy, especially regimens containing TDF. Interference of vitamin D metabolism by PIs and lactic acidosis related to NRTI therapy may be responsible for bone loss in this setting, and HIV infection itself may also be a contributing factor. Immobility, cigarette smoking, excessive alcohol use, chronic renal failure, thyroid disease, hyperparathyroidism, hypogonadism, and chronic steroid therapy may accentuate bone loss. Baseline bone densitometry may be considered in HIV-infected patients who are 50 years old, especially if other risk factor(s) for premature bone loss are present. Calcium and vitamin D should be prescribed in high-risk patients; regular exercise and smoking cessation should be advised in all patients.

Avascular necrosis of the hips has also been described in HIV-infected patients on long-term antiretroviral therapy. It is not associated with traditional risk factors such as alcoholism and chronic steroid therapy. The condition presents as progressive unilateral or bilateral hip pain. Plain x-rays are often normal, and diagnosis is made by MRI scan. Early disease is managed symptomatically, but it may ultimately require hip replacement.

Lactic acidosis with a variety of clinical manifestations (peripheral neuropathy, pancreatitis, myopathy, steatosis with liver failure) has been described in HIV-infected patients on older NRTI-based regimens. It results from the inhibition of mitochondrial

DNA-polymerase. Because asymptomatic lactic acidemia has poor predictive value for decompensated lactic acidosis, screening for this condition is not recommended. However, in patients on NRTI-based regimens who have unexplained constitutional or gastrointestinal symptoms, a venous lactate level is recommended. If symptomatic lactic acidemia is confirmed, modification of the antiretroviral regimen is warranted.

Peripheral neuropathy is common in HIV-infected patients. The virus and certain older NRTI drugs (ddI, d4T) are usually responsible. It manifests with sensory symptoms involving the lower extremities. The diagnosis is made clinically after excluding other common causes of peripheral neuropathy. Management consists of discontinuation of the offending drug and control of HIV infection. If necessary, analgesics and antidepressants and/or anticonvulsants can be used for chronic pain management.

Special Considerations in Pregnant Women

Zidovudine (ZDV) has been shown to decrease the transmission of HIV from mother to child. AIDS Clinical Trials Unit (ACTG) study 076 demonstrated that treating HIV-infected women with ZDV during the second and third trimesters of pregnancy through delivery and treating the newborn can reduce the risk of vertical transmission by two-thirds.

Antiretroviral therapy is recommended in HIV-infected pregnant women. Detailed guidelines are available in "Recommendations for use of antiretroviral drugs in pregnant HIV-infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States" (available as living document on AIDSinfo: Department of Health and Human Services Web site at www.aidsinfo.nih.gov).

Table 3-1. AIDS-Defining Clinical Conditions

- Candidiasis of bronchi, trachea, or lungs
- Candidiasis, esophageal
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (> 1 month's duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes)
- Cytomegalovirus retinitis
- Encephalopathy, HIV-related
- Herpes simplex: chronic ulcer(s) (> 1 month's duration); or bronchitis
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (greater than 1 month's duration)
- Kaposi's sarcoma
- Lymphoma, Burkitt's
- Lymphoma, immunoblastic
- Lymphoma, primary, of brain
- *Mycobacterium avium* complex or *M. kansasii*, disseminated or extrapulmonary
- *Mycobacterium tuberculosis*, any site (pulmonary or extrapulmonary)
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- *Pneumocystis carinii (jiroveci)* pneumonia
- Pneumonia, recurrent bacterial
- Progressive multifocal leukoencephalopathy
- *Salmonella* septicemia, recurrent
- Toxoplasmosis of brain
- Wasting syndrome, HIV-related

Table 3-2. Recommended Drug Regimens for Antiretroviral-Naïve Patients

The optimal antiretroviral (ARV) regimen for a treatment-naive patient consists of two NRTIs in combination with a third active ARV drug from one of three drug classes: an NNRTI, a PI boosted with ritonavir, or an II (AI).

One of the following regimens for ART-naive patients regardless of baseline viral load or CD4 count:

NNRTI-Based Regimen:
- EFV/TDF/FTC[a] (AI)

PI-Based Regimens:
- ATV/r plus TDF/FTC[a] (AI)
- DRV/r plus TDF/FTC[a] (AI)

II-Based Regimens:
- DTG plus ABC/3TC[a] (AI)—only for patients who are HLA-B*5701 negative
- DTG plus TDF/FTC[a] (AI)
- EVG/cobi/TDF/FTC—only for patients with pre-ART CrCl >70 mL/min (AI)
- RAL plus TDF/FTC[a] (AI)

In addition to the regimens listed above, the following regimens are also recommended, but only for patients with pre-ART plasma HIV RNA <100,000 copies/ml:

NNRTI-Based Regimens:
- EFV plus ABC/3TC[a] (AI)—only for patients who are HLA-B*5701 negative
- RPV/TDF/FTC[a] (AI)—only for patients with CD4 count >200 cells/mm^3

PI-Based Regimen:
- ATV/r plus ABC/3TC[a] (AI)–only for patients who are HLA-B*5701 negative

Selection of a regimen should be individualized on the basis of virologic efficacy, toxicity, pill burden, dosing frequency, drug interaction potential, resistance testing results, comorbid conditions, and cost.

[a] 3TC may substitute for FTC or vice versa.

Key to Acronyms: 3TC=lamivudine; ABC=abacavir; ART=antiretroviral therapy; ARV=antiretroviral; ATV/r=atazanavir/ritonavir; cobi=cobicistat; CrCl=creatinine clearance; DRV/r=darunavir/ritonavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; II=integrase inhibitor; LPV/r=lopinavir/ritonavir; NNRTI=non-nucleoside reverse transcriptase inhibitor; NRTI=nucleoside reverse transcriptase inhibitor; PI=protease inhibitor; RAL=raltegravir; RPV=rilpivirine; r=ritonavir; TDF=tenofovir.

Adapted from Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents (available as living document on AIDSinfo: Department of Health and Human Services Web site at www.aidsinfo.nih.gov).

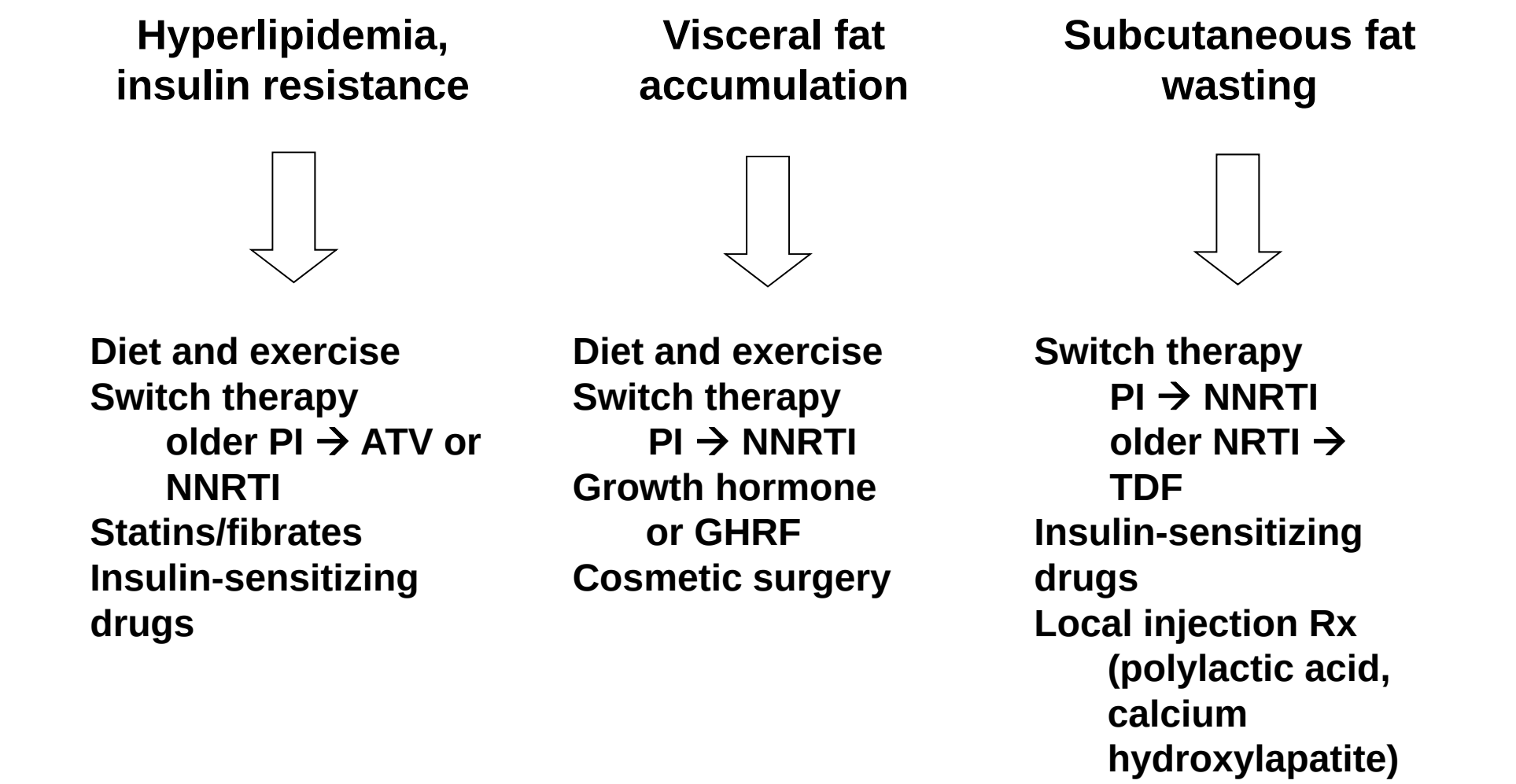
Table 3-3. Factors Having Negative Impact on Medication Adherence

- Lack of education about HIV disease
- Denial, anxiety, or depression
- Alcohol or drug use
- Poor social situation
- Inadequate health insurance
- Number of medications/pills
- Frequency of dosing
- Stringent dosing requirements
- Presence of side effects

Table 3-4. Useful Interventions to Promote Adherence

- Take time to educate and explain goals of therapy and need for adherence
- Develop concrete plan for specific regimen
- Minimize dosing frequency and number of pills
- Simplify food requirements
- Inform patient about potential side effects, and anticipate and treat them
- Avoid adverse drug interactions
- Provide written schedule, pictures of medications, pill boxes, and mechanical aids
- Recruit family and friends to support treatment plan

Figure 3-1
Management of Lipodystrophy Syndrome



Chapter 4. Pneumocystis Pneumonia Prophylaxis

Background

Despite advances in the management of HIV disease, *Pneumocystis jiroveci* (previously known as *carinii*) pneumonia (PCP) remains an important complication and cause of morbidity. PCP antimicrobial prophylaxis is very effective and has been demonstrated to prolong life. The risk of developing PCP becomes significant when the patient's CD4 cell count falls to about 200/mm^3 and increases progressively as it further declines.

PCP presents subacutely with fever, malaise, dyspnea on exertion, and a nonproductive cough. Physical examination may be normal or show scattered rales on auscultation of the lungs. The chest x-ray typically reveals diffuse interstitial infiltrates but may be normal in early infection. Oximetry often shows decreased oxygen saturation following exertion. Diagnosis is generally made by induced sputum with identification of the organism on direct fluorescent antibody test; bronchoscopy with lavage may be necessary in a minority of cases. Treatment of PCP consists of trimethoprim-sulfamethoxazole (TMP-SMX) or an alternative drug for three weeks. Adjuctive corticosteroid therapy is used in patients with significant respiratory dysfunction.

Guidelines

An algorithmic approach to PCP prophylaxis is presented in Figure 4-1. Effective agents for PCP prevention include TMP-SMX, dapsone, aerosol pentamidine (AP), and atovaquone (Table 4-1).

- All HIV-infected patients whose CD4 cell count is less than 200/mm^3 or CD4 percentage is less than 14, who have thrush, or who have a history of PCP and have not been immune reconstituted on antiretroviral therapy (see below) should receive prophylaxis.

- Primary prophylaxis can be safely discontinued in patients whose CD4 cell count rises above 200/mm^3 for 3 months on combination antiretroviral therapy. Secondary prophylaxis (maintenance therapy) in patients with a history of PCP can also be stopped in this context.

- TMP-SMX is the drug of choice for PCP prophylaxis. The recommended dose is one double-strength (DS) or single-strength (SS) tablet per day. It can also be given as one DS three times per week.

- TMP-SMX is preferred to dapsone because of increased efficacy and protection against conventional bacterial infections. It is preferred to AP because of increased efficacy, lower cost, protection against toxoplasmosis and conventional bacterial infections, and lower risk of extrapulmonary pneumocystosis. It is preferred to atovaquone because of much lower cost.

- Many patients with HIV infection develop toxicity to TMP-SMX. The most common side effects include fever, rash, and leukopenia. Strategies for managing mild reactions include discontinuation of the drug and resuming it at same or lower dose or use of a desensitization protocol (gradually increasing doses administered over several days). Many patients can be treated through mild drug reactions using acetaminophen and/or antihistamine for symptom management.

- Dapsone 100 mg po qd is recommended as the alternative agent in patients who cannot tolerate TMP-SMX. Side effects include fever, rash, and hemolytic anemia. G6PD qualitative assay should be performed before starting dapsone therapy; the drug is contraindicated in patients with G6PD deficiency. For dapsone to be effective as toxoplasmosis prophylaxis, which is indicated in context of CD4 cell count < 100/mm^3 and positive IgG serology, it should be given as 50 mg po qd in conjunction with pyrimethamine 50 mg po weekly. Folinic acid is advised to prevent bone marrow suppression from pyrimethamine.

- For patients who cannot tolerate dapsone, AP or atovaquone is recommended.

- AP 300 mg per month is given by Respirgard II jet nebulizer using 6 ml sterile water delivered at 6 L/min from a 50-psi compressed air source until the reservoir is dry, usually over 45 minutes. Active tuberculosis (TB) should be ruled out with PPD, chest x-ray, and other studies if necessary before initiating AP. Appropriate measures should be in place to prevent TB transmission in persons receiving AP. These include use of individual rooms or booths with negative pressure ventilation, air exhaust to the outside, scheduling to permit air exchange prior to use by another patient, use of particulate respirators by workers administering the drug, and restriction of patients from returning to waiting areas until their coughing subsides.

- Atovaquone is dosed as 1500 mg of suspension po qd with food. Side effects include gastrointestinal intolerance, rash, headache, and fever.

Table 4-1. Comparison of PCP Prophylaxis Regimens

Issue	**TMP-SMX**	**Dapsone**	**AP**	**Atovaquone**
Efficacy	High	Moderate	Moderate	Moderate
Toxicity	Moderate	Low-Moderate	Low	Low
Cost	Low	Low	High	High
Toxoplasmosis Protection	Yes	Yes *	No	Probably
Bacterial Infection protection	Yes	?	No	No
Risk of Extrapulmonary Pneumocystosis	No	No	Yes	No

* In conjunction with weekly pyrimethamine

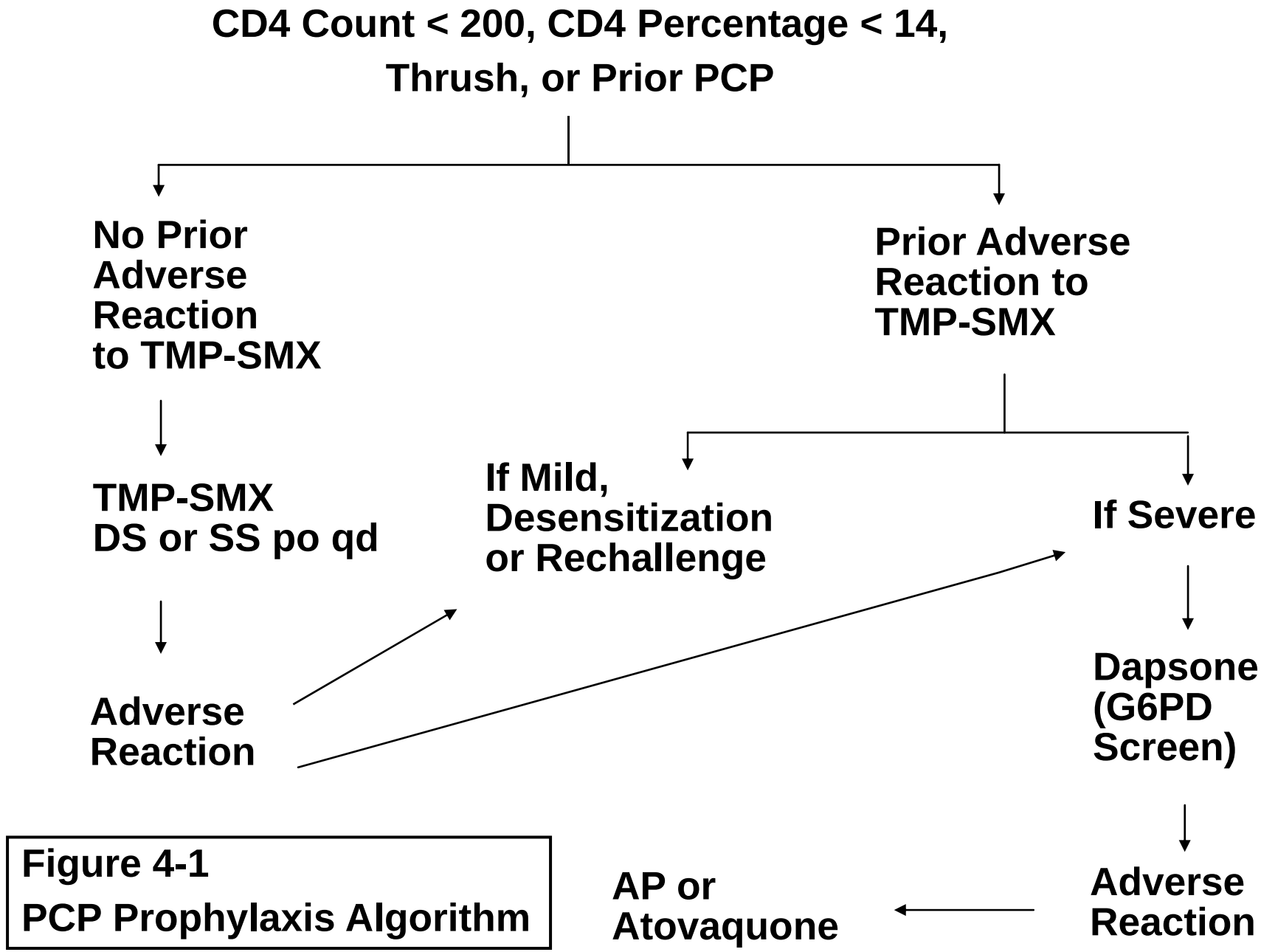


Figure 4-1
PCP Prophylaxis Algorithm

Chapter 5. MAC Infection Prophylaxis

Background

Mycobacterium avium complex (MAC) is a slow-growing bacterium that is an important cause of disseminated infection in patients with advanced HIV disease. The risk of developing MAC infection becomes significant when the patient's CD4 cell count falls to about 50/mm^3 and increases progressively as it further declines. Prophylactic antimicrobial therapy has been shown to be effective in preventing MAC infection, with the risk reduced by one-half in most studies.

MAC infection presents subacutely with nonspecific symptoms, including fever, fatigue, weight loss, and diarrhea. Physical examination may show few, if any, abnormalities. Diagnosis is generally made by isolator blood culture, although the organism can also be cultured from body tissues (e.g., bone marrow, liver). Treatment of MAC infection requires a combination of antimycobacterial drugs given for a prolonged period of time.

Guidelines

Prophylaxis is recommended in all patients with a CD4 cell count of less than 50/mm^3. Effective drugs include the macrolides azithromycin (1200 mg po weekly or 600 mg po twice per week) and clarithromycin (500 mg po bid); and rifabutin (300 mg po qd).

Azithromycin and clarithromycin are preferred to rifabutin because they are more effective. In addition, rifabutin requires dosage adjustment or is contraindicated for use with some protease inhibitors and non-nucleoside reverse transcriptase inhibitors. Both macrolides have the advantage of conferring protection against infection with bacterial respiratory pathogens such as pneumococcus. Clarithromycin is more costly than azithromycin, and their toxicities, which are primarily gastrointestinal, appear comparable. While the combination of a macrolide with rifabutin provides additional protection against MAC infection than either agent alone, there is also a greater risk of drug toxicity.

Before MAC prophylaxis is started, clinical assessment to rule out disseminated infection is recommended. If warranted, an isolator blood culture should be obtained.

Primary prophylaxis can be safely discontinued in patients whose CD4 cell count rises above 100/mm^3 for 3 months on combination antiretroviral therapy. Secondary prophylaxis (maintenance therapy) in patients with established MAC infection can be discontinued if the CD4 cell count rises above 100/mm^3 for 6 months and they are asymptomatic and have completed 12 months of antimicrobial therapy.

Chapter 6. Immunizations

Background

Patients with HIV disease are at increased risk for a variety of infections that can potentially be prevented by using available vaccine preparations.

Immunizations should be given as early in the course of HIV disease as possible for optimal effect. Patients with relatively preserved immune function are more likely to have a favorable response to vaccine challenge than those who are significantly immunocompromised. Booster doses may be necessary in some patients. Initiation of combination antiretroviral therapy in patients with advanced HIV disease may improve the immunologic response to vaccine preparations.

Killed or inactivated vaccines are considered safe in this population. Live pathogen vaccines, such as measles, mumps, rubella (MMR), varicella, and zoster, should be avoided in HIV-infected adults with a CD4 cell count < 200/mm^3. MMR and varicella vaccines can be used in patients with a higher count. Zoster vaccine is contraindicated in HIV-infected patients with a CD4 cell count < 200/mm^3; there are currently no formal recommendations in those with a higher count. Influenza and other vaccine preparations have been shown to transiently stimulate HIV replication and increase the viral load. However, this phenomenon does not appear to have an impact on overall disease progression.

Guidelines

Specific immunization recommendations for HIV-infected patients are presented in Table 6-1. Pneumococcal vaccine should be administered to all HIV-infected patients. There are two types available: a 23-valent polysaccharide vaccine (PPSV23) and a 13-valent conjugate vaccine (PCV13). Recommendations for immunocompromised patients, including HIV-infected persons, have recently been revised.

The HBV immunization series should be given to patients who have a negative screening serologic test for this infection. HAV vaccine should be administered to men who have sex with men and to patients with chronic hepatitis C virus (HCV) infection. HAV vaccine should also be considered in injection-drug users, a population in which outbreaks have been described. Influenza vaccine is especially important in persons with historical risk factors for exposure to the virus and the presence of conditions associated with increased morbidity from influenza. Routine use of hemophilus B (Hib) vaccine is not recommended in adults, but asplenic patients and those with a history of recurrent *Haemophilus influenzae* infection should be immunized. The indications for HPV vaccine in HIV-infected patients are the same as in the general population.

Table 6-1. Immunizations in HIV-infected Adults			
Vaccine	**Status**	**Dose/Regimen**	**Comments**
Pneumococcal vaccine	Recommended	0.5 mL IM Pneumococcal 13-valent conjugate vaccine (PCV13) (Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer, Inc., Collegeville, Pennsylvania) Pneumococcal 23-valent polysaccharide vaccine (PPSV23) (Merck & Co. Inc., Whitehouse Station, New Jersey)	Administer to all patients. Consider booster dose 5 years after initial immunization if given in setting of lower CD4+ cell count. • Pneumococcal vaccine-naive persons: PCV13 first followed by PPSV23 at least 8 weeks later and second PPSV23 dose 5 years later. • Previous vaccination with PPSV23: PCV13 at least 1 year after the last PPSV23 dose; for those who require additional doses of PPSV23, the first should be given no sooner than 8 weeks after PCV13 and at least 5 years after most recent PPSV23 dose.
Hepatitis B virus vaccine	Recommended in selected settings	Recombinant hepatitis B virus vaccine (GlaxoSmithKline, Middlesex, United Kingdom): 20 µg or recombinant hepatitis B vaccine (Merck & Co., Inc., Palo Alto, California): 10 µg IM given at 0, 1, and 6 months	Administer to patients without serologic evidence of past or present hepatitis B virus infection. Vaccinated patients should be tested for HBsAb response 1 month after the third dose; repeating the vaccine series at the same or a higher dose (40 µg) may be considered for those who do not respond.
Hepatitis A virus vaccine	Recommended in selected settings	1 mL IM with revaccination in 6-12 months; also available in combination with recombinant hepatitis B virus vaccine (GSK)	Administer to men who have sex with men, injection drug users, and persons with chronic liver disease. Vaccinated patients should be tested for an antibody response 1 month after vaccination; those who do not respond should be revaccinated.
Haemophilus influenzae, type B, virus vaccine	Consider in selected settings	0.5 mL IM	Administer to asplenic patients and patients with a history of recurrent *Haemophilus spp.* infections.

Influenza virus vaccine	Recommended	0.5 mL IM annually	Especially important in patients at high risk for exposure to or morbidity from influenza. There is evidence that the vaccine may transiently promote HIV replication.
Tetanus toxoid	Same as for patients without HIV infection	Td 0.5 mL IM	Td booster is recommended every 10 years. Tdap should replace a single dose of Td for adults older than 65 years who have not previously received a dose of Tdap.
Human papillomavirus vaccine	Recommended in girls and young women and in boys and young men aged 9 to 26 years	0.5 mL IM at 0, 2, and 6 months	

HBsAb indicates hepatitis B virus surface antibody; IM, intramuscularly; Td, tetanus and diphtheria (vaccine); Tdap, tetanus, diphtheria, and pertussis (vaccine).

Chapter 7. Cervical and Anal Cancer Screening

Rationale and Background

HIV disease is associated with an increased risk of cervical dysplasia, a precursor of cancer, in women. Most patients who develop this condition have a history of human papillomavirus (HPV) infection, which is a sexually transmitted pathogen that causes genital warts. The risk of developing cervical disease is greatest in women with advanced HIV disease.

The Pap smear has been demonstrated to be a useful screening test for cervical dysplasia. Its routine use in populations at risk decreases morbidity and mortality from cervical neoplasia.

Guidelines

A pelvic examination and Pap smear should be performed as part of the initial evaluation of all HIV-infected women, repeated six months later, and, if normal, repeated annually thereafter. Colposcopy is not recommended as a screening test in this population.

More frequent Pap smear evaluations (every 4-6 months) are recommended in the following circumstances:

- If endocervical component is absent
- If there is a history of HPV infection
- After treatment for any cervical abnormality

Women with abnormal Pap smear results showing cellular atypia (atypical squamous cells of undetermined significance [ASCUS]) or any degree of cervical dysplasia (low-grade or high-grade squamous intraepithelial lesion [SIL]) should be referred to a gynecologist for further diagnostic evaluation. In general, colposcopy and biopsy are performed.

Anal Pap Smear

It is unknown whether screening for anal dysplasia with Pap smears confers a morbidity or mortality benefit, and there currently are no consensus guidelines for anal Pap smear screening. However, based upon available information, it may be reasonable to perform an anal Pap smear every 6 to 12 months in HIV-infected patients at risk for HPV infection or with a history of anogenital warts or other HPV-related conditions. The technique consists of inserting a dacron swab 2-4 cm into the anal canal and rotating it 360 degrees while it is removed very slowly. It is fixed in the same manner and interpreted using identical criteria as a cervical Pap smear. Standardized approaches for the management of anal dysplasia have been developed and are being evaluated.

Chapter 8. Stratified Management of Patients

Specific management considerations in HIV-infected patients include initiation and continuation of antiretroviral therapy, prophylaxis against PCP and other opportunistic infection, and health care maintenance issues. Patients are stratified based upon their CD4 cell count.

Stratified Management

CD4 Cell Count > 200/mm^3

- Initiate antiretroviral therapy in all patients after addressing factors that could negatively affect adherence (see Chapter 3)
- Maintain antiretroviral therapy in patient who is already receiving it with modification of regimen as necessary based upon effectiveness and tolerability
- Initiate treatment of latent TB in patient with positive PPD or gamma-interferon release assay (see Chapter 9)
- Address immunizations (see Chapter 6) and health care maintenance (Table 8-1)

CD4 Cell Count 200-50/mm^3

- Initiate antiretroviral therapy in all patients after addressing factors that could negatively affect adherence (see Chapter 3)
- Maintain antiretroviral therapy in patient who is already receiving it with modification of regimen as necessary based upon effectiveness and tolerability
- Initiate PCP prophylaxis * (see Chapter 4)
- Initiate treatment of latent TB in patient with positive PPD or gamma-interferon release assay (see Chapter 9)
- Address immunizations (see Chapter 6) and health care maintenance (Table 8-1)

CD4 Cell Count < 50/mm^3

- Initiate antiretroviral therapy in all patients after addressing factors that could negatively affect adherence (see Chapter 3)
- Maintain antiretroviral therapy in patient who is already receiving it with modification of regimen as necessary based upon effectiveness and tolerability
- Initiate or maintain PCP prophylaxis * (see Chapter 4)
- Initiate prophylaxis for MAC infection (see Chapter 5)
- Initiate treatment of latent TB in patient with positive PPD or gamma-interferon release assay (see Chapter 9)
- Consider dilated ophthalmologic exam every six months to screen for CMV infection
- Address immunizations (see Chapter 6) and health care maintenance (Table 8-1)

* Alternative prophylaxis for toxoplasmosis should be initiated in the patient with CD4 cell count < 100/mm^3 and positive toxoplasmosis serology who is not receiving TMP-SMX for PCP prophylaxis.

Primary prophylaxis against coccidioidomycosis and histoplasmosis may be indicated in patients with a low CD4 cell count who live in endemic areas. See published guidelines for more information.

Follow-up Visits

Medical visits should be scheduled with appropriate frequency to monitor for disease progression and complications and to monitor drug therapies. In general, patients with advanced HIV disease require more frequent visits than those with earlier stages.

Initial evaluation is generally accomplished in two visits. At the first, a history and physical examination are performed and baseline laboratory studies are obtained. At the second, results of evaluation are reviewed, and a management plan is discussed. Issues to be addressed should include any active medical problems, opportunistic infection prophylaxis, antiretroviral therapy, health care maintenance, and patient education.

If antiretroviral therapy is initiated, a follow-up visit is arranged in four weeks to assess tolerability of medical regimen and to repeat laboratory parameters used to determine its effectiveness. Once a patient is on a stable treatment regimen, follow-up visits every three to six months are recommended unless intercurrent problems necessitate more frequent appointments.

Laboratory Testing

Once patients are on a stable antiretroviral regimen, laboratory evaluation at follow-up visits should include the following:

Test	**Interval**
Complete blood and differential counts	1-2 times/year
BUN/creatinine, liver function tests	1-2 times/year
HgbA1c and fasting lipid profile	once/year
CD4 cell count	1-2 times/year
HIV viral load	1-2 times/year

More frequent testing may be warranted based upon specific clinical circumstances.

Table 8-1
HIV Health Care Maintenance

Issue	Intake	Semiannually	Annually
Pneumococcal vaccine *	X		
Hepatitis B vaccine **	X		
Hepatitis A vaccine ***	X		
Influenza vaccine ****			X
RPR	X		X
Chlamydia/GC	X		X
Pap smear +	X	X	
PPD or IGRA ++	X		X

* See text for details; ** In HBV-seronegative patients; *** In at risk patients and those with chronic hepatitis; **** Especially in patients at risk for exposure to or morbidity from influenza; + Annually after first year; ++ In PPD - or IGRA - patients.

Chapter 9. Tuberculosis

Background

Tuberculosis (TB) is a significant cause of morbidity and mortality in HIV-infected patients. The risk of developing active TB in patients with HIV disease if infected with *Mycobacterium tuberculosis* may be as high as 10 percent each year compared to a 10 percent lifetime risk in immunocompetent hosts. Treatment of latent TB is effective in HIV-infected patients with a positive TB test and will decrease the likelihood of active TB.

TB may present with extrapulmonary manifestations in advanced HIV disease, and cutaneous anergy (lack of reactivity to skin tests) is more common in this context. Diagnosis may be delayed because of these characteristics. Multidrug-resistant (MDR) strains, which are problematic to treat, have become common in some parts of the country.

Screening

Screening for latent TB should be part of the initial assessment of HIV-infected patients and repeated annually in high-risk individuals if the test result is negative. Testing options include a skin test (PPD) [purified protein derivative, intermediate strength, 5TU] or interferon-gamma release assay (IGRA).

The PPD is administered intracutaneously and read at 48-72 hours. The routine use of control agents, such as candida, tetanus toxoid, and mumps, is not recommended because of their lack of standardization. A positive test in an HIV-infected patient is defined as 5 mm or more of induration (measured across the forearm). A history of prior BCG administration should not affect the interpretation of PPD results.

The IGRA is an *in vitro* blood test of cell-mediated immune response to *M. tuberculosis*. It is highly specific and not affected by BCG vaccination status of the patient. CDC guidelines state that IGRA can be used in lieu of the PPD in all situations. However, it is preferred in patients with a history of BCG administration and in those in whom a repeat visit for PPD reading is difficult.

Repeat PPD or IGRA testing is recommended in HIV-infected patients with a baseline CD4 cell count less than 200/mm^3 who had a negative result if it increases above this threshold on antiretroviral therapy.

Treatment of Latent TB

Antimicrobial therapy is recommended for HIV-infected patients regardless of age with any of the following:

- Positive PPD or IGRA
- History of a positive PPD or IGRA and no documentation of treatment
- Recent exposure to active pulmonary TB

Antimicrobial therapy is not generally recommended in HIV-infected persons with anergy who have historical risk factors for TB exposure, such as injection drug use, alcoholism, homelessness, incarceration, living in shelter or institution, and originating from a country endemic for TB.

A chest x-ray should be performed on all patients with a positive PPD or IGRA before initiating treatment to rule out active pulmonary TB. If extrapulmonary disease is suspected clinically, the appropriate additional diagnostic evaluation should also be completed.

Isoniazid (INH) 300 mg po qd given with pyridoxine 50 mg po qd *or* 900 mg twice per week given with pyridoxine 50 mg po qd (directly observed therapy [DOT]) is the standard regimen. Treatment is continued for nine months. Alternative regimens, which include rifampin (RIF) 600 mg po qd for four months *or* INH 300 mg po qd and RIF 600 mg po qd for three months, are generally avoided in HIV-infected patients on antiretroviral therapy because of concern about drug interactions.

Hepatotoxicity to INH is uncommon in patients younger than 35 years old but increases with advancing age. Other common side effects include fever and rash. The drug should be discontinued if clinical stigmata of hepatitis develop or if liver transaminases increase to $\geq$ 5 times baseline.

Infectious disease consultation is recommended in the treatment of latent TB with suspected MDR strains.

Treatment of Active TB

A four-drug regimen is preferred for initial empiric treatment of TB pending culture and sensitivity results. The combination of INH, RIF or another rifamycin, ethambutol, and pyrazinamide is given for 8 weeks, after which INH and RIF alone are continued if the organism is sensitive to these drugs. The total duration of treatment is generally 6 months for pulmonary TB and 6-12 months for extrapulmonary TB. DOT is preferred over conventional management whenever possible. All patients with INH-resistant or RIF-resistant isolates, as well as persons with a history of nonadherence, should receive DOT.

The presence of active TB requires immediate initiation of antimicrobial treatment. All HIV-infected patients with active TB should be treated with antiretroviral therapy. In patients with a CD4 cell count $\leq 50/mm^3$, antiretroviral therapy should be started within 2-4 weeks of initiating TB treatment. In patients with higher CD4 counts, antiretroviral therapy can be delayed for up to 4-12 weeks depending upon the specific clinical circumstances (see DHHS guidelines for more information).

Rifampin, an important component of combination therapy for TB, cannot be given with many protease inhibitors and non-nucleoside reverse transcriptase inhibitors (see Chapter 3). In some instances, rifabutin can be substituted for it.

Susceptibility tests should be performed on the initial TB isolate and on any isolate obtained at three months post-treatment.

Antimicrobial drug resistance should be considered if there has been prior ineffective or intermittent treatment or if there is a history of exposure to TB strains from Central or South America, Africa, or the Far East.

Infectious disease consultation is recommended in the treatment of active TB.

Chapter 10. Viral Hepatitis

Epidemiology

Hepatitis A, B, and C infections are common in HIV disease. Because hepatitis A virus (HAV) is transmitted via the fecal-oral route, it is seen mainly in men who have sex with men (MSM) as opposed to patients in other risk groups. Hepatitis B virus (HBV), which can be spread sexually or through exposure to infected blood, occurs in MSM, heterosexuals, and injection-drug users (IDUs). Hepatitis C virus (HCV), which is transmitted primarily through exposure to infected blood, affects mostly IDUs and hemophiliacs who received unscreened blood products in the past, although sexual transmission has also been described in MSM. Of note, HBV and HCV are more easily transmitted (30% and 3% risk, respectively) than HIV (0.3% risk) from needlestick exposure to infected blood.

Hepatitis A causes acute infection but not chronic liver disease. Hepatitis B is self-limited in 96% of HIV-seronegative patients, progressing to chronic infection with a variable clinical course in the remainder of patients. Hepatitis C is a chronic infection in the majority of patients and is often associated with progressive liver disease.

Clinical Manifestations

Acute viral hepatitis classically presents with anorexia, nausea, vomiting, upper abdominal pain, and jaundice but may be a nonspecific illness in some patients; fever is common with HAV infection. Rarely, fulminant hepatitis occurs with rapidly progressive hepatic dysfunction. Physical examination may show a jaundiced patient with tender hepatomegaly. Liver function tests, particularly serum transaminases and bilirubin levels, are increased. Symptoms and signs of acute hepatitis often persist for several weeks before resolving. Patients with hepatitis B or C who develop chronic infection may be asymptomatic or have exacerbations of these same symptoms with variable frequency. Over many years, they become at risk for cirrhosis and hepatoma.

The clinical course of HAV infection does not seem to be altered in the context of HIV disease. HBV infection is more likely to become chronic in HIV-infected patients, and it may progress more rapidly. Chronic HBV infection has been noted to flare when combination antiretroviral therapy is initiated, perhaps representing an immune reconstitution syndrome. It may also do so if lamivudine (3TC), emtricitabine (FTC), or tenofovir (TDF), antiretroviral drugs that also have anti-HBV activity, are interrupted or discontinued.

HCV is often more aggressive in HIV-infected patients, especially in those with significant immunodeficiency. Progression of HCV disease, which takes up to 30 years or longer in an HIV-seronegative patient, may occur in less than half that time in a coinfected patient. HIV disease may progress more rapidly in the

context of HCV infection. Increased hepatotoxicity has been reported in coinfected patients receiving antiretroviral therapy, and impaired immune reconstitution has also been described in coinfected patients.

Diagnosis

Acute viral hepatitis is suggested by the clinical presentation in association with abnormal liver function tests. Differential diagnosis includes hepatotoxicity related to alcohol and medications and biliary tract disease. Diagnosis of viral hepatitis is established by serologic tests, including IgM anti-HAV for hepatitis A, hepatitis B surface antigen (HBsAg) for hepatitis B, and anti-HCV for hepatitis C. If anti-HCV is positive via enzyme-linked immunosorbent assay (ELISA), the diagnosis of active hepatitis C infection should be verified with PCR for HCV RNA. Chronic hepatitis is defined as lasting 6 months or longer. Liver biopsy may be recommended to establish the extent of disease in patients with chronic hepatitis and to identify those who are candidates for drug treatment. In general, liver function test abnormalities do not correlate well with histologic findings.

Management

The management of acute hepatitis, with the possible exception of HCV infection (for which treatment may be warranted if spontaneous clearance does not occur within 12 weeks) is generally supportive. Patients should be asked to maintain adequate oral intake to prevent dehydration and to rest as needed.

Expert consultation is recommended for clinicians with limited experience in the treatment of chronic hepatitis B and C infections. Patients coinfected with HBV are generally treated with two antiretroviral drugs (e.g., TDF/FTC) that also have activity against HBV. Interferon-alpha, adefovir, entecavir, and telbivudine are less commonly used in this setting. The management of patients coinfected with HCV has dramatically changed over the past few years and continues to evolve with the development of new therapeutic drug classes. Pegylated interferon in combination with ribavirin and sofosbuvir (HCV polymerase inhibitor) for 12 weeks is currently the treatment of choice for genotypes 1, 4, 5, and 6. For those who cannot tolerate interferon and for those who have failed prior HCV treatment, sofosbuvir plus simeprevir (HCV protease inhibitor) with or without ribavirin is highly effective. Sofosbuvir and ribavirin is currently the preferred regimen for genotypes 2 and 3. Toxicity from interferon (e.g., constitutional symptoms, depression) is common. In general, control of HIV disease is recommended prior to initiating treatment for HCV infection.

Patients with chronic hepatitis should be cautioned about the use of alcohol, acetaminophen, and other potentially hepatotoxic agents. They should be advised against sharing razors and the importance of practicing safer sex at all times because of the potential for transmission of these viruses to other individuals.

All HIV-infected patients should be tested serologically for HAV, HBV, and HCV infections. Immunization against hepatitis A and B is recommended in those without previous exposure to these pathogens, although the response to vaccines may be diminished in advanced HIV disease. Hepatitis A vaccine is particularly important because of the risk for fulminant hepatitis in HCV-infected patients who subsequently contract HAV.

Chapter 11. Sexually Transmitted Diseases

General Guidelines

Persons identified as having one sexually transmitted disease (STD) are at risk for others and should be screened as appropriate. Partners of persons with an STD should be evaluated and treated as appropriate. Emphasis should be placed on prevention as well as treatment of STDs.

Considerations in HIV-infected Patients

Genital ulcer diseases, such as syphilis and herpes simplex virus (HSV) infection, predispose to transmission and acquisition of HIV infection. The presentation, serology, natural history, and treatment response of syphilis may be altered in the context of HIV disease. HSV infection is often more severe and prone to relapse. It may require a higher dose and longer duration of therapy. Lesions may be atypical in appearance in the context of advanced HIV disease. Human papillomavirus (HPV) infection is common and associated with cervical and anal dysplasia/cancer. See Chapter 7 for Pap smear recommendations in this population. The increasing resistance of gonorrhea has resulted in changes in antibiotic recommendations. Treatment of pelvic inflammatory disease may be problematic. Routine periodic screening for STDs is recommended in at risk HIV-infected patients.

Diagnosis and Treatment

Chancroid

Syndrome is painful genital ulcer(s) with shaggy border and exudate at base associated with tender inguinal adenopathy.

Presumptive diagnosis is made by clinical appearance of lesion and ruling out other causes of genital ulcer disease (RPR; Tzanck smear, HSV culture, or dFA [direct fluorescent antibody] test).

Treatment:

- Ceftriaxone 250 mg IM once *or*
  azithromycin 1 gram po once *or*
  ciprofloxacin 500 mg po bid x 3 days *or*
  erythromycin 500 mg po tid x 7 days

Chlamydial Infection

Syndromes include urethritis, epididymitis, cervicitis, salpingitis, proctitis, and lymphogranuloma venereum.

Diagnosis is made presumptively by demonstration of PMNs without gram-negative diplococci on gram stain of discharge and confirmed by urinary nucleic acid amplification assay (preferably of first void specimen).

Treatment:

- Doxycycline 100 mg po bid x 7 days *or*
  azithromycin 1 gram po once

Recent sex partners of patients with chlamydial infection should be treated presumptively.

Genital Warts

Syndrome is one or more skin-colored papular lesions at sites of sexual contact. These may occur externally on the penis, vulva, or perineal region, or internally in the vagina or rectum. Genital warts are caused by human papillomavirus, which is a risk factor for cervical and anal dysplasia/cancer.

Diagnosis is made by clinical appearance.

Treatment: All of the listed modalities are about equally effective, and there is a high rate of relapse although frequency is variable.

- Podophyllin 0.5% solution or gel (available with prescription)
  Apply bid x 3 days followed by 4 days of no therapy
  May be repeated as necessary for total of 4 cycles

- Imiquimod 5% cream (available with prescription)
  Apply qhs tiw for up to 16 weeks; wash area with soap and water in morning

- Cryotherapy

- Trichloroacetic acid

- Laser therapy

- Surgical removal

Gonorrhea

Syndromes include urethritis, epididymitis in men, cervicitis and salpingitis in women, rectal, pharyngeal, and disseminated infection.

Diagnosis is made presumptively by demonstration of intracellular gram-negative diplococci and confirmed by urinary nucleic acid amplification (men only) or culture.

Treatment of uncomplicated infection:

- Ceftriaxone 250 mg IM once (preferred) *or*
  cefixime 400 mg po once (alternative) *or*
  azithromycin 2 grams po once (alternative)

  plus (in patients not receiving azithromycin for GC treatment)

- Doxycycline 100 mg po bid x 7 days *or*
  azithromycin 1 gram po once

Treatment of complicated infection:

- Ceftriaxone 1 gram IM or IV qd x 7-10 days

Recent sex partners of patients with gonorrhea infection should be treated presumptively for gonorrhea and chlamydial infection.

Herpes Simplex Virus

Syndrome is multiple clustered vesicular lesions on erythematous base; primary infection is followed by variable frequency of recurrences.

Diagnosis is made presumptively by clinical appearance of lesions and confirmed by Tzanck smear, HSV culture, or dFA test.

Treatment:

- Primary infection → acyclovir 400 mg po tid x 7-10 days *or*
  famciclovir 250 mg po tid x 7-10 days *or*
  valacyclovir 1 g po bid x 7-10 days (not recommended in patients with advanced HIV disease; see Chapter 12)

- Recurrent infection → acyclovir 800 mg po bid x 5 days *or*
  famciclovir 1000 mg po bid x 1 day *or*
  valacyclovir 500 mg po bid x 3 days (not recommended in patients with advanced HIV disease; see Chapter 12)

- Topical acyclovir offers little therapeutic benefit

- Prophylaxis for patients with frequent recurrences →
  acyclovir 400 mg po bid *or*
  famciclovir 250 mg po bid *or*
  valacyclovir 500-1000 mg po qd (not recommended in patients with advanced HIV disease; see Chapter 12)

Lymphogranuloma Venereum

Syndrome of proctitis has been described in HIV-infected MSM. It presents with purulent rectal discharge and tenesmus associated with tender inguinal adenopathy. A genital papule or ulceration at the site of inoculation may also be present. It is caused by the L serovars of *Chlamydia trachomatis*.

Diagnosis is suspected clinically and can be confirmed by serologic testing. Other infectious causes of proctitis should be excluded.

Treatment:

- Doxycycline 100 mg po bid x 21 days *or*
  erythromycin 500 mg po qid x 21 days

Molluscum Contagiosum

Syndrome is multiple clustered pearl-like papular lesions on site of physical contact, but autoinoculation may also occur. It is caused by a pox-like virus.

Diagnosis is made by clinical appearance.

Treatment:

- Cryotherapy

- Curettage

- Trichloroacetic acid

Pubic Lice

Syndrome is genital pruritus.

Diagnosis is made by recognition of lice or nits on pubic hair.

Treatment:

- Permethrin 1% cream rinse applied to affected areas and washed off after 10 minutes

- Alternative therapies include pyrethrins with piperonyl butoxide (applied to affected area and washed off after 10 minutes) and oral ivermectin (250 mcg/kg and repeated in 2 weeks)

Recent sex partners of patients with pubic lice should be treated presumptively.

Scabies

Syndrome is a scattered pruritic, papular eruption with characteristic "burrows" sometimes noted. An aggressive form of the infestation with atypical manifestations has been described in immunocompromised patients.

Diagnosis is made by clinical appearance of skin lesions and confirmed by scraping/oil mount demonstrating the parasite.

Treatment:

- Permethrin cream 5% applied from neck down and washed off after 8-14 hours

- Alternative therapies include oral ivermectin (200 mcg/kg and repeated in two weeks) and lindane (1% lotion or 30 grams of cream applied from neck down and washed off after 8 hours)

Recent sex partners and household contacts of patients with scabies should be treated presumptively.

Syphilis

Syndromes: Primary stage manifested by chancre; secondary phase manifested by mucocutaneous disease; and tertiary phase, after prolonged latency period, manifested by neurologic disease.

Diagnosis is made by clinical presentation and positive serology (RPR or VDRL plus confirmatory test [FTA-abs or MHA-Tp]).

Treatment:

- Primary, secondary, and early latent (< 1 yr duration) →
  benzathine penicillin 2.4 mU weekly x 1

- Late latent (> 1 yr duration) and tertiary →
  benzathine penicillin 2.4 mU weekly x 3

- Neurosyphilis (any stage) →
  penicillin G 18-24 mU/day x 10-14 days followed by regimen for late latent syphilis

- Alternative Rx is doxycycline or tetracycline x 2-4 weeks (except for neurosyphilis)

RPR or VDRL will generally convert to negativity within 1-2 years in patients who have primary, secondary, or early latent syphilis. In patients with late latent and tertiary syphilis, RPR or VDRL may remain serofast at a low positive titer.

Lumbar puncture should be performed in patients with neurologic symptoms or signs to assess for central nervous system involvement. Some experts recommend that it be performed in HIV-infected patients in their absence when the RPR or VDRL is positive at a high titer (>1:32) or when the CD4 count is <350 cells/mm^3.

Recent sex partners of patients with primary, secondary, or early latent syphilis should be treated presumptively.

Trichomonas

Syndrome is foamy vaginal discharge sometimes in association with urethritis.

Diagnosis is made by vaginal wet mount showing flagellated single-celled organisms.

Treatment:

- Metronidazole 2 grams po once or 500 mg po bid x 7 days *or*
  tinidazole 2 grams po once

Recent sex partners of patients with trichomonas infection should be treated presumptively.

Prevention

Educate those at risk for STDs regarding effective means for reducing transmission through use of barrier methods and behavioral changes. Identify and screen populations at high risk. Promptly diagnose and treat patients with symptomatic infection. Evaluate, treat, and counsel their sexual partners.

Chapter 12. HIV Drug Glossary

Antiretroviral Therapy

Nucleoside Reverse Transcriptase Inhibitors (NRTIs) *

Abacavir (ABC, Ziagen)

Indications: Treatment of HIV infection in combination with other agents.

HLA-B*5701 testing (presence associated with increased risk of hypersensitivity reaction) is recommended before using this drug in an antiretroviral regimen.

Contraindications: Known or suspected hypersensitivity.

Dosage: 300 mg po bid. Also available as Epzicom, a fixed-dose combination of 3TC 300 mg and ABC 600 mg given once a day; and Trizivir, a fixed-dose combination of ZDV 300 mg, 3TC 150 mg, and ABC 300 mg given twice a day.

Toxicity: Four percent of patients develop a hypersensitivity reaction, usually within 6 weeks of initiating therapy. It is manifested by fever, constitutional or respiratory symptoms, gastrointestinal intolerance, and/or rash. Stopping the drug leads to rapid resolution of symptoms. *Never rechallenge a patient thought to have had a hypersensitivity reaction to abacavir as severe reactions and death have been reported.*

Other side effects include nausea, vomiting, diarrhea, headache, malaise.

Pregnancy category C.

Didanosine (ddI, Videx)

Indications: Treatment of HIV infection in combination with other agents.

Contraindications: Known hypersensitivity, history of pancreatitis or significant peripheral neuropathy.

Dosage: Enteric-coated formulation: 400 mg po qd for weight $\geq$ 60 kg and 250 mg po qd for weight < 60 kg. When co-administered with TDF, the standard dose is 250 mg taken at same time *with light meal*.

Also available in buffered powder: ≥ 60 kg → 250 mg po bid; < 60 kg → 167 mg po bid.

Both formulations are taken on an empty stomach (> 30 minutes before a meal or > 2 hours after a meal).

Toxicity: Peripheral neuropathy, acute pancreatitis, gastrointestinal intolerance, abnormal liver function tests. Co-administration with d4T is not recommended because of overlapping toxicities and an increased risk of lactic acidosis.

Pregnancy category B.

Emtricitabine (FTC, Emtriva)

Indications: Treatment of HIV infection in combination with other agents.
Also has activity against hepatitis B virus.

Contraindications: Known hypersensitivity.

Dosage: 200 mg po qd. Also available as Truvada, a fixed-dose combination of TDF 300 mg and FTC 200 mg given once a day; Atripla, a fixed-dose combination of TDF 300 mg, FTC 200 mg, and efavirenz 600 mg given once a day; and Stribild, a fixed-dose combination of TDF 300 mg, FTC 200 mg, elvitegravir 150 mg, and cobicistat 150 mg given once a day.

Toxicity: Hyperpigmentation on palms and soles.

Pregnancy category B.

Stribild (cobicistat component) has many potential drug interactions, some of which may require dosage modification or preclude its co-administration with other agents; see Physicians Desk Reference, package insert, or guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents at www.aidsinfo.nih.gov for more information.

Lamivudine (3TC, Epivir)

Indications: Treatment of HIV infection in combination with other agents.
Also has activity against hepatitis B virus.

Contraindications: Known hypersensitivity.

Dosage: 150 mg po bid or 300 mg po qd. Also available as Combivir, a fixed-dose combination of ZDV 300 mg with 3TC 150 mg given twice a day; Epzicom, a fixed-dose combination of 3TC 300 mg and ABC 600 mg given once a day; and Trizivir, a fixed-dose combination of ZDV 300 mg, 3TC 150 mg, and ABC 300 mg given twice a day.

Toxicity: Uncommon. Headache, gastrointestinal intolerance, and insomnia have been reported.

Pregnancy category C.

Stavudine (d4T, Zerit)

Indications: Treatment of HIV infection in combination with other agents.

Contraindications: Known hypersensitivity, concurrent ZDV use because of pharmacologic antagonism.

Dosage: Immediate-release formulation: $\geq$ 60 kg → 40 mg po bid; < 60 kg → 30 mg po bid.

Extended-release: $\geq$ 60 kg → 100 mg po qd; < 60 kg → 75 mg po qd.

Toxicity: Peripheral neuropathy, acute pancreatitis, facial lipoatrophy, abnormal liver function tests. Co-administration with ddI is not recommended because of overlapping toxicities and an increased risk of lactic acidosis.

Pregnancy category C.

Tenofovir (TDF, Viread)

Indications: Treatment of HIV infection in combination with other agents.
Also has activity against hepatitis B virus.

Tenofovir is a nucleotide agent.

Contraindications: Known hypersensitivity.

Dosage: 300 mg po qd with food. Also available as Truvada, a fixed-dose combination of FTC 200 mg and TDF 300 mg given once a day; Atripla, a fixed-dose combination of TDF 30 mg, FTC 200 mg, and efavirenz 600 mg given once a day; and Stribild, a fixed-dose combination of TDF 300 mg, FTC 200 mg, elvitegravir 150 mg, and cobicistat 150 mg given once a day.

Toxicity: Gastrointestinal intolerance, renal dysfunction, hypophosphatemia.

Pregnancy category B.

Stribild (cobicistat component) has many potential drug interactions, some of which may require dosage modification or preclude its co-administration with other agents; see Physicians Desk Reference, package insert, or guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents at www.aidsinfo.nih.gov for more information.

Zidovudine (ZDV, AZT, Retrovir)

Indications: Treatment of HIV infection in combination with other agents (rarely used).

In addition, ZDV may have specific benefits for patients who have HIV-related thrombocytopenia or encephalopathy.

Prevention of perinatal transmission when given prenatally and during delivery to HIV-infected mother and to infant postpartum. Combination antiretroviral therapy should be administered in this setting.

Contraindications: Known hypersensitivity.

Dosage: Treatment of HIV infection in adults: 300 mg po bid. Also available as Combivir, a fixed-dose combination of ZDV 300 mg with 3TC 150 mg given twice a day; and Trizivir, a fixed-dose combination of ZDV 300 mg, 3TC 150 mg, and ABC 300 mg given twice a day.

Prevention of perinatal transmission: Pregnancy weeks 14-34 → 300 mg po bid; during labor → 2 mg/kg IV loading dose over 30 minutes to 1 hour, then 1 mg/kg/hr IV through delivery; and infant → 2 mg/kg syrup q6h for 6 weeks.

Toxicity: Gastrointestinal intolerance, headache, fingernail discoloration, myopathy, leukopenia, abnormal liver function tests, macrocytosis.

Pregnancy category C. Recommended for pregnant women after the first trimester to prevent vertical transmission.

Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Delavirdine (Rescriptor)

Indications: Treatment of HIV infection in combination with other agents (rarely used).

Contraindications: Known hypersensitivity.

Dosage: 400 mg po tid. Two tablets must be dissolved in 3 or more ounces of water to produce a slurry. Antacids and ddI should not be taken one hour before or after the dose. *There are many potential drug interactions, some of which may require dosage modification or preclude its co-administration with other agents; see Physicians Desk Reference, package insert, or guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents at www.aidsinfo.nih.gov for more information.*

Toxicity: Rash is common and does not require discontinuation of the drug unless accompanied by fever, mucous membrane involvement, or other systemic manifestations. Stevens-Johnson syndrome has been reported infrequently. Other side effects include headache, abnormal liver function tests.

Pregnancy category C.

Efavirenz (Sustiva)

Indications: Treatment of HIV infection in combination with other agents.

Contraindications: Known hypersensitivity, pregnancy.

Dosage: 600 mg po qhs. Avoid taking with high fat meals. Also available as Atripla, a fixed-dose combination of TDF 300 mg, FTC 200 mg, and efavirenz 600 mg given once a day.

There are many potential drug interactions, some of which may require dosage modification or preclude its co-administration with other agents; see Physicians Desk Reference, package insert, or guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents at www.aidsinfo.nih.gov for more information.

Toxicity: Rash is common and does not require discontinuation of the drug unless accompanied by fever, mucous membrane involvement, or other systemic manifestations. Other side effects include vivid dreams and nightmares, neurocognitive dysfunction, hyperlipidemia, abnormal liver function tests.

Pregnancy category D; teratogenic in non-human primates. Women taking efavirenz should use two forms of contraception.

Etravirine (Intelence)

Indications: Treatment of HIV infection in combination with other agents.

Contraindications: Known hypersensitivity.

Dosage: 200 mg po bid. *There are many potential drug interactions, some of which may require dosage modification or preclude its co-administration with other agents; see Physicians Desk Reference, package insert, or guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents at www.aidsinfo.nih.gov for more information.*

Toxicity: Rash is common and does not require discontinuation of the drug unless accompanied by fever, mucous membrane involvement, or other systemic manifestations. Stevens-Johnson syndrome has been reported infrequently. Other side effects include nausea, diarrhea, abnormal liver function tests.

Pregnancy category B.

Nevirapine (Viramune)

Indications: Treatment of HIV infection in combination with other agents.

Contraindications: Known hypersensitivity, moderate to severe hepatic disease.

Dosage: 200 mg po qd x two weeks; 200 mg po bid thereafter. Patients who develop rash during the first two weeks should not increase the dose until the rash resolves. *There are many potential drug interactions, some of which may require dosage modification or preclude its co-administration with other agents; see Physicians Desk Reference, package insert, or guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents at www.aidsinfo.nih.gov for more information.*

Toxicity: Rash is common (about 17% of patients, although fewer with dose escalation regimen) and does not require discontinuation of the drug unless accompanied by fever, mucous membrane involvement, or other systemic manifestations. Stevens-Johnson syndrome has been reported infrequently. Other side effects include nausea, headache, abnormal liver function tests.

Because of a high incidence of symptomatic hepatic events in women with

CD4 cell count > 250/mm³ and in men with CD4 cell count > 400/mm³, NVP use should be avoided in these settings unless the benefit clearly outweighs the risk.

Pregnancy category B.

Rilpivirine (Edurant)

Indications: Treatment of HIV infection in combination with other agents. Also available as Complera, a fixed-dose combination of TDF 300 mg, FTC 200 mg, and rilpivirine 25 mg given once a day.

Contraindications: Known hypersensitivity.

Dosage: 25 mg po qd. *There are many potential drug interactions, some of which may require dosage modification or preclude its co-administration with other agents; see Physicians Desk Reference, package insert, or guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents at www.aidsinfo.nih.gov for more information.*

Toxicity: Depression, insomnia, headache, rash.

Pregnancy category B.

Protease Inhibitors (PIs) **

Atazanavir (Reyataz)

Indications: Treatment of HIV infection in combination with other agents.

Contraindications: Known hypersensitivity.

Dosage: 300 mg po qd administered with ritonavir 100 mg po qd as pharmacologic booster. *There are many potential drug interactions, some of which may require dosage modification or preclude its co-administration with other agents; see Physicians Desk Reference package insert, or guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents at www.aidsinfo.nih.gov for more information.*

Toxicity: Gastrointestinal intolerance, hyperbilirubinemia. Unlike other protease inhibitors, this drug does not appear to be associated with hyperlipidemia.

Pregnancy category B.

Darunavir (Prezista)

Indications: Treatment of HIV infection in combination with other agents.

Contraindications: Known hypersensitivity.

Dosage: 800 mg po qd (treatment-naïve patients) administered with ritonavir 100 mg po qd *or* 600 mg po bid (treatment-experienced patients) administered with ritonavir 100 mg po bid as pharmacologic booster. *There are many potential drug interactions, some of which may require dosage modification or preclude its co-administration with other agents; see Physicians Desk Reference, package insert, or guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents at www.aidsinfo.nih.gov for more information.*

Toxicity: Gastrointestinal intolerance, rash, headache, abnormal liver function tests, severe hepatotoxicity (rare).

Pregnancy category B.

Fosamprenavir (Lexiva)

Indications: Treatment of HIV infection in combination with other agents.

Contraindications: Known hypersensitivity.

Dosage: 1400 mg po bid. When administered with ritonavir (100 mg po bid) as pharmacologic booster, dose is 700 mg po bid. *There are many potential drug interactions, some of which may require dosage modification or preclude its co-administration with other agents; see Physicians Desk Reference, package insert, or guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents at www.aidsinfo.nih.gov for more information.*

Toxicity: Gastrointestinal intolerance, rash, headache, oral paresthesias.

Pregnancy category C.

Indinavir (Crixivan)

Indications: Treatment of HIV infection in combination with other agents.

Contraindications: Known hypersensitivity.

Dosage: 800 mg po q8h on an empty stomach or with a non-fat meal. When administered with ritonavir (100-200 mg po bid) as pharmacologic booster, dose is 800 mg po bid without food restrictions. Patients should drink at least 48 ounces of fluid a day. *There are many potential drug interactions, some of which may require dosage modification or preclude its co-administration with other agents; see Physicians Desk Reference, package insert, or guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents at www.aidsinfo.nih.gov for more information.*

Toxicity: Nephrolithiasis, gastrointestinal intolerance, hyperbilirubinemia.

Pregnancy category C.

Lopinavir/Ritonavir (Kaletra)

Indications: Treatment of HIV infection in combination with other agents.

Lopinavir is a protease inhibitor combined with ritonavir as pharmacologic booster.

Contraindications: Known hypersensitivity, concurrent use of ritonavir.

Dosage: Two tablets (each 200 mg lopinavir/50 mg ritonavir) po bid; four tablets po qd has been approved in treatment-naïve patients. *There are many potential drug interactions, some of which may require dosage modification or preclude its co-administration with other agents; see Physicians Desk Reference, package insert, or guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents at www.aidsinfo.nih.gov for more information.*

Toxicity: Gastrointestinal intolerance, weakness, headache.

Pregnancy category C.

Nelfinavir (Viracept)

Indications: Treatment of HIV infection in combination with other agents.

Contraindications: Known hypersensitivity.

Dosage: 1250 mg po bid or 750 mg po tid with food. *There are many potential drug interactions, some of which may require dosage modification or preclude its co-administration with other agents; see Physicians Desk Reference, package insert, or guidelines for the use of antiretroviral agents in HIV-*

infected adults and adolescents at www.aidsinfo.nih.gov for more information.

Toxicity: Diarrhea.

Pregnancy category B.

Ritonavir (Norvir)

Indications: Treatment of HIV infection in combination with other agents (infrequently used in this manner because of gastrointestinal toxicity and drug interactions). Often co-administered as pharmacologic booster with other protease inhibitors.

Contraindications: Known hypersensitivity.

Dosage: 600 mg po q12h with food following two week dose escalation regimen (day 1 and 2: 300 mg po bid; days 3-5: 400 mg po bid; days 6-13: 500 mg po bid). When administered as pharmacologic booster, dosage is reduced. *There are many potential drug interactions, some of which may require dosage modification or preclude its co-administration with other agents; see Physicians Desk Reference, package insert, or guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents at www.aidsinfo.nih.gov for more information.*

Toxicity: Gastrointestinal intolerance, circumoral paresthesias, abnormal liver function tests.

Pregnancy category B.

Saquinavir (Invirase)

Indications: Treatment of HIV infection in combination with other agents.

Contraindications: Known hypersensitivity.

Dosage: 1000 mg po bid administered with ritonavir 100 mg po bid as pharmacologic booster. *There are many potential drug interactions, some of which may require dosage modification or preclude its co-administration with other agents; see Physicians Desk Reference, package insert, or guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents at www.aidsinfo.nih.gov for more information.*

Toxicity: Gastrointestinal intolerance, abnormal liver function tests.

Pregnancy category B.

Tipranavir (Aptivus)

Indications: Treatment of HIV infection in combination with other agents.

Contraindications: Known hypersensitivity.

Dosage: 500 mg po bid administered with ritonavir 200 mg po bid as pharmacologic booster. *There are many potential drug interactions, some of which may require dosage modification or preclude its co-administration with other agents; see Physicians Desk Reference, package insert, or guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents at www.aidsinfo.nih.gov for more information.*

Toxicity: Gastrointestinal intolerance, abnormal liver function tests, severe hepatotoxicity (rare), intracranial hemorrhage (rare).

Pregnancy category C.

Entry Inhibitors

Enfuvirtide (Fuzeon*)*

Indications: Treatment of HIV infection in combination with other agents.

Contraindications: Known hypersensitivity.

Dosage: 90 mg SC bid.

Toxicity: Injection site reaction.

Pregnancy category B.

Maraviroc (Selzentry)

Indications: Treatment of HIV infection in combination with other agents.

Maraviroc is a CCR5 antagonist. HIV coreceptor tropism assay is recommended before using this drug in an antiretroviral regimen.

Contraindications: Known hypersensitivity.

Dosage: 300 mg po bid (although dosage may range from 150-600 mg po bid depending upon with what other drugs it is administered). *There are many potential drug interactions, some of which may require dosage modification or preclude its co-administration with other agents; see Physicians Desk Reference, package insert, or guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents at www.aidsinfo.nih.gov for more information.*

Toxicity: Cough, arthralgia, myalgia, diarrhea, sleep disturbance, abnormal liver function tests.

Pregnancy category B.

Integrase Inhibitors

Dolutegravir (Tivicay)

Indications: Treatment of HIV infection in combination with other agents.

Contraindications: Known hypersensitivity.

Dosage: 50 mg po qd (bid when administered with efavirenz, fosamprenavir/ritonavir, tipranavir/ritonavir, or rifampin; or when there is suspected integrase inhibitor resistance).

Toxicity: Insomnia, abnormal liver function tests, increased lipase, increased CPK level.

Pregnancy category B.

Raltegravir (Isentress)

Indications: Treatment of HIV infection in combination with other agents.

Contraindications: Known hypersensitivity.

Dosage: 400 mg po bid.

Toxicity: Diarrhea, nausea, fatigue, myalgia, abnormal liver function tests.

Pregnancy category C.

Pneumocystis jiroveci (carinii) Pneumonia (PCP): Treatment and Prophylaxis

Atovaquone (Mepron)

Indications: Treatment (mild to moderate infection) and prophylaxis of PCP in patients unable to tolerate TMP-SMX or dapsone.

Contraindications: Known hypersensitivity.

Dosage: 750 mg of suspension po bid with food x 3 weeks for treatment.
Same dosing regimen for prophylaxis.

Toxicity: Gastrointestinal intolerance, rash, headache, fever.

Pregnancy category C.

Clindamycin with Primaquine

Indications: Treatment of PCP in patients unable to tolerate TMP-SMX.

Contraindications: Known hypersensitivity; glucose 6-phosphate dehydrogenase (G6PD) deficiency is contraindication to primaquine use.

Dosage: Clindamycin 600 mg IV q6-8h (or 300-450 mg po qid) and primaquine 15-30 mg base po qd x 3 weeks.

Toxicity: Clindamycin: diarrhea, nausea, rash. Primaquine: nausea, dyspepsia, hemolytic anemia (G6PD deficiency).

Pregnancy categories B (clindamycin) and C (primaquine).

Dapsone

Indications: Treatment of PCP (mild to moderate infection) in combination with trimethoprim; prophylaxis of PCP in patients unable to tolerate TMP-SMX; primary prophylaxis of toxoplasmosis in combination with pyrimethamine.

Contraindications: Known hypersensitivity, G6PD deficiency.

Dosage: PCP treatment: dapsone 100 mg qd and trimethoprim 15 mg/kg/day x 3 weeks.

PCP prophylaxis: 100 mg po qd; toxoplasmosis prophylaxis: dapsone 50 mg qd plus pyrimethamine 50 mg weekly with folinic acid 25 mg.

Toxicity: Rash, fever, gastrointestinal intolerance, neutropenia, methemoglobinemia.

Pregnancy category C.

Pentamidine (Aerosol [NebuPent], Intravenous [Pentam])

Indications: Treatment and prophylaxis of PCP in patients unable to tolerate TMP-SMX or dapsone. Corticosteroids are used adjunctively in patients with PCP who have significant respiratory dysfunction (paO2 <70 mm Hg or alveolar-arterial gradient >35 mm Hg).

Contraindications: Known hypersensitivity; severe asthma or bronchospasm, active pulmonary tuberculosis (aerosol preparation).

Dosage: Treatment: intravenous 3-4 mg/kg qd for up to three weeks.

Prophylaxis: aerosol 300 mg via Respirgard II nebulizer once a month.

Toxicity: Aerosol: bronchospasm, particularly in patients with history of asthma or chronic obstructive pulmonary disease; pharyngeal irritation; metallic taste. Intravenous: hypotension, nephrotoxicity, hypoglycemia, hyperglycemia, leukopenia, thrombocytopenia, hypokalemia, hypocalcemia.

Pregnancy category C.

Trimethoprim-sulfamethoxazole (TMP-SMX, Bactrim, Septra)

Indications: Treatment and prophylaxis of PCP; primary prophylaxis of toxoplasmosis. Corticosteroids are used adjunctively in patients with PCP who have significant respiratory dysfunction (paO2 <70 mm Hg or alveolar-arterial gradient >35 mm Hg).

Contraindications: Known hypersensitivity to trimethoprim or sulfonamides, megaloblastic anemia.

Dosage: Treatment of PCP: 5 mg/kg po/IV q8h of trimethoprim component (equivalent to 2 tabs po tid of DS for 65 kg patient) x 3 weeks.

Prophylaxis of PCP: one DS or SS tablet po qd. Prophylaxis of toxoplasmosis: one DS tablet po qd.

Toxicity: Side effects are common in HIV-infected patients and include gastrointestinal intolerance; rash, urticaria, photosensitivity, Stevens Johnson syndrome;

fever; leukopenia, thrombocytopenia, hemolytic anemia; abnormal liver function tests; renal dysfunction, interstitial nephritis; aseptic meningitis.

Patients with history of mild to moderate drug toxicity should be given retrial of TMP-SMX or desensitized using an established protocol.

Pregnancy category C; avoid use at term because of risk of kernicterus in newborn.

Mycobacterium avium Complex (MAC) Infection and Tuberculosis (TB): Treatment and Prophylaxis ***

Amikacin (Amikin)

Indications: Treatment of MAC infection in combination with other agents.

Contraindications: Known hypersensitivity to aminoglycoside antibiotics.

Dosage: 10-15 mg/kg/day IV for first four weeks of MAC therapy.

Toxicity: Ototoxicity, especially with larger total dose and longer duration (more auditory than vestibular and usually irreversible); nephrotoxicity.

Pregnancy category D.

Azithromycin (Zithromax)

Indications: Treatment of MAC infection in combination with other agents; prophylaxis of MAC infection.

Contraindications: Known hypersensitivity to macrolide antibiotics.

Dosage: MAC treatment: 600 mg po qd; prophylaxis: 1200 mg po weekly.

Toxicity: Gastrointestinal intolerance.

Pregnancy category B.

Ciprofloxacin (Cipro)

Indications: Treatment of MAC infection in combination with other agents; treatment of TB in combination with other agents.

Contraindications: Known hypersensitivity.

Dosage: 500-750 mg po bid.

Toxicity: Gastrointestinal intolerance, central nervous system dysfunction, rash.

Pregnancy category C.

Clarithromycin (Biaxin)

Indications: Treatment of MAC infection in combination with other agents; prophylaxis of MAC infection.

Contraindications: Known hypersensitivity to macrolide antibiotics.

Dosage: MAC treatment and prophylaxis: 500 mg po bid.

Toxicity: Gastrointestinal intolerance, abnormal liver function tests.

Pregnancy category C; teratogenic in animals.

Ethambutol (Myambutol)

Indications: Treatment of MAC infection in combination with other agents; treatment of TB in combination with other agents.

Contraindications: Known hypersensitivity, history of optic neuritis.

Dosage: 15-20 mg/kg po qd; adjusted dose can be administered 2-3 times per week for TB treatment (DOT).

Toxicity: Optic neuritis, rash, gastrointestinal intolerance, abnormal liver function tests.

Pregnancy category C; teratogenic in animals.

Isoniazid (INH)

Indications: Treatment of TB in combination with other agents; treatment of latent TB.

Contraindications: Known hypersensitivity, significant hepatic disease.

Dosage: Treatment of active TB: 300 mg po qd; adjusted dose can be administered 2-3 times per week for TB treatment (DOT); treatment of latent TB: 300 mg po

qd or 900 mg po twice per week (DOT) for nine months. Pyridoxine 50 mg po qd should be given concurrently for prevention of peripheral neuropathy.

Toxicity: Rash, hepatotoxicity, especially in alcoholics and persons older than 50; fever; peripheral neuropathy.

Pregnancy category C.

Pyrazinamide

Indications: Treatment of TB in combination with other agents.

Contraindications: Known hypersensitivity, significant hepatic disease.

Dosage: 25 mg/kg po qd; adjusted dose can be administered 2-3 times per week for TB treatment (DOT).

Toxicity: Rash, abnormal liver function tests, hyperuricemia.

Pregnancy category C.

Rifabutin (Mycobutin)

Indications: Treatment of MAC infection in combination with other agents; treatment of TB in combination with other agents; prophylaxis of MAC infection in patients unable to tolerate clarithromycin or azithromycin.

Contraindications: Known hypersensitivity.

Dosage: Treatment and prophylaxis: 300 mg po qd; adjusted dose can be administered 2-3 times per week for TB treatment (DOT). *There are many potential drug interactions, some of which may require dosage modification or preclude its co-administration with other agents; see Physicians Desk Reference or package insert for more information.*

Toxicity: Rash, orange discoloration of body secretions, gastrointestinal intolerance, abnormal liver function tests. Acute uveitis has been reported when used in association with clarithromycin.

Pregnancy category C.

Rifampin

Indications: Treatment of TB in combination with other agents.

Contraindications: Known hypersensitivity.

Dosage: 600 mg po qd; adjusted dose can be administered 2-3 times per week for TB treatment (DOT). *There are many potential drug interactions, some of which may require dosage modification or preclude its co-administration with other agents; see Physicians Desk Reference or package insert for more information.*

Toxicity: Rash, orange discoloration of body secretions, gastrointestinal intolerance, abnormal liver function tests.

Pregnancy category C.

Streptomycin

Indications: Treatment of TB in combination with other agents.

Contraindications: Hypersensitivity to aminoglycoside antibiotics.

Dosage: 15 mg/kg IM qd adjusted dose can be administered 2-3 times per week for TB treatment (DOT).

Toxicity: Ototoxicity, vestibular toxicity.

Pregnancy category D.

Toxoplasmosis: Treatment and Prophylaxis +

Clindamycin

Indications: Treatment of toxoplasmic encephalitis (for patients unable to tolerate sulfadiazine) in combination with pyrimethamine.

Contraindications: Known hypersensitivity.

Dosage: Initial therapy: 600 mg IV or po q6h x 6 weeks.

Maintenance therapy (secondary prophylaxis): 600 mg po q8h.

Toxicity: Diarrhea, nausea, rash.

Pregnancy category B.

Dapsone See section on PCP Treatment and Prophylaxis.

Pyrimethamine

Indications: Treatment of toxoplasmic encephalitis in combination with sulfadiazine or clindamycin.

Primary prophylaxis of toxoplasmosis in combination with dapsone.

Contraindications: Known hypersensitivity.

Dosage: Initial therapy: 100-200 mg po loading dose, followed by 50-75 mg po qd x 6 weeks in conjunction with folinic acid 10 mg po qd.

Maintenance therapy (secondary prophylaxis): 25-50 mg po with folinic acid 10 mg po qd.

Prophylaxis: 50 mg weekly with folinic acid 25 mg.

Toxicity: Reversible bone marrow suppression, gastrointestinal intolerance.

Pregnancy category C; teratogenic in animals.

Sulfadiazine

Indications: Treatment of toxoplasmic encephalitis in combination with pyrimethamine.

Contraindications: Known hypersensitivity to sulfonamides.

Dosage: Initial therapy: 1000-1500 mg po qid x 6 weeks.

Maintenance therapy (secondary prophylaxis): 500-1000 mg po qid.

Toxicity: Fever, rash, pruritus, bone marrow suppression.

Pregnancy category C; avoid use at term because of risk of kernicterus in newborn.

Trimethoprim-Sulfamethoxazole See section on PCP Treatment and Prophylaxis.

Cytomegalovirus (CMV) Infection: Treatment and Prophylaxis

Cidofovir (Vistide)

Indications: Treatment of CMV infection, including ganciclovir-resistant strains.

Contraindications: Known hypersensitivity, significant renal dysfunction, use of other nephrotoxic medications.

Dosage: Initial therapy: 5 mg/kg IV once a week x 2.

Maintenance therapy (secondary prophylaxis): 5 mg/kg IV once every other week.

Probenecid 2 gm po 3 hr prior, and 1 gm po 2 hr prior and 8 hr after infusion should be administered to prevent nephrotoxicity; 1 liter normal saline is also given prior to cidofovir dosing.

Toxicity: Nephrotoxicity, neutropenia. Probenecid is associated with fever, chills, headache, rash, nausea.

Pregnancy category C.

Foscarnet (Foscavir)

Indications: Treatment of CMV infection, including ganciclovir-resistant strains.

Contraindications: Known hypersensitivity, significant renal dysfunction.

Dosage: Initial therapy: 60 mg/kg IV q8h or 90 mg/kg IV q12h x 14 days.

Maintenance therapy (secondary prophylaxis): 90-120 mg/kg IV qd.

Toxicity: Nephrotoxicity, hypocalcemia, hypophosphatemia, hypokalemia, headache, fatigue, nausea, anemia, seizures.

Pregnancy category C.

Ganciclovir (Cytovene)

Indications: Treatment and prophylaxis of CMV infection.

Contraindications: Known hypersensitivity, neutropenia, thrombocytopenia.

Dosage: Initial therapy: 5 mg/kg IV q12h x 14-21 days.

Maintenance therapy (secondary prophylaxis): 5 mg/kg IV qd.

Toxicity: Neutropenia, thrombocytopenia, anemia, nausea, abdominal pain, headache, confusion.

Pregnancy category C; teratogenic in animals.

Valganciclovir (Valcyte)

Indications: Treatment and prophylaxis of CMV infection.

Contraindications: Known hypersensitivity, neutropenia, thrombocytopenia.

Dosage: Initial therapy: 900 mg po bid x 3 weeks.

Maintenance therapy (secondary prophylaxis): 900 mg po qd.

Toxicity: Neutropenia, thrombocytopenia, anemia, nausea, abdominal pain, headache, confusion.

Pregnancy category C.

Herpes Simplex Virus (HSV) and Varicella-Zoster Virus (VZV) Infections: Treatment and Prophylaxis ++

Acyclovir (Zovirax)

Indications: Treatment and prophylaxis of HSV and VZV infections.

Contraindications: Known hypersensitivity.

Dosage: HSV treatment: 400 mg po tid x 7-10 days (primary infection); 800 mg po bid x 5 days (recurrent infection); suppression: 400 mg po bid. For extensive or disseminated disease, intravenous therapy (10 mg/kg q8h) is given.

VZV treatment: 800 mg po 5x/day for 7 days. For disseminated zoster or ophthalmic involvement, intravenous therapy (10-12 mg/kg q8h) is given.

Toxicity: Nausea, renal dysfunction.

Pregnancy category C.

Famciclovir (Famvir)

Indications: Treatment and prophylaxis of HSV and VZV infections.

Contraindications: Known hypersensitivity.

Dosage: HSV treatment: 250 mg po tid x 7-10 days (primary infection); 1000 mg po bid x 1 day (recurrent infection); suppression: 250 mg po bid.

VZV treatment: 500 mg po tid x 7 days.

Toxicity: Headache, nausea.

Pregnancy category B.

Valacyclovir (Valtrex)

Indications: Treatment and prophylaxis of HSV and VZV infections.

Contraindications: Known hypersensitivity.

Dosage: HSV treatment: 1 gram po bid x 7-10 days (primary infection); 500 mg po bid x 3 days (recurrent infection); suppression: 500-1000 mg po qd.

VZV treatment: 1 gram po tid x 7 days.

Toxicity: Headache, nausea, abnormal liver function tests.

Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome has been reported in patients with advanced HIV disease.

Pregnancy category B.

Fungal Infections: Treatment and Prophylaxis

Amphotericin B

Indications: Pharmacist-prepared suspension for treatment of oral candidiasis; intravenous drug for treatment of systemic fungal infections.

Contraindications: Known hypersensitivity.

Dosage: Oral candidiasis: 1-5 ml of suspension po qid x 14 days.

Systemic fungal infections: intravenous doses range from 0.3-1.0 mg/kg/day depending on the pathogen and type of infection. Lipid complex preparations are less toxic but very expensive.

Toxicity: Oral suspension: nausea, vomiting, diarrhea, rash; intravenous drug: infusion-related fever, chills, phlebitis, hypotension, nausea, vomiting, nephrotoxicity, hypokalemia, hypomagnesemia, hypocalcemia, anemia.

Pregnancy category B.

Caspofungin (Cancidas)

Indications: Treatment of resistant mucosal candidiasis.

Contraindications: Known hypersensitivity.

Dosage: 50 mg IV qd.

Toxicity: Rash, gastrointestinal intolerance, abnormal liver function tests. *There are many potential drug interactions, some of which may require dosage modification or preclude its co-administration with other agents; see Physicians Desk Reference or package insert for more information.*

Pregnancy category C.

Clotrimazole

Indications: Treatment of mucosal candidiasis.

Contraindications: Known hypersensitivity.

Dosage: Oral candidiasis: 10 mg lozenge dissolved in the mouth 5 times a day; vaginal candidiasis: 100 mg tablet per vagina bid x 3 days.

Toxicity: Nausea, abnormal liver function tests.

Pregnancy category C.

Fluconazole (Diflucan)

Indications: Treatment and secondary prophylaxis of mucosal candidiasis; secondary prophylaxis of cryptococcal infection.

Contraindications: Known hypersensitivity.

Dosage: Treatment of oral candidiasis: 100 mg po qd x 7-14 days; candida esophagitis: 200 mg po qd x 14-21 days; vaginal candidiasis: 150 mg po x one. Secondary prophylaxis of mucosal candidiasis: 50-200 mg po qd. *There are many potential drug interactions, some of which may require dosage modification or preclude its co-administration with other agents; see Physicians Desk Reference or package insert for more information.*

Cryptococcal infection maintenance therapy (secondary prophylaxis): 200 mg po qd. Most experts recommend initial treatment of cryptococcal infection with amphotericin B x two weeks followed by high-dose fluconazole (400 mg po qd) x 8 weeks.

Toxicity: Nausea, headache, abnormal liver function tests.

Pregnancy category C.

Itraconazole (Sporanox)

Indications: Treatment of histoplasmosis and resistant mucosal candidiasis.

Contraindications: Known hypersensitivity.

Dosage: 200 mg po qd to bid.

Toxicity: Gastrointestinal intolerance, abnormal liver function tests. *There are many potential drug interactions, some of which may require dosage modification or preclude its co-administration with other agents; see Physicians Desk Reference or package insert for more information.*

Pregnancy category C.

Nystatin

Indications: Treatment of mucosal candidiasis.

Contraindications: Known hypersensitivity.

Dosage: Oral candidiasis: 5 ml suspension to be gargled and swallowed 5 times a day x 7-14 days; vaginal candidiasis: 100,000 unit tab intravaginally 1-2 times a day x 7-14 days.

Toxicity: Nausea, vomiting, diarrhea

Pregnancy category C.

Posaconazole (Noxafil)

Indications: Treatment of resistant mucosal candidiasis.

Contraindications: Known hypersensitivity.

Dosage: 400 mg po bid.

Toxicity: Gastrointestinal intolerance, abnormal liver function tests. *There are many potential drug interactions, some of which may require dosage modification or preclude its co-administration with other agents; see Physicians Desk Reference or package insert for more information.*

Pregnancy category C.

Voriconazole (Vfend)

Indications: Treatment of resistant mucosal candidiasis.

Contraindications: Known hypersensitivity.

Dosage: 200 mg po or IV bid.

Toxicity: Rash, gastrointestinal intolerance, peripheral edema, abnormal liver function tests. *There are many potential drug interactions, some of which may require dosage modification or preclude its co-administration with other agents; see Physicians Desk Reference or package insert for more information.*

Pregnancy category D.

Miscellaneous Therapeutic Agents

Dronabinol (Marinol)

Indications: Appetite stimulant for treatment of AIDS wasting syndrome.

Contraindications: Known hypersensitivity, significant cognitive dysfunction.

Dosage: 2.5 mg po bid.

Toxicity: Neuropsychiatric symptoms, gastrointestinal intolerance.

Pregnancy category C.

Erythropoietin (Epogen, Procrit)

Indications: Treatment of HIV- or ZDV-associated anemia (HCT $\leq$ 30) in patients with serum erythropoietin levels $\leq$ 500 milliunits/ml.

Contraindications: Known hypersensitivity to mammalian cell derived products or human albumin, uncontrolled hypertension.

Dosage: 40,000 units SC once a week; response usually seen between 2 and 6 weeks.

Toxicity: Headache, nausea, arthralgia, hypertension, seizures.

Pregnancy category C; teratogenic in animals.

Granulocyte-Colony Stimulating Factor [Filgrastim] (Neupogen, Neulasta)

Indications: Treatment of neutropenia, defined as ANC < 500-750/mm^3, as a result of HIV disease, chemotherapy, or other drugs (hydroxyurea, ganciclovir, ZDV, TMP-SMX).

Contraindications: Known hypersensitivity to drug or *Escherichia* coli-derived products.

Dosage: 5-10 mcg/kg/day SC.

Toxicity: Bone pain.

Pregnancy category C.

Human Growth Hormone [Somatropin] (Serostim)

Indications: Hormonal treatment of AIDS wasting syndrome.

Contraindications: Known hypersensitivity, presence of an actively growing intracranial tumor.

Dosage: For patients > 55 kg, dose is 6 mg SC qd; for patients 45-55 kg, dose is 5 mg SC qd; for patients 35-45 kg, dose is 4 mg SC qd.

Toxicity: Arthralgia, edema, hypertension, hyperglycemia.

Pregnancy category B.

Human Growth Hormone-Releasing Factor [Tesamorelin] (Egrifta)

Indications: Hormonal treatment of HIV-related lipodystrophy.

Contraindications: Known hypersensitivity, active malignancy, pregnancy.

Dosage: 2 mg SC once daily.

Toxicity: Injection site reaction, arthralgia, edema, rash.

Pregnancy category X.

Megestrol Acetate (Megace)

Indications: Appetite stimulant for treatment of AIDS wasting syndrome.

Contraindications: Known hypersensitivity, pregnancy.

Dosage: Oral suspension: 400-800 mg po qd; tablets: 80 mg po qid up to 800 mg/day.

Toxicity: Hypogonadism, adrenal insufficiency, diarrhea, impotence, rash, hyperglycemia.

Pregnancy category D.

Oxandrolone (Oxandrin)

Indications: Anabolic steroid for treatment of AIDS wasting syndrome.

Contraindications: Known hypersensitivity, history of breast or prostate cancer, significant hepatic dysfunction, nephrosis, pregnancy.

Dosage: 5-10 mg po bid.

Toxicity: Edema, hypertension, virilization, glucose intolerance, hyperlipidemia, abnormal liver function tests.

Pregnancy category X.

Pegylated Interferon (PEGASYS, PEG-Intron)

Indications: Treatment of chronic hepatitis C infection in combination with ribavirin (and HCV protease inhibitor [boceprevir or telaprevir] for genotype 1).

Contraindications: Known hypersensitivity.

Dosage: Pegylated interferon alfa-2a (PEGASYS) 180 mcg SC weekly with ribavirin 400 mg po bid.

Pegylated interferon alfa-2b (PEG-Intron) 1.5 mcg/kg SC weekly with ribavirin 400 mg po bid.

Toxicity: Constitutional symptoms, depression.

Pregnancy categories C (PEGASYS) and X (PEG-Intron).

Ribavirin

Indications: Treatment of chronic hepatitis C infection in combination with pegylated interferon.

Contraindications: Known hypersensitivity, severe anemia, pregnancy.

Dosage: 400 mg po bid with pegylated interferon regimen as above. A higher dose of ribavirin may be necessary with genotype 1 infection. *There are many potential drug interactions, some of which require dosage modification or preclude its co-administration with other agents; see Physicians Desk Reference or package insert for more information.*

Toxicity: Rash, hemolytic anemia.

Pregnancy category X.

Simeprevir (Olysio)

Indications: Treatment of chronic hepatitis C infection in combination with other agents. Simeprevir is an HCV protease inhibitor.

Contraindications: Known hypersensitivity.

Dosage: 150 mg po qd. *There are many potential drug interactions, some of which may require dosage modification or preclude its co-administration with other agents; see Physicians Desk Reference or package insert for more information.*

Toxicity: Rash, pruritus, nausea, myalgia, dyspnea, increased bilirubin level.

Pregnancy category C (X for use with pegylated interferon and ribavirin).

Sofosbuvir (Sovaldi)

Indications: Treatment of chronic hepatitis C infection in combination with other agents. Sofosbuvir is an HCV polymerase inhibitor.

Contraindications: Known hypersensitivity.

Dosage: 400 mg po qd.

Toxicity: Fatigue, headache, insomnia, fever, chills, myalgia, rash, pruritus, gastrointestinal intolerance, anemia, neutropenia.

Pregnancy category B (X for use with pegylated interferon and ribavirin).

Testosterone

Indications: Treatment of hypogonadism; treatment of AIDS wasting syndrome.

Contraindications: Known hypersensitivity, history of male breast or prostate cancer, pregnancy.

Dosage: 200-400 mg IM q 2 weeks. Topical treatment is also available: 1) gel preparation (Androgel) 5 g topically qd; and 2) transdermal systems via non-scrotal patch including Androderm and Testoderm.

Toxicity: Coagulopathy, cholestatic jaundice, increased libido, edema, flushing, priapism, local reaction with patches.

Pregnancy category X.

Thalidomide (Thalomid)

Indications: Treatment of refractory aphthous ulcers; treatment of refractory AIDS wasting syndrome.

Contraindications: Known hypersensitivity, pregnancy.

Dosage: 50-200 mg po qd. Physicians and pharmacists must be registered in the STEPS program (System for Thalidomide Education and Prescribing Safety) at 1-888-423-5436 to prescribe thalidomide. Female patients must have a negative pregnancy test within 24 hours of starting therapy, weekly pregnancy tests in the first month of therapy, monthly pregnancy tests thereafter, and agree to use two forms of contraception. Male patients must use a condom for contraception.

Toxicity: Peripheral neuropathy, drowsiness, orthostatic hypotension, fever, rash, neutropenia.

Pregnancy category X.

Footnotes

* Lactic acidosis, rarely with hepatomegaly and steatosis, has been associated with all drugs in this class.

** Hyperlipidemia, glucose intolerance/diabetes mellitus, and alterations in body fat distribution have been associated with combination antiretroviral therapy, especially regimens containing protease inhibitors.

*** Drugs for TB can also be administered as directly observed therapy (DOT) in different dosage regimens. Consultation with an expert clinician in this area is recommended.

+ For primary prophylaxis, see PCP Treatment and Prophylaxis section.

++ Cidofovir and foscarnet also have activity against HSV and VZV and may have a role in the treatment of resistant strains. Valacyclovir, an acyclovir analogue, has been associated with cases of thrombotic thrombocytopenic purpura (TTP) in patients with advanced HIV disease.

Pregnancy Categories: A: Controlled studies show no risk; B: No evidence of risk in humans; C: Risk cannot be excluded; D: Evidence of risk; X: Contraindicated in pregnancy.

References

Review Articles and Monographs

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2. Centers for Disease Control and Prevention. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents (Available as a living document on AIDSinfo: Department of Health and Human Services Web site at www.aidsinfo.nih.gov).

3. Centers for Disease Control and Prevention. Public Health Service Task Force recommendations for the use of antiretroviral drugs in pregnant women infected with HIV-1 for maternal health and for reducing perinatal HIV-1 transmission in the United States (Available as a living document on AIDSinfo: Department of Health and Human Services Web site at www.aidsinfo.nih.gov).

4. Centers for Disease Control and Prevention. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. MMWR 2006; 55(RR14);1-17.

5. Libman H. Clinical Crossroads. Screening for HIV infection: a healthy, "low-risk" 42-year-old man. JAMA 2011;306:637-644.

6. Sax PE, editor. AIDS Clinical Care. Monthly publication of the Massachusetts Medical Society, Waltham, MA.

7. Thompson MA, Aberg JA, Hoy JF, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society-USA panel. JAMA 2012;308:387-402.

8. United States Public Health Service/Infectious Disease Society of America guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus (Available as a living document on AIDSinfo: Department of Health and Human Services Web site at www.aidsinfo.nih.gov).

Web Sites

1. AETC National Resource Center
http://www.aids-ed.org

2. AIDSinfo: Department of Health and Human Services
http://www.aidsinfo.nih.gov

3. The Body
http://www.thebody.com

4. Centers for Disease Control and Prevention
http://www.cdc.gov/hiv/pubs/facts.htm

5. HIV InSite
http://hivinsite.ucsf.edu

6. The Johns Hopkins HIV Guide
http://www.hopkinsguides.com/hopkins/ub/index/Johns_Hopkins_HIV_Guide/All_Topics/A

7. National HIV/AIDS Clinician Consultation Center
http://nccc.ucsf.edu

8. National Library of Medicine
http://sis.nlm.nih.gov/hiv.html