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. The Food and Drug Administration has approved twenty-four antiretroviral agents and seven fixed-dose drug combinations. 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).

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### Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Abbreviation</th>
<th>Brand Name</th>
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<tbody>
<tr>
<td>zidovudine</td>
<td>ZDV, AZT</td>
<td>Retrovir</td>
</tr>
<tr>
<td>didanosine</td>
<td>ddI</td>
<td>Videx</td>
</tr>
<tr>
<td>stavudine</td>
<td>d4T</td>
<td>Zerit</td>
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<tr>
<td>lamivudine</td>
<td>3TC</td>
<td>Epivir</td>
</tr>
<tr>
<td>abacavir</td>
<td>ABC</td>
<td>Ziagen</td>
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<tr>
<td>emtricitabine</td>
<td>FTC</td>
<td>Emtriva</td>
</tr>
<tr>
<td>tenofovir (nucleotide)</td>
<td>TDF</td>
<td>Viread</td>
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### Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

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<tr>
<th>Generic Name</th>
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<tbody>
<tr>
<td>nevirapine</td>
<td>NVP</td>
<td>Viramune</td>
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<tr>
<td>delavirdine</td>
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<td>Rescriptor</td>
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<tr>
<td>efavirenz</td>
<td>EFV</td>
<td>Sustiva</td>
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<tr>
<td>etravirine</td>
<td>ETR</td>
<td>Intelence</td>
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<td>rilpivirine</td>
<td>RPV</td>
<td>Edurant</td>
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### Protease Inhibitors (PIs)

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<tr>
<th>Generic Name</th>
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<tbody>
<tr>
<td>saquinavir</td>
<td>SQV</td>
<td>Invirase</td>
</tr>
<tr>
<td>ritonavir</td>
<td>RTV</td>
<td>Norvir</td>
</tr>
<tr>
<td>indinavir</td>
<td>IDV</td>
<td>Crixivan</td>
</tr>
<tr>
<td>nelfinavir</td>
<td>NFV</td>
<td>Viracept</td>
</tr>
<tr>
<td>lopinavir/ritonavir</td>
<td>LPV/rtv</td>
<td>Kaletra</td>
</tr>
<tr>
<td>atazanavir</td>
<td>ATV</td>
<td>Reyataz</td>
</tr>
<tr>
<td>fosamprenavir</td>
<td>FPV</td>
<td>Lexiva</td>
</tr>
<tr>
<td>tipranavir</td>
<td>TPV</td>
<td>Aptivus</td>
</tr>
<tr>
<td>darunavir</td>
<td>DRV</td>
<td>Prezista</td>
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Entry Inhibitors (EIs)

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<tr>
<th>Generic Name</th>
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<tbody>
<tr>
<td>Enfuvirtide (fusion inhibitor)</td>
<td>Fuzeon</td>
</tr>
<tr>
<td>Maraviroc (CCR5 antagonist)</td>
<td>Selzentry</td>
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Integrase Inhibitors (IIs)

<table>
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<tr>
<th>Generic Name</th>
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<tbody>
<tr>
<td>Raltegravir</td>
<td>Isentress</td>
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Fixed-dose combination preparations include ZDV/3TC (Combivir), ZDV/3TC/ABC (Trizivir), ABC/3TC (Epzicom), TDF/FTC (Truvada), 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/mm³ (AI)
- CD4 cell count 350 to 500/mm³ (AII)
- CD4 cell count > 500/mm³ (BIII)

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

- Pregnancy (AI)
- History of an AIDS-defining condition (Table 3-1) (AI)
- HIV-associated nephropathy (AII)
- HIV/hepatitis B coinfection (AII)
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 most patients. Preferred combinations include two NRTIs (TDF/FTC) given in conjunction with an NNRTI or RTV-boosted PI or raltegravir (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 (Table 3-3). Useful adherence interventions are listed in Table 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](http://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 an appropriate 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.*

If the regimen is being modified because of toxicity to one drug, an agent from the same class may be substituted for it.

**HIV Resistance Testing**

The 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 the II raltegravir is available but not included in conventional genotypes.

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 long-term combination antiretroviral therapy. These include: 1) lipodystrophy syndrome; 2) lactic acidemia/acidosis; 3) premature bone loss (osteopenia and osteoporosis); 4) avascular necrosis of hips; and 5) 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 epidemiology and pathogenesis of lipodystrophy syndrome are not fully understood, and its management is syndromic (Figure 3-1). An evolving literature suggests that patients receiving long-term antiretroviral therapy, especially regimens that include older PIs or ABC, may be at increased risk for coronary artery disease.

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 lactic acidemia has poor predictive value for decompensated lactic acidosis, screening for this condition in asymptomatic individuals 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.

Premature bone loss (osteopenia/osteoporosis) has been reported in HIV-infected patients on long-term antiretroviral therapy. 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 if other risk factor(s) for premature bone loss are present; otherwise it is recommended in women aged 65 years and older or aged 60 years and older with other risk factor(s). Calcium and vitamin D should be prescribed in high-risk patients; regular exercise and smoking cessation should be advised.

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.
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.

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](http://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. Preferred and Alternative Drug Regimens for Antiretroviral-Naïve Patients

<table>
<thead>
<tr>
<th>Preferred *</th>
<th>PI-based</th>
<th>II-based</th>
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<tbody>
<tr>
<td>NNRTI-based</td>
<td>TDF/FTC</td>
<td>TDF/FTC</td>
</tr>
<tr>
<td>TDF/FTC/EFV **</td>
<td>plus ATV + rtv</td>
<td>plus raltegravir</td>
</tr>
<tr>
<td>or</td>
<td>DRV + rtv</td>
<td></td>
</tr>
<tr>
<td>or</td>
<td>raltegravir</td>
<td></td>
</tr>
<tr>
<td>or</td>
<td>TDF/FTC/elvitegravir/cobicistat *****</td>
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<table>
<thead>
<tr>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI-based</td>
</tr>
<tr>
<td>ABC ***/3TC plus EFV or TDF/FTC or ABC ***/3TC plus RPV ****</td>
</tr>
<tr>
<td>TDF/FTC or ABC ***/3TC plus LPV/rtv</td>
</tr>
</tbody>
</table>

* Preferred drug regimen in pregnant women is ZDV/3TC plus LPV/rtv (twice daily).
** Do not use EFV during the first trimester of pregnancy or in women with high pregnancy potential.
*** For patients who test negative for HLA-B*5701; caution is advised if patient has CAD risk factors or if VL > 100,000 copies/ml.
**** Not recommended if VL > 100,000 copies/ml; also note that higher rates of virologic failure have been reported in patients with CD4 count < 200/mm³.
***** For patients with pre-treatment creatinine clearance > 70 ml/min.

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

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).
Figure 3-1
Management of Lipodystrophy Syndrome

Hyperlipidemia, insulin resistance

- Diet and exercise
- Switch therapy
  - Older PI → ATV or NNRTI
- Statins/fibrates
- Insulin-sensitizing drugs

Visceral fat accumulation

- Diet and exercise
- Switch therapy
  - PI → NNRTI
  - Growth hormone or GHRF
- Insulin-sensitizing drugs
- Cosmetic surgery

Subcutaneous fat wasting

- Switch therapy
  - PI → NNRTI
  - Older NRTI → TDF
  - Insulin-sensitizing drugs
- Local injection Rx
  - (polylactic acid, calcium hydroxylapatite)