Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

November 3, 2008

Developed by the DHHS Panel on
Antiretroviral Guidelines for Adults
and Adolescents – A Working Group of the
Office of AIDS Research Advisory Council (OARAC)

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It is emphasized that concepts relevant to HIV management evolve rapidly. The Panel has a mechanism to update recommendations on a regular basis, and the most recent information is available on the **AIDS*info* Web site** (**http://AIDSinfo.nih.gov**).

What's New in the Document?

The following changes have been made to the January 29, 2008 version of the guidelines. Key new updates are highlighted throughout the document.

Format Changes

This revision is developed under a new format, whereby the relevant tables and references for each section are incorporated into the body of the document. Some larger tables are placed in an appendix at the end of the document. A separate PDF file with all the tables can be found at the AIDS*info* Web site.

Rating Changes

A new rating scheme is used in this guideline to be more consistent with other guidelines in infectious diseases. The changes are outlined below:

Strength of Recommendations

The **D** (should usually not be offered) and **E** (should never be offered) ratings have been removed. The **A**, **B**, and **C** ratings rate the strength of the statement. For example, an A rating for "not to initiate nevirapine in women with pre-treatment CD4 cell count >250 cells/mm^3" indicates a strong recommendation to not initiate nevirapine in these patients.

Quality of Evidence

Previously, only randomized trials with clinical endpoints were given a **I** ranking. In this new rating scheme, a **I** ranking includes randomized trials with either clinical or validated laboratory outcomes (e.g., viral load). A **II** rating includes non-randomized trials or well-designed observational cohort studies with long term clinical outcomes. A **III** rating remains a recommendation based on expert opinion.

Content Changes

The key changes to the different sections of the guidelines are outlined below:

Laboratory Monitoring

- A new table (**Table 3**) provides recommendations for laboratory tests to obtain at baseline and while receiving antiretroviral therapy to monitor for safety and treatment responses.
- The Panel recommends that resistance testing be considered in patients with viral loads of 500–1,000 copies/mL but recognizes that it may not always be reliable at those levels **(BII)**.

What to Start in Antiretroviral-Naïve Patients

Protease Inhibitor–Based Regimens:

- Ritonavir-boosted darunavir has been added as a preferred PI component **(AI)**.
- Once-daily ritonavir-boosted lopinavir has been moved from alternative to preferred PI component (except for pregnant women) **(AI)**.

Dual-NRTI Options:

- Abacavir + lamivudine has been moved from a preferred to an alternative dual-NRTI component because of concerns regarding an increased risk of myocardial infarction in patients with high cardiac risk factors, as suggested by large observational cohort studies, and concerns regarding virologic potency in patients with baseline viral loads >100,000 copies/mL **(BI)**.

Combinations Not to Use or to Use with Caution:

- A combination of unboosted atazanavir + didanosine + emtricitabine (or lamivudine) is not recommended because of efficacy concerns **(BI)**.

- A combination of nevirapine + tenofovir + emtricitabine (or lamivudine) should be used with caution and with close monitoring of virologic responses because of reports of early virologic failure in several small studies **(CII)**.

Management of Treatment-Experienced Patients

Regimen Simplification:

- A new section on Regimen Simplification for virologically suppressed patients has been added to the discussion of Management of the Treatment-Experienced Patient.

Additional Updates

The following sections and their relevant tables have been updated:

- Introduction
- CD4+ T-cell count
- Viral Load Testing
- Coreceptor Tropism Assay
- What Not to Use
- Exposure Response and Therapeutic Drug Monitoring (and table for recommended antiretroviral drug concentrations)
- HIV-Infected Adolescents
- HIV-Infected Illicit Drug Users
- HIV-Infected Women
- Adherence to Antiretroviral Therapy (with a new table)
- Antiretroviral-Associated Adverse Effects (and table for detection and management of adverse effects)
- Antretroviral Drug Interactions (with a new format for interactions between antiretroviral and other drugs)
- Tables describing the characteristics of antiretroviral drugs

November 3, 2008

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DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents Panel Roster

These Guidelines were developed by the Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents (a Working Group of the Office of AIDS Research Advisory Council).

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Guidelines Acknowledgement List
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Updated November 2008

Introduction (Updated November 3, 2008)

Antiretroviral therapy for treatment of human immunodeficiency virus type 1 (HIV-1) infection has improved steadily since the advent of potent combination therapy in 1996. New drugs have been approved that offer new mechanisms of action, improvements in potency and activity even against multidrug–resistant viruses, dosing convenience, and tolerability.

The Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) is a working group of the Office of AIDS Research Advisory Council (OARAC). The primary goal of the Panel is to provide recommendations for HIV practitioners based on current knowledge of antiretroviral drugs used to treat adults and adolescents with HIV infection in the United States. The Panel reviews new evidence and updates recommendations when needed. The primary areas of attention have included baseline assessment, treatment goals, indications for initiation of antiretroviral therapy, choice of the initial regimen in treatment-naïve patients, drugs or combinations to be avoided, management of adverse effects and drug interactions, management of treatment failure, and special considerations in specific patient populations.

These guidelines generally represent the state of knowledge regarding the use of antiretroviral agents. However, as the science rapidly evolves, the availability of new agents and new clinical data may rapidly change therapeutic options and preferences. The guidelines, therefore, are updated frequently by the Panel and are available as a "living document" at the **http://www.aidsinfo.nih.gov** Web site. However, these guidelines cannot always keep pace with the rapid evolution of new data in this field, and the guidelines cannot provide guidance for all patients. Therefore, clinicians need to exercise good judgment in management decisions tailored to unique patient circumstances.

GUIDELINES DEVELOPMENT PROCESS

An outline of the composition of the Panel and guidelines process can be found in Table 1.

Table 1. Outline of the Guidelines Development Process

Topic	Comment
Goal of the guidelines	Provide guidance to HIV care practitioners on the optimal use of antiretroviral agents for the treatment of HIV infection in adults and adolescents in the United States.
Panel members	The Panel is composed of approximately 30 voting members who have expertise in HIV care and research. The U.S. government representatives include at least one representative from each of the following DHHS agencies: Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), Health Resource Services Administration (HRSA), and National Institutes of Health (NIH). These members are appointed by their respective agencies. Approximately 2/3 of the Panel are nongovernmental scientific members. There are 4–5 community members. Members who do not represent U.S. government agencies are selected after an open announcement to call for nominations. Each member serves on the Panel for a 4-year term, with an option to be reappointed for an additional term. A list of the current members can be found on **Page vi** of this document.
Financial Disclosure	All members of the Panel submit a written financial disclosure annually. A list of the latest disclosures can be found in **Appendix A** of this document.
Users of the guidelines	HIV treatment providers
Developer	Panel on Antiretroviral Guidelines for Adults and Adolescents—a working group of the Office of AIDS Research Advisory Council (OARAC)
Funding Source	Office of AIDS Research, NIH
Evidence collection	The recommendations generally are based on studies published in peer-reviewed journals. On some occasions, particularly when new information may affect patient safety, unpublished data presented at major conferences or prepared by the FDA and/or manufacturers as warnings to the public may be used as evidence to revise the guidelines.

Recommendation grading	As described in **Table 2**
Method of synthesizing data	Each section of the guidelines is assigned to a working group with expertise in the area of interest. The members synthesize the available data and propose a recommendation to the Panel. All proposals are discussed at monthly teleconferences and then are voted on by the Panel members before being endorsed as official recommendations.
Other guidelines	These guidelines focus on treatment for adults and adolescents. Separate guidelines outline the use of antiretroviral therapy for such populations as pregnant women, children, and those who experience occupational or nonoccupational exposure to HIV. These guidelines are also available at the **http://www.aidsinfo.nih.gov** Web site. There is a brief discussion of the management of women of reproductive age and pregnant women in this document. However, for more detailed and up-to-date discussion on this and other special populations, the Panel defers to the designated expertise offered by panels that have developed those guidelines.
Public comments	After release of an update in the AIDS*Info* Web site, the public is given a 2-week period to submit comments to the Panel. These comments are reviewed, and a determination is made as to whether or not revisions are indicated. The public is also able to submit comments to the Panel at **aidsinfowebmaster@aidsinfo.nih.gov**.
Update plan	The Panel meets monthly by teleconference to review data that may warrant modification of the guidelines. Updates may be prompted by new drug approvals (or new indications, dosing formulations, or frequency), new significant safety or efficacy data, or other information that may have a significant impact on the clinical care of patients. For cases in which significant new data become available that may affect patient safety, a warning announcement with the Panel's recommendations may be made on the Web site until appropriate changes can be made in the guidelines document. Updated guidelines are available at the **http://www.aidsinfo.nih.gov** Web site.

Basis for Recommendations

Recommendations in these guidelines are based upon scientific evidence and expert opinion. Each recommended statement is rated with a letter of **A**, **B**, or **C** that represents the strength of the recommendation and with a numeral **I**, **II**, or **III**, according to the quality of the evidence.

Table 2. Rating Scheme for Recommendations

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement. **B:** Moderate recommendation for the statement. **C:** Optional recommendation.	**I:** One or more randomized trials with clinical outcomes and/or validated laboratory endpoints. **II:** One or more well designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes. **III:** Expert opinion.

HIV Expertise in Clinical Care

Multiple studies have demonstrated that better outcomes are achieved in HIV-infected outpatients cared for by a clinician with HIV expertise *[1-6]*, which reflects the complexity of HIV infection and its treatment. Thus, appropriate training and experience, as well as ongoing continuing medical education (CME), are important components for optimal care. Primary care providers without HIV experience, such as those who provide service in rural or underserved areas, should identify experts in the region who will provide consultation when needed.

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1. Kitahata MM, Koepsell TD, Deyo RA, et al. Physicians' experience with the acquired immunodeficiency syndrome as a factor in patients' survival. *N Engl J Med*, 1996. 334(11):701-6.

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Baseline Evaluation (Updated November 3, 2008)

Each HIV-infected patient initially entering into care should have a complete medical history, physical examination, laboratory evaluation, and counseling. The purpose is to confirm the presence of HIV infection, obtain appropriate baseline historical and laboratory data, assure patient understanding about HIV infection, and initiate care as recommended by the HIV primary care guidelines and by the opportunistic treatment and prevention guidelines *[1, 2]*. Baseline information then is used to define management goals and plans.

The following laboratory tests should be performed for a new patient during initial patient visits:

- HIV antibody testing (if prior documentation not available) or if HIV RNA is undetectable **(AI)**;
- CD4 T-cell count **(AI)**;
- Plasma HIV RNA (viral load) **(AI)**;
- Complete blood count, chemistry profile, transaminase levels, BUN and creatinine, urinalysis, screening test for syphilis (e.g., RPR, VDRL, or treponema EIA), tuberculin skin test (TST) or interferon-γ release assay (IGRA) (unless there is a history of prior tuberculosis or positive TST or IGRA), anti-*Toxoplasma gondii* IgG, hepatitis A, B, and C serologies, and Pap smear in women **(AIII)**;
- Fasting blood glucose and serum lipids if the patient is considered at risk for cardiovascular disease and for baseline evaluation prior to initiation of combination antiretroviral therapy **(AIII)**; and
- For patients who have pretreatment HIV RNA >1,000 copies/mL, genotypic resistance testing when the patient enters into care, regardless of whether therapy will be initiated immediately **(AIII)**. For patients who have HIV RNA levels of 500–1,000 copies/mL, resistance testing also may be considered, even though amplification may not always be successful **(BII)**. If therapy is deferred, repeat testing at the time of antiretroviral initiation should be considered **(CIII)**. (See **Drug Resistance Testing** section.)

In addition:

- Testing for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* is encouraged to identify both recent high-risk sexual behavior and the need for sexually transmitted disease (STD) therapy **(BII)**; and
- Chest x-ray in the presence of pulmonary symptoms or with a positive TST or IGRA test. **(BIII)**.

Patients living with HIV infection must often cope with multiple social, psychiatric, and medical issues that are best addressed through a multidisciplinary approach to the disease. The evaluation also must include assessment of substance abuse, economic factors (e.g., unstable housing), social support, mental illness, comorbidities, high-risk behaviors, and other factors that are known to impair the ability to adhere to treatment and to promote HIV transmission. Once evaluated, these factors should be managed accordingly.

Lastly, education about HIV risk behaviors and effective strategies to prevent HIV transmission to others should be provided at each patient clinic visit.

References

1. Aberg JA, Gallant JE, Anderson J, et al. Primary care guidelines for the management of persons infected with human immunodeficiency virus: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis*, 2004. 39(5):609-29.
2. Adult Prevention and Treatment of Opportunistic Infections Guidelines Working Group. Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents [DRAFT]. June 18, 2008; pp 1-289. Available at: **http://aidsinfo.nih.gov/contentfiles/Adult_OI.pdf**. Accessed November 2008.

Laboratory Testing for Initial Assessment and Monitoring While on Antiretroviral Therapy

(Updated November 3, 2008)

A number of laboratory evaluations are important for initial assessment in HIV-1 infected patients upon entry into care, during follow-up if therapy is not yet initiated, and prior to and after initiation of therapy to assess virologic and immunologic efficacy of antiretroviral therapy and to monitor for laboratory abnormalities that may be associated with antiretroviral drugs. **Table 3** outlines the Panel's recommendations for the frequency of testing. As noted in the table, some of the tests may be repeated more frequently if clinically indicated.

Two surrogate markers are used routinely to assess the immune function and level of HIV viremia: CD4 T-cell count and plasma HIV RNA (viral load). Resistance testing should be used to guide selection of an antiretroviral regimen in both treatment-naïve and -experienced patients; viral tropism assay should be performed prior to initiation of a CCR5 antagonist; and HLA-B*5701 testing should be performed prior to initiation of abacavir. The rationale and utility of these laboratory tests are discussed below.

Table 3. Laboratory Monitoring for Patients Prior to and After Initiation of Antiretroviral Therapy

Note: The following is a schedule for baseline and follow-up laboratory parameters to monitor prior to and after antiretroviral therapy initiation, for assessment of treatment response and detection of laboratory abnormalities. Some laboratory testing may require more frequent monitoring as clinically indicated.

	Entry into care	**Follow-up before ART**	**ART initiation or switch[1]**	**2-8 weeks post–ART initiation**	**Every 3 -6 months**	**Every 6 months**	**Every 12 months**	**Treatment Failure**	**Clinically indicated**
CD4 T-cell count	√	Every 3-6 months	√		√[2]			√	√
HIV RNA	√	Every 3-6 months	√	√	√[2]			√	√
Resistance testing	√		√[3]					√	√
HLA-B*5701 testing			√ (if considering ABC)						
Tropism testing								√ (if considering CCR5 antagonist)	√
Basic chemistry[4]	√	Every 6-12 months	√	√	√				√
ALT, AST, T. bili, D. bili,	√	Every 6-12 months	√	√	√				√
CBC w/ differential	√	Every 3-6 months	√	√ (if on ZDV)	√				√
Fasting lipid profile	√	If normal, annually	√	√ (consider after starting new ART)		√ (borderline or abnormal at last measurement)	√ (normal at last measurement)		√
Fasting glucose	√	If normal, annually	√		√ (borderline or abnormal at last measurement)	√ (normal at last measurement)			√
Urinalysis[5]	√		√			√ (patients with HIVAN)	√ (if on TDF)		√
Pregnancy test			√ (if starting EFV)						√

[1]Antiretroviral switch may be for treatment failure, adverse effects, or simplification.
[2]For adherent patients with suppressed viral load and stable clinical and immunologic status for >2-3 years, some experts may extend the interval for CD4 count and HIV RNA monitoring to every 6 months
[3]For treatment-naïve patients, if resistance testing was performed at entry into care, repeat testing is optional; for patients with viral suppression who are switching therapy for toxicity or convenience, resistance testing will not be possible and therefore, is not necessary.
[4]Serum Na, K, HCO_3, Cl, BUN, creatinine, glucose (preferably fasting); some experts suggest monitoring phosphorus while on tenofovir; determination of renal function should include estimation of creatinine clearance using Cockroft & Gault equation or estimation of glomerular filtration rate based on MDRD equation.
[5]For patients with renal disease, consult "Guidelines for the Management of Chronic Kidney Disease in HIV-Infected Patients: Recommendations of the HIV Medicine Association of the Infectious Diseases Society of America" (*Clin Infect Dis* 2005; 40: 1559-85).
Abbreviations: ART = antiretroviral therapy; HIVAN = HIV-associated nephropathy; ABC = abacavir; TDF = tenofovir.

CD4+ T-CELL COUNT

The CD4+ T-cell count (or CD4 count) serves as the major clinical indicator of immunodeficiency in patients who have HIV infection. It is the most important factor in deciding whether to initiate antiretroviral therapy and opportunistic infection prophylaxis, and it is the strongest predictor of subsequent disease progression and survival according to clinical trials and cohort studies *[1, 2]*. A significant change (2 standard deviations) between two tests is approximately a 30% change in the absolute count or an increase or decrease in CD4 percentage by 3 percentage points.

- **Use of CD4 Count for Initial Assessment**. The CD4 count is usually the most important consideration in the decision to initiate antiretroviral therapy and/or prophylaxis for opportunistic infections. All patients should have a baseline CD4 count at entry into care **(AI)**. Recommendations for initiation of antiretroviral therapy based on CD4 count are found in the **When to Start: Indications for Initiation of Antiretroviral Therapy** section of these guidelines.
- **Use of CD4 Count for Monitoring Therapeutic Response**. An adequate CD4 response for most patients on therapy is defined as an increase in CD4 count in the range of 50–150 cells/mm^3 per year with an accelerated response in the first 3 months. Subsequent increases in patients with good virologic control show an average increase of approximately 50–100 cells/mm^3 per year for the subsequent years until a steady state level is reached *[3]*. Some patients who initiate therapy with a severely depleted CD4 count may have a blunted increase in their count despite virologic suppression.
- **Frequency of CD4 Count Monitoring.** In general, CD4 counts should be determined every 3–4 months to (1) determine when to start antiretroviral therapy in patients not being treated; (2) assess immunologic response to antiretroviral therapy; and (3) assess the need for initiation or discontinuation of prophylaxis for opportunistic infections **(AI)**. For those patients who are adherent to therapy with sustained viral suppression and stable clinical status for more than 2–3 years, the frequency of CD4 count monitoring may be extended to every 6 months **(BIII)**.

Factors that affect absolute CD4 count – The absolute CD4 count is a calculated value based on the total white blood cell count (WBC) and the percentages of total and CD4+ T-lymphocytes. This absolute number may fluctuate among individuals or may be influenced by factors that may affect the total WBC and lymphocyte percentages, such as use of bone marrow–suppressive medications or the presence of acute infections. Splenectomy *[4, 5]* or coinfection with HTLV-1 *[6]* may cause misleadingly elevated absolute CD4 counts. Alpha-interferon, on the other hand, may reduce the absolute CD4 number without changing the CD4 percentage *[7]*. In all these cases, CD4 percentage remains stable and may be a more appropriate parameter to assess the patient's immune function.

PLASMA HIV RNA TESTING

Plasma HIV RNA (viral load) should be measured in all patients at baseline and on a regular basis thereafter, especially in patients who are on treatment, as viral load is the most important indicator of response to antiretroviral therapy **(AI)**. Analysis of 18 trials that included more than 5,000 participants with viral load monitoring showed a significant association between a decrease in plasma viremia and improved clinical outcome *[8]*. Thus, viral load testing serves as a surrogate marker for treatment response *[9]* and can be useful in predicting clinical progression *[10, 11]*. The minimal change in viral load considered to be statistically significant (2 standard deviations) is a threefold, or a 0.5 $\log_{10}$ copies/mL change. One key goal of therapy is suppression of viral load to below the limits of detection (below 40–75 copies/mL by most commercially available assays). For most individuals who are adherent to their antiretroviral regimens and who do not harbor resistance mutations to the prescribed drugs, viral suppression is generally achieved in 16–24 weeks, even though it may take a longer time in some patients. Recommendations for the frequency of viral load monitoring are summarized below.

- **At Initiation or Change in Therapy.** Plasma viral load should be measured before initiation of therapy and preferably within 2–4 weeks, and not more than 8 weeks, after treatment initiation or after treatment modification **(BI)**. Repeat viral load measurement should be performed at 4–8 week intervals until the level falls below the assay's limit of detection **(BII)**.
- **In Patients Who Have Viral Suppression but Therapy Was Modified Due to Drug Toxicity or Regimen Simplification.** Viral load measurement should be performed within 2–8 weeks after changing therapy. The purpose of viral load monitoring at this point is to confirm potency of the new regimen **(BII)**.

- **In Patients on a Stable Antiretroviral Regimen.** Viral load should be repeated every 3–4 months or as clinically indicated **(BII)**. In adherent patients who have suppressed viral loads for more than 2–3 years and who are at stable clinical and immunologic status, some clinicians may extend the interval to every 6 months **(BIII)**.

Monitoring in Patients with Suboptimal Response. In addition to viral load monitoring, a number of additional factors should be assessed, such as nonadherence, altered pharmacology, or drug interactions. Patients who fail to achieve viral suppression should undergo resistance testing to aid in the selection of an alternative regimen, as discussed in the **Drug Resistance Testing** section **(AI)**.

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DRUG RESISTANCE TESTING (Updated November 3, 2008)

Panel's Recommendations:

- ***HIV drug resistance testing is recommended for persons with HIV infection when they enter into care regardless of whether therapy will be initiated immediately (AIII). If therapy is deferred, repeat testing at the time of antiretroviral therapy initiation should be considered (CIII).***
- ***A genotypic assay is generally preferred for antiretroviral-naïve persons (AIII).***
- ***HIV drug resistance testing should be performed to assist in the selection of active drugs when changing antiretroviral regimens in cases of virologic failure and HIV RNA levels >1,000 copies/mL (AII). In persons with >500 but <1000 copies/mL, testing may be unsuccessful but should still be considered (BII).***
- ***Drug resistance testing should also be performed when managing suboptimal viral load reduction (AII).***
- ***Drug resistance testing in the setting of virologic failure should be performed while the patient is taking his/her antiretroviral drugs, or immediately (i.e., within 4 weeks) after discontinuing therapy (AII).***
- ***Genotypic resistance testing is recommended for all pregnant women prior to initiation of therapy (AIII) and for those entering pregnancy with detectable HIV RNA levels while on therapy (AII).***

Genotypic and Phenotypic Resistance Assays

Two types of resistance assays are used to assess viral strains and select treatment strategies: genotypic and phenotypic assays.

Genotypic Assays

Genotypic assays detect drug resistance mutations present in relevant viral genes. Certain genotypic assays involve sequencing of the entire reverse transcriptase and protease genes, whereas others use probes to detect selected mutations that are known to confer drug resistance. Genotypic assays can be performed rapidly, and results can be reported within 1–2 weeks of sample collection. Interpretation of test results requires knowledge of the mutations that different antiretroviral drugs select for and of the potential for cross resistance to other drugs conferred by certain mutations. The International AIDS Society-USA (IAS-USA) maintains a list of updated significant resistance-associated mutations in the reverse transcriptase, protease, and envelope genes. (See **http://www.iasusa.org/resistance_mutations**.) *[1]*. Various techniques are now available to assist the provider in interpreting genotypic test results *[2-5]*. Clinical trials have demonstrated the benefit of consultation with specialists in HIV drug resistance in improving virologic outcomes *[6]*. Clinicians are thus encouraged to consult a specialist to facilitate interpretation of genotypic results and design of an optimal new regimen.

Phenotypic Assays

Phenotypic assays measure the ability of a virus to grow in different concentrations of antiretroviral drugs. Reverse transcriptase and protease gene sequences derived from patient plasma HIV RNA are inserted into the backbone of a laboratory clone of HIV, either by cloning or by *in vitro* recombination. Replication of the recombinant virus at different drug concentrations is monitored by expression of a reporter gene and is compared with replication of a reference HIV strain. The drug concentration that inhibits 50% of viral replication (i.e., the median inhibitory concentration $[IC]_{50}$) is calculated, and the ratio of the IC_{50} of test and reference viruses is reported as the fold increase in IC_{50} (i.e., fold resistance).

Automated, recombinant phenotypic assays are commercially available with results available in 2–3 weeks. However, phenotypic assays cost more to perform than genotypic assays. In addition, interpretation of phenotypic assay results is complicated by incomplete information regarding the specific resistance level (i.e., fold increase in IC_{50}) that is associated with drug failure, although clinically significant fold increase cutoffs are now available for some drugs *[7-11]*. Again, consultation with a specialist can be helpful for interpreting test results.

Further limitations of both genotypic and phenotypic assays include lack of uniform quality assurance for all available assays, relatively high cost, and insensitivity for minor viral species. If drug-resistant viruses are present but constitute <10%–20% of the circulating virus population, they probably will not be detected by available assays. This

limitation is important because, after drugs exerting selective pressure on drug-resistant populations are discontinued, a re-emergence of wild-type virus as the predominant plasma population often occurs, resulting in a decrease of the proportion of virus with resistance mutations to below these thresholds *[12-14]*. This reversion to predominantly wild-type virus often occurs in the first 4–6 weeks after drugs are stopped. Prospective clinical studies have shown that, despite this plasma reversion, reinstitution of the same antiretroviral agents (or those sharing similar resistance pathways) is usually associated with early drug failure, and the virus present at failure is derived from previously archived resistant virus *[15]*. Therefore, resistance testing is of greatest value when performed before or within 4 weeks after drugs are discontinued **(AII)**. Because detectable resistant virus may persist in the plasma of some patients for longer periods of time, resistance testing beyond 4 to 6 weeks after discontinuation may still reveal mutations. Yet, the absence of detectable resistance in such patients must be interpreted with caution in designing subsequent antiretroviral regimens.

Use of Resistance Assays in Clinical Practice (Table 4)

No definitive prospective data exist to support using one type of resistance assay over another (i.e., genotypic versus phenotypic) in different clinical situations. Therefore, one type of assay is recommended per sample. However, for patients with a complex treatment history, results derived from both assays might provide critical and complementary information to guide regimen changes.

Use of Resistance Assays in Determining Initial Treatment

Transmission of drug-resistant HIV strains has been well documented and has been associated with suboptimal virologic response to initial antiretroviral therapy *[16-19]*. The likelihood that a patient will acquire drug-resistant virus is related to the prevalence of drug resistance in persons engaging in high-risk behaviors in the community. In the United States and Europe, recent studies suggest the risk that transmitted virus will be resistant to at least one antiretroviral drug is in the range of 6%–16% *[20-25]*, with 3%–5% of transmitted viruses exhibiting reduced susceptibility to drugs from more than one class *[16, 24]*. If the decision is made to initiate therapy in a person with acute HIV infection, resistance testing at baseline will likely optimize virologic response. Therefore, resistance testing in this situation is recommended **(AIII)**, and a genotypic assay is generally preferred because of its more rapid turnaround time **(AIII)**. In the absence of therapy, resistant viruses may decline over time to less than the detection limit of standard resistance tests but may still increase the risk of treatment failure when therapy is eventually initiated. Therefore, if the decision is made to defer therapy, resistance testing during acute HIV infection should still be performed **(AIII)**. In this situation, the genotypic resistance test result might be kept on record for several years before it becomes clinically useful. Because of the possibility of acquisition of drug-resistant virus during this period of time, repeat resistance testing at the time ART is initiated should be considered **(CIII)**.

Performing drug resistance testing before initiation of antiretroviral therapy in patients with chronic HIV infection is less straightforward. The rate at which transmitted resistance-associated mutations revert to wild-type virus has not been completely delineated, but mutations present at the time of HIV transmission are more stable than those selected under drug pressure, and it is often possible to detect resistance-associated mutations in viruses that were transmitted several years earlier *[26, 27]*. No prospective trial has addressed whether drug resistance testing prior to initiation of therapy confers benefit in this population. However, limited data from several, but not all, studies suggest suboptimal virologic responses in persons with baseline mutations *[16-19, 28-30]*. In addition, a cost-effectiveness analysis of early genotypic resistance testing suggests that baseline testing in this population should be performed *[31]*. Therefore, resistance testing in chronically infected persons at the time of entry into HIV care is recommended **(AIII)**. Genotypic testing is generally preferred in this situation **(AIII)**. Repeat testing at the time ART is initiated should be considered because of the possibility that the patient may have acquired drug-resistant virus **(CIII)**.

Use of Resistance Assays in the Event of Virologic Failure

Resistance assays are useful in guiding decisions for patients experiencing virologic failure while on antiretroviral therapy. Prospective data supporting drug-resistance testing in clinical practice at this time are derived from trials in which test utility was assessed for cases of virologic failure. These studies involved genotypic assays, phenotypic assays, or both *[6, 32-38]*. In general, these studies indicated that early virologic response to salvage regimens was improved when results of resistance testing were available to guide changes in therapy, compared with responses

observed when changes in therapy were guided only by clinical judgment. Thus, resistance testing appears to be a useful tool in selecting active drugs when changing antiretroviral regimens in cases of virologic failure with HIV RNA >1,000 copies/mL **(AII)**. (See **Management of the Treatment-Experienced Patient**.) In persons with >500 but <1,000 copies/mL, testing may be unsuccessful but should still be considered **(BII)**.

Resistance testing also can help guide treatment decisions for patients with suboptimal viral load reduction **(AII)**. Virologic failure in the setting of combination antiretroviral therapy is, for certain patients, associated with resistance to only one component of the regimen *[39-41]*. In that situation, substituting individual drugs in a failing regimen might be possible, although this concept will require clinical validation. (See **Management of the Treatment-Experienced Patient**.)

Use of Resistance Assays in Pregnant Patients

In pregnant women, the goal of antiretroviral therapy is to maximally reduce plasma HIV RNA to provide appropriate maternal therapy and to prevent mother-to-child transmission of HIV. Genotypic resistance testing is recommended for all pregnant women prior to initiation of therapy **(AIII)** and for those entering pregnancy with detectable HIV RNA levels while on therapy **(AII)**. Optimal prevention of perinatal transmission may require initiation of antiretroviral therapy before results of resistance testing are available.

Table 4. Recommendations for Using Drug Resistance Assays (Updated November 3, 2008)

Clinical Setting/Recommendation	Rationale
Drug-resistance assay recommended	
In acute HIV infection: Drug resistance testing is recommended, regardless of whether treatment will be initiated immediately **(AIII)**. A genotypic assay is generally preferred **(AIII)**.	If treatment is to be initiated, drug resistance testing will determine whether drug-resistant virus was transmitted and will help in the design of initial or changed (if therapy was initiated prior to test results) regimens.
If therapy is deferred, repeat resistance testing should be considered at the time ART is initiated **(CIII)**.	If treatment is deferred, testing still should be performed because of the potentially greater likelihood that transmitted resistance-associated mutations will be detected earlier in the course of HIV infection; results of testing may be important when treatment is eventually initiated. Repeat testing at the time ART is initiated should be considered because of the possibility that the patient may have acquired drug-resistant virus.
In chronic HIV infection: Drug resistance testing is recommended at the time of entry into HIV care, regardless of whether therapy will be initiated **(AIII)**. A genotypic assay is generally preferred **(AIII)**.	Transmitted HIV with baseline resistance to at least one drug may be seen in 6%–16% of patients, and suboptimal virologic responses may be seen in patients with baseline resistant mutations.
If therapy is deferred, repeat resistance testing should be considered at the time ART is initiated **(CIII)**.	Repeat testing at the time ART is initiated should be considered because of the possibility that the patient may have acquired drug-resistant virus.
With virologic failure during combination antiretroviral therapy with HIV RNA levels >1,000 copies/mL **(AII)**. In persons with >500 but <1,000 copies/mL, testing may be unsuccessful but should still be considered **(BII)**.	Testing can help determine the role of resistance in drug failure and thus maximize the number of active drugs in the new regimen, if indicated. Drug resistance testing should be performed while the patient is taking his/her antiretroviral drugs or immediately (i.e., within 4 weeks) after discontinuing therapy.
With suboptimal suppression of viral load after antiretroviral therapy initiation **(AIII)**.	Testing can help determine the role of resistance and thus maximize the number of active drugs in the new regimen, if indicated.
In HIV-Infected Pregnant Women: Genotypic resistance testing is recommended for all pregnant women prior to initiation of therapy **(AIII)** and for those entering pregnancy with detectable HIV RNA levels while on therapy **(AII)**.	The goals of antiretroviral therapy in HIV-infected pregnant women are to achieve maximal viral suppression for treatment of maternal HIV infection as well as for prevention of perinatal HIV transmission. Genotypic resistance testing will assist the clinician in selecting the optimal regimen for the patient.
Drug resistance assay not usually recommended	
After discontinuation (>4 weeks) of drugs **(BIII)**.	Drug resistance mutations might become minor species in the absence of selective drug pressure, and available assays might not detect minor drug-resistant species. If testing is performed in this setting, the detection of drug resistance may be of value, but its absence does not rule out the presence of minor drug-resistant species.
When plasma viral load <500 copies/mL **(AIII)**.	Resistance assays cannot be consistently performed because of low HIV RNA levels.

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HLA-B*5701 SCREENING

(Updated December 1, 2007)

Panel's Recommendations:

- ***The Panel recommends screening for HLA-B*5701 before starting patients on an abacavir-containing regimen, to reduce the risk of hypersensitivity reaction (AI).***
- ***HLA-B*5701-positive patients should not be prescribed abacavir (AI).***
- ***The positive status should be recorded as an abacavir allergy in the patient's medical record (AII).***
- ***When HLA-B*5701 screening is not readily available, it remains reasonable to initiate abacavir with appropriate clinical counseling and monitoring for any signs of hypersensitivity reaction (CIII).***

The abacavir hypersensitivity reaction (ABC HSR) is a multiorgan clinical syndrome typically seen within the initial 6 weeks of abacavir treatment. This reaction has been reported in 5%–8% of patients participating in clinical trials when using clinical criteria for the diagnosis, and it is the major reason for early discontinuation of abacavir. (See **Table 13**.) Discontinuing abacavir usually promptly reverses HSR, whereas subsequent rechallenge can cause a rapid, severe, and even life-threatening recurrence.

Studies that evaluated demographic risk factors for ABC HSR have shown racial background as a risk factor, with white patients generally having a higher risk (5%–8%) than black patients (2%–3%). Several groups reported a highly significant association between ABC HSR and the presence of the MHC class I allele HLA-B*5701 *[1, 2]*. An abacavir skin patch test (ABC SPT) was developed as a research tool to immunologically confirm ABC HSR, because the clinical criteria used for ABC HSR are overly sensitive and may lead to false-positive ABC HSR diagnoses *[3]*. A positive ABC SPT is an abacavir-specific delayed hypersensitivity reaction that results in redness and swelling at the skin site of application. All ABC SPT–positive patients studied were also positive for the HLA-B*5701 allele *[4]*. The ABC SPT could be falsely negative for some patients with ABC HSR. It is not recommended to be used as a clinical tool at this point. The PREDICT-1 study randomized patients before starting abacavir either to be prospectively screened for HLA-B*5701 (in which HLA-B*5701–positive patients were not offered abacavir) or to standard of care at the time of the study (i.e., no screening, with all patients receiving abacavir) *[5]*. The overall HLA-B*5701 prevalence in this predominately white population was 5.6%. In this cohort, screening for HLA-B*5701 eliminated immunologic ABC HSR (defined as ABC SPT positive) compared with standard of care (0% vs. 2.7%), yielding a 100% negative predictive value with respect to SPT as well as significantly decreasing the rate of clinically suspected ABC HSR (3.4% vs. 7.8%). The SHAPE study corroborated the low rate of immunologically validated ABC HSR in black patients and confirmed the utility of HLA-B*5701 screening for the risk for ABC HSR (100% sensitivity in black and white populations) *[6]*.

On the basis of the results of these studies, the Panel recommends screening for HLA-B*5701 before starting patients on an abacavir-containing regimen **(AI)**. HLA-B*5701–positive patients should not be prescribed abacavir **(AI)**, and the positive status should be recorded as an abacavir allergy in the patient's medical record **(AII)**. HLA-B*5701 testing needs to be performed only once in a patient's lifetime, so efforts to carefully record and maintain the result and to educate the patient about its implications are important. The specificity of the HLA-B*5701 test in predicting ABC HSR is lower than the sensitivity (i.e., 33%–50% of HLA-B*5701 positive patients would likely not develop confirmed ABC HSR if exposed to ABC). HLA-B*5701 should not be used as a substitute for clinical judgment or pharmacovigilance, because a negative HLA-B*5701 result does not absolutely rule out the possibility of some form of ABC HSR. When HLA-B*5701 screening is not readily available, it remains reasonable to initiate ABC with appropriate clinical counseling and monitoring for any signs of ABC HSR **(CIII)**.

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CORECEPTOR TROPISM ASSAYS

(Updated November 3, 2008)

Panel's Recommendations:

- ***Coreceptor tropism assay should be performed whenever the use of a CCR5 inhibitor is being considered (AII).***
- ***Coreceptor tropism testing might also be considered for patients who exhibit virologic failure on a CCR5 inhibitor (BIII).***

HIV enters cells by a complex process that involves the sequential attachment to the CD4 receptor followed by binding to either the CCR5 or CXCR4 molecules and fusion of the viral and cellular membranes *[1]*. The CCR5 inhibitors (i.e., maraviroc, vicriviroc) prevent HIV entry into target cells by binding to the CCR5 receptor *[2]*. Phenotypic and, to a lesser degree, genotypic assays have been developed that can determine the coreceptor tropism (i.e., CCR5, CXCR4, or both) of the patient's dominant virus population. One assay (*Trofile*, Monogram Biosciences, Inc., South San Francisco, CA) was used to screen patients who were participating in studies that formed the basis of approval for maraviroc, the only CCR5 inhibitor currently available. Other assays are under development and are currently used primarily for research purposes or in clinical situations in which the *Trofile* assay is not readily available.

Background

The vast majority of patients harbor a CCR5-utilizing virus (R5 virus) during acute/recent infection, which suggests that the R5 variant is preferentially transmitted compared with the CXCR4 (X4) variant. Viruses in many untreated patients eventually exhibit a shift in coreceptor tropism from CCR5 to either CXCR4 or both CCR5 and CXCR4 (i.e., dual- or mixed-tropic; D/M-tropic). This shift is temporally associated with a more rapid decline in CD4 T-cell counts *[3, 4]*, although whether this shift is a cause or a consequence of progressive immunodeficiency remains undetermined *[1]*. Antiretroviral-treated patients who have extensive drug-resistance are more likely to harbor detectable X4- or D/M-tropic variants than untreated patients who have comparable CD4 T-cell counts *[5]*. The prevalence of X4- or D/M-tropic variants increases to more than 50% in treated patients who have CD4 T-cell counts <100 cells/mm^3 *[5, 6]*.

Phenotypic Assays

There are now at least two high-throughput phenotypic assays that can quantify the coreceptor characteristics of plasma-derived virus. Both involve the generation of laboratory viruses that express patient-derived envelope proteins (i.e., gp120 and gp41). These pseudoviruses are either replication-competent (*Phenoscript* assay, VIRalliance, Paris, France) or replication-defective (*Trofile* assay, Monogram Biosciences, Inc.) *[7, 8]*. These pseudoviruses then are used to infect target cell lines that express either CCR5 or CXCR4. In the *Trofile* assay, the coreceptor tropism of the patient-derived virus is confirmed by testing the susceptibility of the virus to specific CCR5 or CXCR4 inhibitors *in vitro*. The *Trofile* assay takes about 2 weeks to perform and requires a plasma HIV RNA level ≥1,000 copies/mL.

The performance characteristics of these assays have evolved. Most, if not all, patients enrolled in premarketing clinical trials of maraviroc and other CCR5 inhibitors were screened with an earlier, less-sensitive version of the *Trofile* assay *[7]*. This earlier assay failed to routinely detect low levels of CXCR4-utilizing variants. As a consequence, some patients enrolled in these clinical trials harbored low, undetectable levels of CXCR4-utilizing viruses at baseline and exhibited rapid virologic failure after initiation of a CCR5 inhibitor *[9]*. This assay has since been revised and is now able to detect lower levels of CXCR4-utlizing viruses. *In vitro*, the assay can detect CXCR4-utilizing clones with 100% sensitivity when those clones make up 0.3% of the population; per **http://www.trofileassay.com** *[10]*. Although this more sensitive

assay has had limited use in prospective clinical trials, it is now the only one that is commercially available. For unclear reasons, a minority of samples cannot be successfully phenotyped with either generation of the *Trofile* assay.

Genotypic Assays

These assays are under investigation *[11, 12]* but are not commercially available.

Use of Coreceptor Tropism Assays in Clinical Practice

Coreceptor tropism assays should be used whenever the use of a CCR5 inhibitor is being considered **(AII)**. Coreceptor tropism testing might also be considered for patients who exhibit virologic failure on maraviroc (or any CCR5 inhibitor) **(BIII)**.

Other potential clinical uses for the tropism assay are for prognostic purposes or for assessment of tropism prior to starting antiretroviral therapy, in case a CCR5 inhibitor is required later (e.g., in a regimen change for toxicity). Currently, there are not sufficient data to support these uses.

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Treatment Goals (Updated December 1, 2007)

Eradication of HIV infection cannot be achieved with available antiretroviral regimens. This is chiefly because the pool of latently infected CD4 T-cells is established during the earliest stages of acute HIV infection *[1]* and persists with a long half-life, even with prolonged suppression of plasma viremia *[2-5]*. The primary goals driving the decision to initiate antiretroviral therapy therefore are to:

- reduce HIV-related morbidity and prolong survival,
- improve quality of life,
- restore and preserve immunologic function,
- maximally and durably suppress viral load, and
- prevent vertical HIV transmission.

Adoption of treatment strategies recommended in these guidelines has resulted in substantial reductions in HIV-related morbidity and mortality *[6-8]* and has reduced vertical transmission *[9, 10]*. Higher plasma HIV RNA levels (viral load) are associated with more rapid disease progression *[11]*, although other factors likely contribute as well to the rate of CD4 T-cell decline *[12]*. Maximal suppression of plasma viremia for as long as possible to delay the selection of drug resistance mutations, to preserve CD4 T-cell numbers, and to confer substantial clinical benefits are the most important goals of antiretroviral therapy *[13]*.

The goal of maximal viral suppression in initial therapy may be difficult in some cases of HIV with pre-existing resistance mutations. To be successful, antiretroviral regimens need to contain at least two, and preferably three, active drugs from multiple drug classes. When maximal initial suppression is not achieved or is lost, changing to a new regimen with at least two active drugs is required for this goal. If this is not possible in a clinically and immunologically stable patient, an interval of persisting viremia may be acceptable while waiting for arrival of potent new therapies.

Viral load reduction to below limits of assay detection in a treatment-naïve patient usually occurs within the first 12–24 weeks of therapy. Predictors of virologic success include:

- high potency of antiretroviral regimen,
- excellent adherence to treatment regimen *[14, 15]*,
- low baseline viremia,
- higher baseline CD4 T-cell count *[14, 15]*, and
- rapid (i.e., $\geq$1 $\log_{10}$ in 1 to 4 months) reduction of viremia in response to treatment *[15]*.

Successful outcomes are not always observed. Viral suppression rates in clinical practice may be lower than the 80%–90% seen in clinical trials, although the use of current compact, potent, and well-tolerated regimens has probably decreased this difference in outcomes between clinical trials and clinical practice *[16]*. (See also **Management of the Treatment-Experienced Patient: Assessment of Antiretroviral Treatment Failure and Changing Therapy**.)

STRATEGIES TO ACHIEVE TREATMENT GOALS

Achieving treatment goals requires a balance of sometimes competing considerations, outlined below. Providers and patients must work together to define priorities and determine treatment goals and options.

Selection of Initial Combination Regimen

Several preferred and alternative antiretroviral regimens are recommended for use. (See **What to Start: Initial Combination Regimens for the Antiretroviral-Naïve Patient**.) They vary in efficacy, pill burden, and potential side effects. A regimen tailored to the patient may be more successful in fully suppressing the virus by allowing more complete medication adherence. Individual tailoring is based on such considerations as expected side effects, convenience, comorbidities, interactions with other required medications, and results of pretreatment genotypic drug resistance testing.

Pretreatment Drug Resistance Testing

Current studies suggest a prevalence of HIV drug resistance of 6%–16% in antiretroviral treatment-naïve patients, and some studies suggest that the presence of transmitted drug-resistant viruses, particularly those with non-nucleoside reverse transcriptase inhibitor (NNRTI) mutations, may lead to suboptimal virologic responses. Therefore, pretreatment genotypic resistance testing should be used in guiding selection of the most optimal initial antiretroviral regimen. (See **Drug Resistance Testing** section.)

Improving Adherence

Suboptimal adherence may result in reduced treatment response. Incomplete adherence can result from complex medication regimens; patient factors, such as active substance abuse and depression; and health system issues, including interruptions in medication access and inadequate treatment education and support. Conditions that promote adherence should be maximized prior to initiating antiretroviral therapy. (See **Adherence** section).

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When to Start: Indications for Initiation of Antiretroviral Therapy (Table 5) (Updated December 1, 2007)

Panel's Recommendations:

- ***Antiretroviral therapy should be initiated in patients with a history of an AIDS-defining illness or with a CD4 T-cell count <350 cells/mm^3. The data supporting this recommendation are stronger for those with a CD4 T-cell count <200 cells/mm^3 and with a history of AIDS (AI) than for those with CD4 T-cell counts between 200 and 350 cells/mm^3 (AII).***
- ***Antiretroviral therapy should also be initiated in the following groups of patients regardless of CD4 T-cell count:***
  - ***a. Pregnant women (AI);***
  - ***b. Patients with HIV-associated nephropathy (AI); and***
  - ***c. Patients coinfected with HBV when treatment is indicated (BIII).***
- ***Antiretroviral therapy may be considered in some patients with CD4 T-cell counts >350 cells/mm^3. (See text for further discussion.)***
- ***The necessity for patient adherence to a long-term drug regimen should be discussed in depth between the patient and clinician (AIII). Potential barriers to adherence should be identified and addressed before therapy is initiated.***

The primary goals of antiretroviral therapy are to improve and/or preserve immune function and reduce HIV-associated morbidity and mortality. A potential secondary benefit is the theoretical likelihood of reducing HIV transmission because of continued high-risk behaviors *[1]*.

Large observational cohort studies and prognostic models provide some guidance based on the prognosis for disease-free survival as determined by baseline CD4 T-cell count (**Appendix Figure A** and **Appendix Tables 1a, 1b**) *[2-4]*. Potent combination antiretroviral therapy can increase and potentially normalize CD4 T-cell count in the majority of patients with maximal viral suppression regardless of baseline CD4 T-cell count *[5, 6]*.

Currently recommended antiretroviral regimens can achieve sustained viral suppression for many years. However, immediate virologic rebound followed by CD4 T-cell count decline is seen with most patients upon therapy interruption. Thus, once the decision is made to initiate antiretroviral therapy with currently available drugs, treatment should be continued without interruption, except for serious toxicities or concurrent conditions that preclude oral therapy. (See **Treatment Interruption** section.)

Before initiating therapy, patient counseling and education should be conducted. The patient should understand the potential benefits and risks of antiretroviral therapy, including short- and long-term adverse drug effects and the need for long-term commitment and adherence to the prescribed treatment regimen.

The Panel recommends initiation of antiretroviral therapy in patients with a history of AIDS-defining illness or with a CD4 T-cell count of <350 cells/mm^3. The following sections discuss the evidence used to support this recommendation.

For patients with a history of an AIDS-defining illness or a CD4 T-cell count <200 cells/mm3, antiretroviral therapy should be initiated (AI). HIV-infected patients with CD4 T-cell counts <200 cells/mm^3 are at higher risk for development of opportunistic diseases. The role of antiretroviral therapy is best defined in this population.

Randomized controlled trials strongly support initiation of therapy in patients with CD4 T-cell count <200 cells/mm^3. A prospective, controlled study provided strong evidence that treating symptomatic patients and patients with CD4 T-cell counts <200 cells/mm^3 improved survival and reduced disease progression *[7]*.

Subsequent long-term data from multiple observational cohort studies have provided strong support for the recommendation that therapy should always be initiated before the CD4 T-cell counts decline to <200 cells/mm^3 (**Appendix Figure A** and **Appendix Table 1a**) *[3, 4, 8-12]*.

For patients with CD4 T-cell counts between 200 and 350 cells/mm3, antiretroviral therapy is also recommended (AII). No randomized trial definitively addresses the optimal time to initiate antiretroviral therapy in chronically infected patients with CD4 T-cell counts >200 cells/mm^3. The Panel's recommendation for initiating antiretroviral therapy in these patients is based on several large, long-term observational cohort studies assessing immunological responses as defined by CD4 T-cell count increases and progression of HIV disease in patients with various baseline CD4 T-cell counts.

Data from the ART Cohort Collaboration, which included 61,798 patient-years of follow-up, showed that, at 3 to 5 years after starting therapy, the risk for AIDS/death was significantly less in those who started therapy with a CD4 T-cell count between 200 and 350 compared with those who initiated antiretroviral treatment at a CD4 threshold of 200 cells/mm^3 *[13]*. This study also demonstrated that baseline viral load was not significantly associated with risk of AIDS or death. However, patients with high viral loads 6-months posttreatment were found to have higher rates of disease progression, which indicates that virologic response to antiretroviral therapy remains a critical factor.

In the era of combination antiretroviral therapy, several large observational studies have indicated that the risk of several non-AIDS-defining conditions, including cardiovascular diseases, liver-related events, renal disease, and certain non-AIDS malignancies *[14-19]* is greater than the risk for AIDS in persons with CD4 T-cell counts >200 cells/mm^3; the risk for these events increases progressively as the CD4 T-cell count decreases from 350 to 200 cells/mm^3.

The SMART study, a prospective, randomized, multicenter, cohort study, compared treatment involving CD4 count–guided treatment interruption (i.e., therapy was discontinued when the CD4 T-cell count exceeded 350 cells/mm^3 and reinitiated when the CD4 T-cell count declined to <250 cells/mm^3) with continuous antiretroviral therapy. The risks for all-cause mortality, which was largely attributed to causes other than AIDS, and several non-AIDS defining conditions (including hepatic failure, renal disease, cardiovascular disease, and non-AIDS malignancy) were greater in participants randomized to CD4 count–guided treatment interruption than in those who received continuous therapy *[20, 21]*.

In a subgroup analysis of the SMART study, in which treatment-naïve patients with CD4 T-cell counts >350 cells/mm^3 were randomized to receive antiretroviral therapy either immediately or after the CD4 T-cell count dropped to <250 cells/mm^3, the risk of opportunistic diseases and serious non-AIDS events was higher in the deferred-therapy arm than in the treatment arm (absolute risk of 4.9% vs. 1.0%, respectively). These data for this small subgroup suggest that delaying therapy until the CD4 T-cell count decreases to <250 cells/mm^3 should be avoided *[22]*.

Collectively, the studies cited above support the use of antiretroviral therapy in all individuals with a CD4 T-cell count <350 cells/mm^3.

Antiretroviral therapy should be initiated in the following patients regardless of CD4 T-cell count:

Pregnant Women – All HIV-infected pregnant women should be started on antiretroviral therapy to manage maternal HIV infection and to maximize viral suppression, in order to reduce the risk for perinatal HIV transmission **(AI)**. For women who do not require antiretroviral therapy for their own health, postpartum discontinuation of antiretroviral drugs can be considered. For more detailed discussion, please refer to the ***Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women and Interventions to Reduce Perinatal HIV Transmission in the United States*** *[23]* and the **HIV-Infected Women** section.

HIV-Associated Nephropathy (HIVAN) – HIVAN is the most frequent cause of chronic renal failure in persons living with HIV infection. This entity, which is more common in black than in white patients, is not clearly related to CD4 T-cell depletion. Ongoing viral replication appears to be directly involved in renal injury. Antiretroviral therapy for individuals with HIVAN has been associated with both preserved renal function and prolonged survival, and therefore should be initiated for patients with a diagnosis of HIVAN regardless of CD4 T-cell count **(AI)** *[24, 25]*. When prescribing antiretroviral drugs, clinicians should note that most nucleoside reverse transcriptase inhibitors (NRTIs), except for abacavir, are renally excreted. Dosage adjustment for these agents may be necessary based on renal function; prescribers can refer to **Appendix Table 8** for dosing recommendations based on calculated creatinine clearance.

Hepatitis B virus (HBV) coinfection requiring treatment of HBV – HIV-infected patients may also be coinfected with HBV. The two-NRTI combination of tenofovir plus either lamivudine or emtricitabine is a component of many recommended first-line antiretroviral regimens and is also an effective treatment for HBV infection. In the HIV-infected patients, if therapy for either HIV or HBV infection is indicated, initiation of a fully suppressive antiretroviral regimen that includes tenofovir and either lamivudine or emtricitabine is recommended in order to prevent development of antiretroviral drug resistance **(BIII)**. If antiretroviral therapy is not initiated, HBV therapy should include only agent(s) with the least potential of selecting HIV resistance mutations. (See **Hepatitis B Coinfection** section.)

Antiretroviral therapy may be considered in some patients with CD4 T-cell count greater than 350 cells/mm^3.

Existing data are inadequate to recommend initiation of antiretroviral therapy in all patients with CD4 T-cell counts >350 cells/mm^3. Any theoretical potential benefits could be outweighed by unknown risks or by patient-specific preferences. The clinician should refer to **Table 5** for a list of potential risks and benefits of intiating therapy in these patients.

The short-term risk for AIDS or death at CD4 T-cell counts 350 cells/mm^3 is low (**Appendix Table 1b**). Thus, the potential absolute risk reductions associated with treatment in such patients are small (**Appendix Table 1a**). Within the ART Cohort Collaboration, the absolute 3-year risk differences between those with CD4 T-cell counts 200 to 349 cells/mm^3 and those with CD4 T-cell counts ≥350 cells/mm^3 were only 1.3% (for those with HIV-RNA <100,000 copies/mL) and 1.7% (for those with HIV-RNA ≥100,000 copies/mL) *[3]*. These differences were similar through 5 years of observation *[13]*. The cost-effectiveness of early initiation of antiretroviral therapy in these patients is unknown.

Data from the AIDS Therapy Evaluation Project, Netherlands (ATHENA), have demonstrated that patients who started therapy at CD4 T-cell counts >350 cells/mm^3 were significantly more likely to achieve CD4 T-cell counts >800 cells/mm^3 after 7 years of therapy than those who initiated therapy at lower CD4 T-cell counts *[6]*. A long-term study based on the Johns Hopkins Clinical Cohort demonstrated that patients who initiated ART with a CD4 T-cell count <350 cells/mm^3 were significantly less likely to achieve a CD4 T-cell count >500 cells/mm^3 after 6 years of highly active antiretroviral therapy (HAART) compared with those who started therapy at CD4 T-cell counts >350 cells/mm^3 *[26]*.

Earlier treatment of HIV infection may also have positive public health implications, as it may reduce HIV transmission *[1]*. This may have significant implication in individuals in discordant relationships (i.e., HIV-infected individuals with HIV-negative sexual partners) or in individuals who continue to engage in risky behaviors.

Despite possible benefits of treatment of persons with CD4 T-cell counts >350 cells/mm^3, there are also considerations that argue against therapy. First, the potential absolute reduction in risk of non-AIDS events/morbidity resulting from antiretroviral responses in CD4 T-cell count increase and viral load suppression is not large. Second, although there are now several reasonably safe and well-tolerated options for first-line regimens, the long-term toxicities remain unknown. Third, antiretroviral treatment requires life-long adherence to therapy. Some patients may find that the need to take daily medications decreases quality of life, even without side effects. Lastly, nonadherence to the regimen may promote the development of drug resistance.

The level of HIV RNA in a patient with a higher CD4 T-cell count is not strongly associated with short-term risk of AIDS/death and is a less important criterion for initiation of therapy than the CD4 T-cell count. Nevertheless, a high viral load is a predictor of more rapid progression to AIDS overall. Some experts may take viral load into consideration when deciding whether or not to start therapy in patients with CD4 T-cell counts >350 cells/mm^3 *[2, 27]*.

Clinical scenarios, the presence of comorbidities, age, patient readiness, potential impact on quality of life, and adherence should be considered in the decision of when and if to initiate therapy in patients with a CD4 T-cell count >350 cells/mm^3. Some experts suggest that antiretroviral therapy should be initiated in the subset of persons who have evidence of a rapid decline in CD4 T-cells (e.g., a decrease of >120 cells/mm^3 per annum) before it drops to a CD4 T-cell count of 350 cells/mm^3 in order to avoid rapid immunologic deterioration and subsequent clinical progression.

Special considerations in patients presenting with an opportunistic disease.

The timing of when to start therapy in patients presenting with an opportunistic disease is controversial and is covered in detail in the **Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Patients** *[28]*. The optimal time to start therapy varies, depending on the clinical scenarios. In patients with conditions for which there is no effective therapy except for improvement of immune function as a result of antiretroviral therapy (e.g., cryptosporidiosis, microsporidiosis, progressive multifocal leukoencephalopathy, and HIV-associated dementia), the early benefits of potent antiretroviral therapy outweigh any increased risk, and therefore therapy should be started as soon as possible **(AIII)**. In the setting of *Mycobacterium avium* complex infection, *Pneumocysitis jiroveci* pneumonia (PCP), and cryptococococcal meningitis, in which immediate therapy may increase the risk of immune reconstitution inflammatory syndrome (IRIS), a short delay may be warranted before initiating antiretroviral treatment **(CIII)**. With concomitant *M. tuberculosis* infection, delay of ART for 2 to 8 weeks after initiation of tuberculosis treatment is recommended in order to avoid confusion in the event of adverse drug reactions and to prevent or minimize IRIS **(BIII)**. (See **TB/HIV Coinfection** section.)

Adherence Considerations. Concern about adherence to therapy is a major determinant for timing of initiation of therapy, with patient readiness to start treatment being a key factor in future adherence *[29]*. Depression and substance abuse may negatively affect adherence and response to therapy and should therefore be addressed, whenever possible, before therapy is initiated. However, no patient should automatically be excluded from consideration for antiretroviral therapy simply because the clinician judges that the patient exhibits behaviors or characteristics affecting adherence. Instead, the necessity for patient adherence to a long-term drug regimen should be discussed in detail by the patient and clinician before therapy is initiated. To achieve the level of adherence necessary for effective therapy, providers are encouraged to use strategies for assessing and assisting adherence. (See **Adherence** section.)

Table 5a. Indications for Initiating Antiretroviral Therapy for the Chronically HIV-1 Infected Patient (Updated December 1, 2007)

Clinical Condition and/or CD4 Count	Recommendations
• History of AIDS-defining illness **(AI)** • CD4 count <200 cells/mm^3 **(AI)** • CD4 count 200-350 cells/mm^3 **(AII)** • Pregnant women* **(AI)** • Persons with HIV-associated nephropathy **(AI)** • Persons coinfected with hepatitis B virus (HBV), when HBV treatment is indicated (Treatment with fully suppressive antiviral drugs active against both HIV and HBV is recommended.) **(BIII)**	Antiretroviral therapy should be initiated.
• Patients with CD4 count >350 cells/mm^3 who do not meet any of the specific conditions listed above.	The optimal time to initiate therapy in asymptomatic patients with CD4 count >350 cells/mm^3 is not well defined. Patient scenarios and comorbidities should be taken into consideration. (See **Table 5b** and text regarding risks and benefits of therapy in patients with CD4 count >350 cells/mm^3).

***** For women who do not require antiretroviral therapy for their own health, consideration can be given to discontinuing antiretroviral drugs postpartum. For more detailed discussion, please refer to the ***Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women and Interventions to Reduce Perinatal HIV-1 Transmission in the United States*** and the **HIV-Infected Women** section.

Table 5b. Benefits and Risks of Initiating Antiretroviral Therapy in Asymptomatic Patients with CD4 T-Cell Count >350 cells/mm^3 (Updated December 1, 2007)

Benefits and Risks of Treatment

In addition to the risks of disease progression, the decision to initiate antiretroviral therapy should also be influenced by an assessment of other potential risks and benefits associated with treatment. Potential benefits and risks of early (CD4 counts >350 cells/mm^3) or deferred (CD4 count <350 cells/mm^3) therapy initiation for the asymptomatic patient are outlined below.

Potential Benefits of Early Therapy Include:

- Maintenance of a higher CD4 count and prevention of potentially irreversible damage to the immune system
- Decreased risk for HIV-associated complications that can sometimes occur at CD4 counts >350 cells/mm3, including tuberculosis, non-Hodgkin's lymphoma, Kaposi's sarcoma, peripheral neuropathy, HPV-associated malignancies, and HIV-associated cognitive impairment
- Decreased risk of nonopportunistic conditions, including cardiovascular disease, renal disease, liver disease, and non–AIDS-associated malignancies and infections
- Decreased risk of HIV transmission to others, which will have positive public health implications

Potential Risks of Early Therapy Include:

- Development of treatment-related side effects and toxicities
- Development of drug resistance because of incomplete viral suppression, resulting in loss of future treatment options
- Less time for the patient to learn about HIV and its treatment and less time to prepare for the need for adherence to therapy
- Increased total time on medication, with greater chance of treatment fatigue
- Premature use of therapy before the development of more effective, less toxic, and/or better studied combinations of antiretroviral drugs
- Transmission of drug-resistant virus in patients who do not maintain full virologic suppression

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What to Start: Initial Combination Regimens for the Antiretroviral-Naïve Patient (Updated November 3, 2008)

There are more than 20 approved antiretroviral drugs in six mechanistic classes with which to design combination regimens. These six classes include the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (FIs), CCR5 antagonists, and integrase inhibitors.

Summary of Recommended Regimens

The most extensively studied combination antiretroviral regimens for treatment-naïve patients generally consist of two NRTIs plus either one NNRTI or a PI (with or without ritonavir boosting). A list of Panel-recommended components for initial therapy in treatment-naïve patients can be found in **Table 6**. Potential advantages and disadvantages of the components recommended as initial therapy for treatment-naïve patients are listed in **Table 7** to guide prescribers in choosing the regimen best suited for an individual patient. A list of agents or components not recommended for initial treatment can be found in **Table 8**. Some agents or components that are not recommended for use because of lack of potency or potential serious safety concerns are listed in **Table 9**.

CONSIDERATIONS WHEN SELECTING A FIRST ANTIRETROVIRAL REGIMEN FOR TREATMENT-NAÏVE PATIENTS

Data Used for Making Recommendations

In its deliberations, the Panel reviews clinical trial data published in peer-reviewed journals and data prepared by manufacturers for FDA review. In selected cases, data presented in abstract format in major scientific meetings also are reviewed. The first criteria for selection are data from a randomized, prospective clinical trial with an adequate sample size that demonstrate durable viral suppression and immunologic enhancement (as evidenced by increased CD4 T-cell count). Few of these trials include clinical end points, such as development of AIDS-defining illness or death. Thus, assessment of regimen efficacy and potency is primarily based on surrogate marker endpoints (viral load and CD4 responses). The Panel reviewed data from randomized clinical trials to arrive at preferred versus alternative ratings in **Table 6**. Components are designated as preferred for use in treatment-naïve patients when clinical trial data have demonstrated optimal efficacy and durability with acceptable tolerability and ease of use. Alternative components refer to those for which clinical trial data show efficacy but also show disadvantages compared with preferred components. On the basis of individual patient characteristics and needs, a regimen listed as an alternative regimen may actually be the preferred regimen.

With the improved choices available for more effective and convenient regimens, some of the agents or combinations previously recommended by the Panel as alternative regimens have been removed from the list.

Factors to Consider When Selecting an Initial Regimen

Regimen selection should be individualized and should be based on a number of factors, including:

- comorbid conditions (e.g., cardiovascular disease, chemical dependency, liver disease, psychiatric disease, renal diseases, or tuberculosis);
- potential adverse drug effects;
- potential drug interactions with other medications;
- pregnancy or pregnancy potential;
- results of genotypic drug resistance testing;
- gender and pretreatment CD4 T-cell count if considering nevirapine;
- HLA-B*5701 testing if considering abacavir;
- patient adherence potential; and

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

Considerations for Therapies

A listing of characteristics (i.e., dosing, pharmacokinetics, and common adverse effects) of individual antiretroviral agents can be found in **Appendix Tables 2–7**. Additionally, **Appendix Table 8** provides clinicians with antiretroviral dosing recommendations for patients who have renal or hepatic insufficiency.

NNRTI- versus PI-Based Regimens

Currently, preferred regimens use combinations of two NRTIs and either an NNRTI or a ritonavir-boosted PI. Both NNRTI- and PI-based regimens result in suppression of HIV RNA levels and CD4 T-cell increases in a large majority of patients *[1-5]*. Some comparative data are available (See below).

Efavirenz-based regimens were superior to indinavir- and nelfinavir-based regimens in comparative studies *[3, 6]*. Neither indinavir nor nelfinavir is recommended now as part of initial therapy. The A1424-034 study demonstrated comparable virologic and immunologic responses with atazanavir- and efavirenz-based regimens *[5]*. The ACTG A5142 study showed better virologic responses with an efavirenz-based regimen compared with a lopinavir/ritonavir-based regimen, but it showed better CD4 cell responses and less resistance after virologic failure with lopinavir/ritonavir plus two NRTIs *[4]*. A smaller randomized trial in Mexico, which compared the same agents in treatment-naïve participants who had CD4 cell counts <200/mm^3, also suggested a virologic advantage among efavirenz recipients *[7]*.

The adverse effect profiles of the two-class–based regimens differ. PI-based regimens generally are associated with more gastrointestinal symptoms and lipid abnormalities, whereas NNRTI-based regimens are associated with more rash and central nervous system adverse effects (e.g., with efavirenz). Both kinds of regimens may cause hepatic transaminase elevations. Surprisingly, the A5142 study showed more lipoatrophy (>20% loss of limb fat by DEXA scan) in the efavirenz group than in the lopinavir/ritonavir group; higher rates of lipoatrophy were seen when stavudine and, to a lesser degree, zidovudine were part of the regimens *[8]*.

Drug resistance to most PIs requires multiple mutations in the HIV protease, and it seldom develops after early virologic failure *[9]*, especially when ritonavir boosting is used. Resistance to efavirenz or nevirapine, however, is conferred by a single mutation in reverse transcriptase, and it develops rapidly after virologic failure *[9]*. An estimated 7% of HIV-infected patients in the United States are infected with NNRTI-resistant viruses *[10]*. Because of the concern for primary resistance in the treatment-naïve population, genotypic testing results should be used to guide the selection of the initial antiretroviral regimen. (See **Drug Resistance Testing** section.) In terms of convenience, NNRTI-based regimens are among the simplest to take, particularly with the coformulated tablet of tenofovir, emtricitabine, and efavirenz, which allows for once-daily dosing with a single tablet. All preferred PI-based regimens include ritonavir, may be dosed once or twice daily, and generally require more pills in the regimen, although the pill burden associated with PI-based regimens has decreased. Drug-drug interactions are important with both kinds of regimens, but more clinically significant interactions are seen with ritonavir-boosted regimens.

In summary, regimens that contain two NRTIs with either an NNRTI or a ritonavir-boosted PI are recommended as first-line therapy, and the choice should be individualized.

NNRTI–BASED REGIMENS (1 NNRTI + 2 NRTIs)

Panel's Recommendations:
Preferred NNRTI (AI):

- ***Efavirenz (except during first trimester of pregnancy or in women with high pregnancy potential*)***

Alternative NNRTI (BI):

- ***Nevirapine may be used as an alternative in adult females with CD4 T-cell counts ≤250 cells/mm^3 and in adult males with CD4 T-cell counts ≤400 cells/mm^3.***

**** Women of child bearing age with high pregnancy potential are those who are trying to conceive or who are sexually active with men and not using effective and consistent contraception.***

Summary: NNRTI-Based Regimens

Four NNRTIs (namely, delavirdine, efavirenz, etravirine, and nevirapine) are currently FDA approved.

Use of NNRTI-based regimens as initial therapy can preserve PIs for later use, thus reducing or delaying patient exposure to some of the adverse effects more commonly associated with PIs. The major disadvantages of currently available NNRTIs involve prevalence of NNRTI-resistant viral strains in treatment-naïve patients *[10-13]* and the low genetic barrier of NNRTIs for development of resistance. Resistance testing is now recommended for treatment-naïve patients prior to starting therapy. (See **Drug Resistance Testing** section.) The first three approved NNRTIs (i.e., efavirenz, nevirapine, or delavirdine) only require a single mutation to confer resistance, and cross resistance affecting these three NNRTIs is common. Etravirine, an NNRTI approved for treatment-experienced patients, has in vitro activity against some viruses with mutations that confer resistance to delavirdine, efavirenz, and nevirapine *[14]*.

On the basis of clinical trial results and safety data, the Panel recommends the use of efavirenz as the preferred NNRTI as part of initial antiretroviral therapy **(AI)**. Efavirenz should not be used in pregnant women (especially during the first trimester) or in women of childbearing potential who are planning to conceive or who are sexually active with men and not using effective and consistent contraception.

Nevirapine may be used as an alternative to efavirenz for the initial NNRTI-based regimen in women with pretreatment CD4 counts ≤250 cells/mm^3 or in men with pretreatment CD4 counts ≤400 cells/mm^3 **(BI)** (See discussion below).

Among these four agents, delavirdine is dosed three times daily, has the least supportive clinical trial data, and appears to have the least antiviral activity. As such, it is not recommended as part of an initial regimen **(BIII)**. Etravirine has not been studied in large, randomized trials in treatment-naïve participants. Thus, it cannot currently be recommended as part of initial therapy **(BIII)**.

Following is a more detailed discussion of preferred and alternative NNRTI-based regimens for initial therapy.

Efavirenz as Preferred NNRTI (AI)

Large randomized, controlled trials and cohort studies of treatment-naïve patients have demonstrated potent viral suppression in efavirenz-treated patients; a substantial proportion of these patients had HIV RNA <50 copies/mL during up to 7 years of follow-up *[1, 2, 15]*. Studies that compared efavirenz-based regimens with other regimens have demonstrated that regimens that contained efavirenz with two NRTIs were superior virologically to some PI-based regimens, including indinavir *[3]*, lopinavir/ritonavir *[4]*, and nelfinavir *[6]*, and to triple-NRTI–based regimens *[16, 17]*. Efavirenz-based regimens also had comparable activities to nevirapine- *[18, 19]* and atazanavir-based regimens *[5]*.

The ACTG 5142 study randomized patients to receive two NRTIs together with either efavirenz or lopinavir/ritonavir (or an NRTI-sparing regimen of efavirenz and lopinavir/ritonavir) *[4]*. The dual-NRTI and efavirenz regimen was associated with a significantly better virologic response than the dual-NRTI and lopinavir/ritonavir regimen at 96 weeks, whereas the dual-NRTI with lopinavir/ritonavir regimen was associated with a significantly better CD4 cell response and less drug resistance after virologic failure.

The 2NN trial compared efavirenz and nevirapine, both given with stavudine and lamivudine, in treatment-naïve patients. Virologic responses were similar for both drugs, although nevirapine was associated with greater toxicity and did not meet criteria for noninferiority compared with efavirenz *[18]*.

Two major limitations of efavirenz are its central nervous system adverse effects, which usually resolve over a few weeks, and its potential teratogenic effects. In animal reproductive studies, efavirenz caused major congenital anomalies in the central nervous system in nonhuman primates at drug exposure levels similar to those achieved in humans *[20]*. Several cases of neural tube defects in human newborns, when mothers were exposed to efavirenz during first trimester of pregnancy, have been reported in the literature and to the Antiretroviral Pregnancy Registry *[21, 22]*. Therefore, efavirenz is not recommended in pregnant women during the first trimester of pregnancy or in women with high pregnancy potential (women who are of childbearing potential who are trying to conceive or who are sexually active with men and are not using effective and consistent contraception) **(AIII)**.

Studies that use efavirenz and two-NRTI combinations (abacavir, didanosine, stavudine, tenofovir, or zidovudine together with emtricitabine or lamivudine) show durable virologic activity. A single tablet of coformulated tenofovir, emtricitabine, and efavirenz provides one-pill, once-daily dosing.

Nevirapine as Alternative NNRTI (BI)

In the 2NN trial, 70% of participants in the efavirenz arm and 65.4% in the twice-daily nevirapine arm had virologic suppression (defined as HIV RNA <50 copies/mL) at 48 weeks. This difference did not reach criteria necessary to demonstrate noninferiority of nevirapine *[18]*. Two deaths were attributed to nevirapine use. One resulted from fulminant hepatitis and one from staphylococcal sepsis as a complication of Stevens-Johnson syndrome.

Three small studies (n <100) have suggested more virologic failures than would be expected in treatment-naïve participants who receive nevirapine plus tenofovir and either lamivudine or emtricitabine. In two of these studies, nevirapine was administered twice daily; in the third, once daily *[23-25]*. Larger randomized trials that address this combination are underway. While awaiting the results from these trials, clinicians should closely monitor virologic responses if using this combination **(CII)**.

Serious hepatic events have been observed when nevirapine was initiated in treatment-naïve patients. These events generally occur within the first few weeks of treatment. In addition to experiencing elevated serum transaminases, approximately half of the patients also develop skin rash, with or without fever or flu-like symptoms. Women with higher CD4 counts appear to be at highest risk *[26, 27]*. A 12-fold higher incidence of symptomatic hepatic events was seen in women (including pregnant women) with CD4 counts >250 cells/mm^3 at the time of nevirapine initiation when compared with women with CD4 counts $\leq$250 cells/mm^3 (11.0% vs. 0.9%). An increased risk was also seen in men with pretreatment CD4 counts >400 cells/mm^3 when compared with men with pretreatment CD4 counts $\leq$400 cells/mm^3 (6.3% vs. 1.2%). Most of these patients had no identifiable underlying hepatic abnormalities. In some cases, hepatic injuries continued to progress despite discontinuation of nevirapine *[26, 28]*. Symptomatic hepatic events have not been reported with single doses of nevirapine given to mothers or infants for prevention of perinatal HIV infection.

On the basis of the safety data described, the Panel recommends that nevirapine may be used as an alternative to efavirenz as initial therapy for women with pretreatment CD4 counts $\leq$250 cells/mm^3 or in men with CD4 counts $\leq$400 cells/mm^3 **(BI)**. Patients who experience CD4 count increases to levels above these thresholds as a result of nevirapine-containing therapy can safely continue therapy without an increased risk of adverse hepatic events.

At the initiation of nevirapine, a 14-day lead-in period at a dosage of 200mg once daily should be instituted before increasing to the maintenance dosage of 200mg twice daily. Some experts recommend monitoring serum transaminases at baseline, prior to and 2 weeks after dose escalation, then monthly for the first 18 weeks. Clinical and laboratory parameters should be assessed at each visit. More detailed recommendations on the management of nevirapine-associated hepatic events can be found in **Table 13**.

PI-BASED REGIMENS (RITONAVIR-BOOSTED OR UNBOOSTED PI + 2 NRTIs)

Panel's Recommendations:

Preferred PI (in alphabetical order):

- ***atazanavir + ritonavir once daily (AI)***
- ***darunavir + ritonavir once daily (AI)***
- ***fosamprenavir + ritonavir twice daily (BI)***
- ***lopinavir/ritonavir (coformulated) once or twice daily (AI)***

Alternative PI (BI) (in alphabetical order):

- ***atazanavir* (unboosted) once daily***
- ***fosamprenavir (unboosted) twice daily***
- ***fosamprenavir + ritonavir once daily***
- ***saquinavir + ritonavir twice daily***

**** Ritonavir 100mg per day must be given when tenofovir or efavirenz is used with atazanavir.***

Summary: PI-Based Regimens

Each PI has its own virologic potency, adverse effect profile, and pharmacokinetic properties. The characteristics, advantages, and disadvantages of each PI can be found in **Table 8** and **Appendix Table 4**. In selecting a PI-based regimen for a treatment-naïve patient, clinicians should consider factors such as dosing frequency, food requirements, pill burden, drug interaction potential, baseline hepatic function, toxicity profile of the individual PI, and pregnancy status. (See ***"Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States"*** for specific recommendations in pregnancy.) A number of metabolic abnormalities, including dyslipidemia, fat maldistribution, and insulin resistance, have been associated with PI use. PIs differ in their propensity to cause these metabolic complications. The extent to which these complications may result in adverse long-term consequences, such as increased cardiac events, is unknown.

The potent inhibitory effect of ritonavir on the cytochrome P450 3A4 isoenzyme has allowed the addition of low-dose ritonavir to other PIs (with the exception of nelfinavir) as a pharmacokinetic booster to increase drug exposure and prolong plasma half-lives of the active PI. This allows for reduced dosing frequency and/or pill burden, which may improve overall adherence to the regimen. The increased trough concentration (C_{min}) may improve the antiretroviral activity of the active PI, which can be beneficial when the patient harbors HIV strains with reduced susceptibility to the PI *[29-31]*. The drawbacks associated with this strategy are the potential for increased risk of hyperlipidemia and a greater potential of drug-drug interactions from the addition of ritonavir.

The list of Panel-recommended PIs can be found in **Table 6**. The following are preferred PIs for the treatment-naïve patients: atazanavir + ritonavir (once daily) **(AI)**, darunavir + ritonavir (once daily) **(AI)**, fosamprenavir + ritonavir (twice daily) **(BI)**, or lopinavir/ritonavir (coformulated) (once or twice daily) **(AI)**. This recommendation is based on clinical trial efficacy, the barrier for virologic resistance, convenience, and tolerability. Alternative PIs include atazanavir (unboosted, once daily) **(BI)**, fosamprenavir (unboosted, twice daily) **(BI)**, fosamprenavir + ritonavir (once daily) **(BI),** or saquinavir + ritonavir (twice daily) **(BI)**. PIs not recommended as initial treatment regimens include indinavir (with or without ritonavir), nelfinavir, ritonavir alone, and tipranavir with ritonavir.

Preferred PI Components

Ritonavir-Boosted Atazanavir (AI). Atazanavir is an azapeptide PI that is dosed once daily. Ritonavir-boosting of atazanavir enhances the concentrations of atazanavir, and there is a suggestion of improved virologic activity when boosted atazanavir is employed in clinical trials *[32, 33]*.

The CASTLE study compared once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir/emtricitabine, in 883 antiretroviral-naive participants *[34]*. In this open-label, noninferiority study, analysis at 48 weeks showed similar virologic and CD4 T-cell count responses of the two

regimens. More hyperbilirubinemia and less gastrointestinal toxicity were seen in the ritonavir-boosted atazanavir arm. This study supports the designation of boosted atazanavir as a preferred regimen.

The main adverse effect associated with atazanavir + ritonavir is indirect hyperbilirubinemia, with or without jaundice or scleral icterus, but without concomitant hepatic transaminase elevations. Several cases of nephrolithiasis have been reported in patients who received ritonavir-boosted or unboosted atazanavir *[35]*. The causal relationship is still uncertain. Atazanavir + ritonavir require acidic gastric pH for dissolution. Thus, concomitant use of drugs that raise gastric pH, such as antacids, H_2 antagonists, and particularly proton pump inhibitors, may impair absorption of atazanavir + ritonavir. **Table 15a** provides recommendations for how to use ritonavir-boosted atazanavir with these agents.

Ritonavir-Boosted Darunavir (AI). The ARTEMIS study compared darunavir/ritonavir (800/100mg once daily) with lopinavir/ritonavir (once or twice daily), both in combination with tenofovir/emtricitabine, in a randomized, open-label, noninferiority trial. The study enrolled 689 treatment-naïve participants who had a median CD4 count of 225 cells/mm^3 and a median plasma HIV RNA level of 4.85 $\log_{10}$ copies/mL. At 48 weeks, darunavir/ritonavir was noninferior to lopinavir/ritonavir; plasma HIV RNA levels were <50 copies/mL in 84% of darunavir/ritonavir recipients and in 78% of lopinavir/ritonavir recipients ($p < 0.001$). The virologic response rates were lower in the lopinavir/ritonavir arm among those participants whose baseline HIV RNA levels were >100,000 copies/mL ($p < 0.05$). Lopinavir/ritonavir recipients received either the soft-gel capsule or tablet formulation in this trial, depending on the availability of the formulation in the study countries. Grades 2 to 4 adverse events, primarily diarrhea, were seen in 7% of darunavir/ritonavir recipients and in 14% of lopinavir/ritonavir recipients ($p < 0.01$) *[36]*.

Ritonavir-Boosted Fosamprenavir (twice daily) (BI). Fosamprenavir is a prodrug of the PI amprenavir. The KLEAN trial compared twice-daily ritonavir-boosted fosamprenavir with lopinavir/ritonavir, each in combination with abacavir and lamivudine, in treatment-naïve patients. At Week 48, 73% of the patients in the ritonavir-boosted fosamprenavir arm and 71% of those in the lopinavir/ritonavir arm achieved viral loads of <400 copies/mL (95% confidence interval [CI] around treatment difference, -4.84 to 7.05) *[37]*. Clinical and laboratory adverse events did not differ between the regimens. In this study of treatment-naïve participants, twice-daily ritonavir-boosted fosamprenavir was noninferior to twice-daily lopinavir/ritonavir, which supports the recommendation of twice-daily ritonavir-boosted fosamprenavir as a preferred PI component. Similar virologic responses were seen at 96 weeks *[38]*. As with other ritonavir-boosted PIs, resistance is uncommon in previously PI-naïve patients who fail boosted fosamprenavir. Metabolic adverse effects occurred at similar frequencies with boosted fosamprenavir as with lopinavir/ritonavir in the KLEAN study. There are limited data regarding the use of twice-daily boosted fosamprenavir with nucleoside/nucleotide combinations other than abacavir/lamivudine.

Lopinavir/Ritonavir (coformulated) (AI). Several clinical trials show that regimens containing twice-daily lopinavir/ritonavir with two NRTIs have substantial virologic activity in treatment-naïve patients. Early studies showed that lopinavir/ritonavir was superior to nelfinavir in maintaining undetectable viral loads *[39]*. A 7-year follow-up study of lopinavir/ritonavir and two NRTIs showed sustained virologic suppression in patients who were maintained on the originally assigned regimen *[40]*. Results of clinical trials that compare lopinavir/ritonavir with ritonavir-boosted atazanavir, darunavir, fosamprenavir, or saquinavir are discussed in the respective sections of this document. The ACTG 5142 study showed that the regimen of twice-daily lopinavir/ritonavir plus two NRTIs was associated with decreased virologic efficacy when compared with efavirenz plus two NRTIs. However, the CD4 T-cell count response was greater with lopinavir/ritonavir, and there was less drug resistance associated with virologic failure *[4]*.

Lopinavir/ritonavir can also be administered once daily to PI-naïve patients. Several trials have evaluated different formulations and dosages administered once or twice daily *[36, 41-44]*. In the largest trial that compared once-daily versus twice-daily lopinavir/ritonavir, both in combination with tenofovir and emtricitabine, 664 treatment-naïve participants were randomized to receive once- or twice-daily soft-gel capsules or once- or twice-daily tablets for 8 weeks; at Week 8, all participants received the tablet formulation and maintained their same randomized dosing schedule *[45]*. At Week 48, 77% of once-daily and 76% of twice-daily lopinavir/ritonavir recipients achieved viral loads <50 copies/mL. Within subgroups defined by baseline viral loads above or below 100,000 copies/mL, or by CD4 counts <50, 50–200, and >200 cells/mm^3, similar proportions of once- and twice-daily recipients achieved viral loads <50 copies/mL. Rates of moderate to severe drug-related diarrhea were similar between the two groups. The tablet formulation was greatly preferred by study participants, and the study conclusion was that once-daily and twice-daily tablet formulations of lopinavir/ritonavir have similar overall safety and tolerability. In addition to

diarrhea, major adverse effects of lopinavir/ritonavir include insulin resistance and hyperlipidemia, especially hypertriglyceridemia; these require pharmacologic management in some patients.

Once-daily lopinavir/ritonavir should not be used in patients who have HIV mutations associated with protease inhibitor resistance, because higher lopinavir trough levels may be required to suppress resistant virus. Lopinavir/ritonavir given twice daily is the preferred PI for use in pregnant women *[46]*. Once-daily dosing should not be used in this situation, especially during the third trimester, when lopinavir levels are expected to decline. For more detailed information regarding antiretroviral drug choices and related issues in pregnancy, see ***"Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States,"*** available at **http://aidsinfo.nih.gov**.

Alternative PI Components

Atazanavir (BI). Unboosted atazanavir is given once daily and has fewer adverse effects on lipid profiles than other available PIs. Three studies compared atazanavir-based combination regimens to either nelfinavir- or efavirenz-based regimens. These studies established similar virologic efficacy among atazanavir 400mg once daily and both comparator treatment groups in antiretroviral-naïve patients after 48 weeks of therapy *[5, 32, 47, 48]*. The ACTG 5175 trial compared three regimens in treatment-naïve patients. The Data Safety Monitoring Board for this trial recommended that participants be unblinded and switched to alternative therapy if they were randomized to a regimen that consisted of atazanavir + enteric-coated didanosine + emtricitabine because of an inferior virologic response when compared with the other two arms—once-daily efavirenz plus either zidovudine/lamivudine (twice daily) or tenofovir/emtricitabine (once daily) *[49]*. If unboosted atazanavir is prescribed for a treatment-naïve patient, clinicians should consider using an alternative dual-NRTI backbone than didanosine + emtricitabine (or lamivudine).

Unboosted atazanavir may be chosen as initial therapy for patients when a once-daily regimen without ritonavir is desired and in patients who have underlying risk factors with which hyperlipidemia may be particularly undesirable. However, ritonavir-boosting is preferred and is recommended in PI-experienced patients. Patients who receive concomitant therapy with tenofovir or efavirenz should use ritonavir-boosted atazanavir to overcome the adverse pharmacokinetic interactions between unboosted atazanavir and these two agents. Atazanavir requires acidic gastric pH for dissolution. Thus, concomitant use of drugs that raise gastric pH, such as antacids, H_2 antagonists, and proton pump inhibitors, may significantly impair its absorption. Proton pump inhibitors should not be used in patients who are taking unboosted atazanavir. H_2 antagonists and antacids should be used with caution and with careful dose separation. (See **Tables 14 and 15a**.)

Fosamprenavir (twice daily) (BI) and Ritonavir-Boosted Fosamprenavir (once daily) (BI). Fosamprenavir is recommended as an alternative PI when given without ritonavir (1,400mg twice daily) or as a once-daily ritonavir-boosted regimen (1,400/200 or 1,400/100 mg once daily). Two studies compared twice-daily fosamprenavir and once-daily ritonavir-boosted fosamprenavir (1,400 mg with ritionavir 200 mg once-daily) with nelfinavir *[50, 51]*. In the first trial, more participants who were randomized to fosamprenavir achieved viral suppression at 48 weeks than those who were assigned to nelfinavir, and greater differences were seen in those who had pretreatment viral loads >100,000 copies/mL *[50]*. Once-daily ritonavir-boosted fosamprenavir had similar virologic activity to nelfinavir in the second trial *[51]*. A comparison of once-daily ritonavir-boosted fosamprenavir (1,400/100 mg) with once-daily ritonavir-boosted atazanavir, both in combination with tenofovir/emtricitabine, was conducted in 106 antiretroviral-naïve participants *[52]*. Similar virologic and CD4 T-cell benefits were seen with both regimens. Because of the relatively small sample size of this study, and because the FDA approval of the 1,400/100mg regimen was primarily based on pharmacokinetic data and not clinical trial results, this remains an alternative regimen pending additional data.

Ritonavir-Boosted Saquinavir (BI). The GEMINI study compared saquinavir/ritonavir (1,000/100mg twice daily) with lopinavir/ritonavir, both given twice daily, in combination with tenofovir/emtricitabine given once daily, in 337 treatment-naïve participants who were monitored over 48 weeks. Similar levels of viral suppression and increases in CD4 counts were seen in both arms *[53]*. There is a higher pill burden for saquinavir/ritonavir than for some other boosted PI regimens.

DUAL-NUCLEOSIDE OPTIONS AS PART OF INITIAL COMBINATION THERAPY

Panel's Recommendations:

Preferred dual-NRTI (AI):

- ***tenofovir/emtricitabine*(coformulated)***

Alternative dual-NRTIs (BI) (in alphabetical order):

- ***abacavir/lamivudine* (coformulated) in patients tested negative of HLA-B*5701***
- ***didanosine + (lamivudine or emtricitabine)***
- ***zidovudine/lamivudine*(coformulated)***

** Emtricitabine may be used in place of lamivudine or vice versa.*

Summary: Dual-NRTI Components

Dual-NRTI combinations are commonly utilized components of combination antiretroviral regimens with the addition of an NNRTI or a PI (usually boosted with ritonavir). Most dual-NRTI combinations used in clinical practice consist of a primary NRTI in combination with lamivudine or emtricitabine. Both lamivudine and emtricitabine have few adverse effects, and each selects for the M184V resistance mutation, which confers high-level resistance to both drugs, a modest decrease in susceptibility to didanosine and abacavir, and improved susceptibility to zidovudine, stavudine, and tenofovir *[54]*.

All NRTIs except didanosine can be taken without food restrictions. Adherence may be additionally improved with once-daily dosing (currently possible with all NRTIs except stavudine and zidovudine) and with fixed-dosage combination products, such as abacavir/lamivudine, tenofovir/emtricitabine (with or without efavirenz), or zidovudine/lamivudine.

The Panel's recommendations on specific dual-NRTI options are made on the basis of virologic potency and durability, short- and long-term toxicities, the propensity to select for resistance mutations, and dosing convenience.

Preferred Dual-NRTI Components

Tenofovir/Emtricitabine (coformulated) (AI). Tenofovir is a nucleotide analog with potent activity against HIV and hepatitis B virus (HBV) and with a long intracellular half-life that allows for once-daily dosing. The fixed-dose combinations of tenofovir/emtricitabine and tenofovir/emtricitabine/efavirenz are both administered as one pill once daily and are designed to improve adherence.

Tenofovir, when used with either lamivudine or emtricitabine as part of an efavirenz-based regimen in treatment-naïve patients, demonstrated potent virologic suppression *[15]* and was superior to zidovudine/lamivudine in virologic efficacy at up to 144 weeks *[55]*. In the 934 study, more participants in the zidovudine/lamivudine arm developed loss of limb fat as assessed by DEXA scans and anemia at 96 and 144 weeks compared with the tenofovir/emtricitabine arm *[55]*. Emergence of the M184V mutation was less frequent than with zidovudine/lamivudine, and no participant had developed the K65R mutation after 144 weeks of therapy, in contrast to other studies in which tenofovir was combined with lamivudine. Tenofovir with emtricitabine or lamivudine has been studied in combination with several different boosted PIs in randomized clinical trials; all such trials demonstrate good virologic benefit *[34, 36, 42, 52]*.

Tenofovir/emtricitabine was compared to abacavir/lamivudine in the ACTG 5202 study and the HEAT trial. The final results of these studies have not been published. Preliminary data from the ACTG trial suggest potential of inferior virologic responses in participants randomized to abacavir/lamivudine and had a pre-treatment HIV-RNA >100,000 copies/mL. See the section below for more detailed discussions regarding the results of these trials.

Three small studies (n <100) have suggested more virologic failures than would be expected in treatment-naïve participants who received nevirapine plus tenofovir and either lamivudine or emtricitabine. In two of these studies, nevirapine was administered twice daily; in the third, once daily *[23-25]*. Larger randomized trials that address this

combination are underway. While awaiting the results from these trials, clinicians should closely monitor virologic responses if using this combination **(CIII)**.

Renal impairment, manifested by increases in serum creatinine, glycosuria, hypophosphatemia, and acute tubular necrosis, has been reported with tenofovir use *[56, 57]*. Risk factors may include advanced HIV disease, greater treatment experience, and pre-existing renal impairment *[58, 59]*. Renal function, urinalysis, and electrolytes should be monitored in patients who are on tenofovir. In patients who have some degree of pre-existing renal insufficiency (creatinine clearance [CrCl] <50 mL/min; **Appendix Table 8** for dosage recommendations), tenofovir dosage adjustment is required. However, because no safety and efficacy data that use the dosage adjustment guidelines for renal dysfunction are available, the use of alternative NRTIs (especially abacavir) may be preferred over dose-adjusted tenofovir in this setting.

Tenofovir levels can be increased by some PIs; some studies have suggested a greater risk for renal dysfunction when tenofovir is used in PI-based regimens *[56, 60, 61]*, but others have not found this association *[58]*. Tenofovir has been used in combination with PIs in several clinical trials that involved patients who had CrCl >50–60 mL/min without renal toxicity.

Tenofovir plus either emtricitabine or lamivudine is the preferred NRTI combination for patients coinfected with both HIV and HBV, as these drugs have activity against both viruses. The use of a single HBV-active NRTI (e.g., lamivudine or emtricitabine) can lead to HBV resistance and is not recommended. (See **Hepatitis B (HBV)/HIV Coinfection**.)

Alternative Dual-NRTI Components (in alphabetical order)

Abacavir/Lamivudine (coformulated) for Patients Who Test Negative for HLA-B*5701 (BI). Abacavir has the potential for serious hypersensitivity reactions (HSRs). Clinically suspected HSRs have been observed in 5%–8% of patients who start this drug. The risk for this reaction is highly associated with the presence of the HLA-B*5701 allele (See **HLA-B*5701 Screening** section) *[62, 63]*. Whenever possible, HLA-B*5701 testing should precede the use of abacavir. Abacavir should not be given to patients who test positive for HLA-B*5701, and abacavir hypersensitivity should be noted on the patient's allergy list based on these results. Those who test negative are less likely to experience HSR, but they should be counseled about the symptoms of the reaction.

In a comparative trial of abacavir/lamivudine and zidovudine/lamivudine (both given twice daily and combined with efavirenz), participants from both arms achieved similar virologic responses. The abacavir-treated participants experienced a greater CD4 T-cell increase at 48 weeks *[64]*. The fixed-dose combination of abacavir/lamivudine allows for one-pill, once-daily dosing.

The ACTG 5202 study, a randomized controlled trial in more than 1,800 participants, evaluated the efficacy and safety of abacavir/lamivudine versus tenofovir/emtricitabine when used in combination with either efavirenz or ritonavir-boosted atazanavir. Treatment randomization was stratified based on a screening HIV RNA of <100,000 copies/mL or ≥100,000 copies/mL. An independent Data Safety Monitoring Board recommended early termination of the >100,000 copies/mL stratification group because of a significantly shorter time to study-defined virologic failure in the abacavir/lamivudine arm compared with the tenofovir/emtricitabine arm *[65]*. Participants who had HIV RNA levels <100,000 copies/mL at study screening remain randomized and on study.

In a contrasting smaller study (HEAT), 688 participants received abacavir/lamivudine or tenofovir/emtricitabine in combination with once-daily lopinavir/ritonavir. A subgroup analysis according to baseline HIV RNA of <100,000 copies/mL or >100,000 copies/mL yielded similar percentages of participants with HIV RNA <50 copies/mL at 96 weeks for the two regimens (63% vs. 59% for those who had <100,000 copies/mL and 56% vs. 58% for those who had >100,000 copies/mL, respectively) *[66]*.

Concern has also been raised regarding the potential cardiovascular risks of abacavir-containing regimens. The D:A:D study group reported an analysis of myocardial infarction (MI) risk in a large, multinational, observational cohort that involved 33,345 participants and had 157,912 person-years of follow-up *[67]*. Recent (within 6 months) or current, but not cumulative or past use (last use >6 months) of abacavir predicted an increased risk of MI

(relative risk [RR], 1.9; 95% CI, 1.5–2.6). The heightened risk of MI with recent abacavir exposure was accentuated in participants who had pre-existing cardiac risk factors.

A second study also suggested an increased risk of MI associated with abacavir use *[68]*. An analysis of 2,752 participants in the continuous treatment arm of the SMART study indicated that abacavir use was associated with an increased risk of MI when compared with other NRTI use (RR, 4.3; 95% CI, 1.4–13.0). Risk was concentrated in individuals with five or more known cardiovascular risk factors.

In contrast to these two studies that suggested an increased MI risk among abacavir users, Cutrell et al found no increased MI risk in a pooled analysis of 54 clinical trials, which involved 9,639 abacavir recipients, compared with 5,044 participants who received regimens without abacavir (RR, 0.9; 95% CI, 0.4–1.9) *[69]*.

Although conflicting data exist regarding abacavir-based regimens, the combination of abacavir/lamivudine is now considered to be an alternative, rather than a preferred, dual-NRTI option. Pending additional data, abacavir/lamivudine should be used with caution in individuals who have plasma HIV RNA levels >100,000 copies/mL, as well as in persons at higher risk for cardiovascular disease.

Didanosine + (Emtricitabine or Lamivudine) (BI). The FTC-301A trial tested didanosine + emtricitabine with efavirenz and demonstrated potent virologic suppression (78% of patients achieved HIV RNA <50 copies/mL at 48 weeks) *[70]*. The GESIDA 3903 study compared didanosine/lamivudine with zidovudine/lamivudine, and both were given with food and were combined with efavirenz *[71]*. At 48 weeks, virologic response for didanosine/lamivudine was noninferior to zidovudine/lamivudine, as 70% and 63% of the participants, respectively, achieved HIV RNA <50 copies/mL.

The ACTG 5175 trial compared three regimens in treatment-naïve patients. The Data Safety Monitoring Board for this trial recommended that participants be unblinded and switched to alternative therapy if they were randomized to a regimen that consisted of atazanavir + enteric-coated didanosine + emtricitabine because of an inferior virologic response when compared with the other two arms (once daily efavirenz plus either zidovudine/lamivudine twice daily, or tenofovir/emtricitabine once daily) *[49]*. Alternative PIs should be considered if didanosine + (emtricitabine or lamivudine) are used. Didanosine use also is associated with an increased risk for pancreatitis, peripheral neuropathy, and possibly other mitochondria-associated toxicities. In the D:A:D study of MI risk, the use of didanosine within the previous 6 months was associated with an increased risk of MI (RR, 1.5; 95% CI, 1.1–2.1), when compared with the use of other NRTIs *[67]*. This increase in cardiovascular risk was not seen in the SMART study *[68]*.

Zidovudine/Lamivudine (coformulated) (BI). The dual-NRTI combination of zidovudine/lamivudine has extensive durability, safety, and tolerability experience. *[3, 5, 6, 16, 72-74]*. A fixed-dose combination of zidovudine/lamivudine is available for one-tablet, twice-daily dosing. Selection of the lamivudine-associated M184V mutation has been associated with increased susceptibility to zidovudine. In a comparative trial of abacavir/lamivudine versus zidovudine/lamivudine (both given twice daily and combined with efavirenz), even though virologic responses were similar in both arms, the CD4 T-cell count increase was greater in the abacavir/lamivudine–treated patients than in the zidovudine/lamivudine–treated patients *[64]*.

Bone marrow suppression, manifested by macrocytic anemia and/or neutropenia, is seen in some patients. Zidovudine also is associated with gastrointestinal toxicity, fatigue, and possibly mitochondrial toxicity, including lactic acidosis/hepatic steatosis and lipoatrophy. In the 934 study, participants who took zidovudine had significantly less limb fat at 96 and 144 weeks than those who took tenofovir, and there was a significant loss of fat among zidovudine recipients between 48, 96, and 144 weeks *[55]*. In ACTG 5142, limb fat was lowest in patients treated with stavudine, but those treated with zidovudine had significantly less limb fat than those treated with tenofovir *[8]*. Primarily because of its greater toxicity compared with tenofovir/emtricitabine, zidovudine/lamivudine is now considered an alternative rather than a preferred dual-NRTI option **(BI)**.

However, zidovudine/lamivudine remains as the preferred option in pregnant women. This dual-NRTI has the most safety and efficacy data for both mother and newborn. For more detailed information regarding antiretroviral drug choices and related issues in pregnancy, see

"Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States," available at **http://aidsinfo.nih.gov**.

NRTIs and Hepatitis B. Three of the current NRTIs—emtricitabine, lamivudine, and tenofovir—have activity against HBV. Most coinfected patients should use coformulated tenofovir/emtricitabine (or tenofovir + lamivudine) as their nucleoside backbone to provide additional activity against HBV and to avoid lamivudine/emtricitabine resistance. It is important to note that patients who have HBV/HIV coinfection may be at risk of acute exacerbation of hepatitis after initiation or upon discontinuation of these drugs *[75-77]*. Thus, these patients should be monitored closely for clinical or chemical hepatitis if these drugs are initiated or discontinued. (See **Hepatitis B (HBV)/HIV Coinfection** and **When to Start** sections.)

ALL-NRTI REGIMENS

A triple-NRTI combination regimen has multiple potential advantages: fewer drug-drug interactions (e.g., none with rifampin), low pill burden, availability of a fixed-dose combination (e.g., zidovudine/lamivudine/abacavir), and the ability to spare patients from potential adverse effects seen with PIs and NNRTIs. However, several clinical trials that studied triple-NRTI regimens have shown suboptimal virologic activity *[16, 17, 78-81]*, and current PI- and NNRTI-based regimens have improved convenience and tolerability compared with older regimens.

Abacavir/Lamivudine/Zidovudine (coformulated). Abacavir/lamivudine/zidovudine is the only triple-NRTI combination for which randomized, controlled trials are available. Abacavir/lamivudine/zidovudine demonstrated comparable antiretroviral activity to indinavir-based *[72, 73]* and nelfinavir-based *[81]* but was inferior virologically to an efavirenz-based regimen *[16]*. This combination is **generally not recommended (BI)** and should be used only when a preferred or an alternative NNRTI-based or a PI-based regimen is less desirable because of concerns about toxicities, drug interactions, or regimen complexity.

Zidovudine/Lamivudine + Tenofovir. The DART study demonstrated that the combination of zidovudine/lamivudine + tenofovir has antiviral activity *[82]*; however, comparative data with standard regimens are not available and therefore **cannot be recommended** in routine clinical practice **(BIII)**.

A quadruple-NRTI regimen of zidovudine + lamivudine + abacavir + tenofovir showed comparable virologic responses to an efavirenz-based regimen in a small pilot study *[83]*, but definitive data are lacking. Thus, this regimen **cannot be recommended** at this time **(BII)**.

OTHER TREATMENT OPTIONS UNDER INVESTIGATION: INSUFFICIENT DATA TO RECOMMEND

Several novel treatment regimens that use agents approved for treatment-experienced patients are currently in Phase II or III clinical trials evaluating their safety and efficacy in treatment-naïve patients. Preliminary data from these trials are summarized below.

Raltegravir-Based Regimen. The integrase inhibitor raltegravir has been studied in a Phase II trial that initially involved monotherapy in 35 treatment-naïve participants and then expanded into a larger trial that compared different doses of raltegravir with efavirenz, both in combination with tenofovir and lamivudine *[84]*. At 48 weeks, no substantial differences were observed among any of the arms, and all raltegravir recipients who were not taking 400mg twice daily switched to that dose. At a 96-week analysis, similar numbers of patients achieved plasma HIV RNA <50 copies/mL with efavirenz-based regimens or with the combined raltegravir-based regimens (n = 198). CD4 T-cell increases were also comparable across arms. Adverse events were comparable except that headache, dizziness, and abnormal dreams occurred more frequently with efavirenz *[85]*. Phase III trials of raltegravir-based regimens in treatment-naïve participants are underway.

Maraviroc-Based Regimen. The MERIT study compared the CCR5 antagonist maraviroc with efavirenz, both in

combination with zidovudine/lamivudine, in a randomized, double-blind trial in treatment-naïve participants *[86]*. Only participants who had CCR5 virus and no evidence of resistance to any drugs used in the study were enrolled (n = 633). At 48 weeks, virologic suppression (defined as HIV RNA <400 copies/mL) was seen in 75.3% of maraviroc recipients and in 78.9% of efavirenz recipients, and HIV RNA <50 copies/mL was observed in 65.2% of maraviroc recipients and in 69.2% of efavirenz recipients. The HIV RNA <50 copies/mL results did not meet the criteria set by the investigators to demonstrate noninferiority for maraviroc in this study. CD4 counts increased by an average of 170 cells/mm^3 in the maraviroc arm and by an average of 143 cells/mm^3 in the efavirenz arm. Through 48 weeks, more participants discontinued maraviroc because of lack of efficacy (11.9% vs. 4.2%), whereas fewer participants discontinued maraviroc because of toxicity (4.2% vs. 13.6%).

Table 6. Antiretroviral Therapy for Treatment-Naïve Patients (Updated November 3, 2008)

Patients naïve to antiretroviral therapy should be started on a combination regimen that consists of either:

- **1-NNRTI + 2 NRTI or**
- **PI (preferably boosted with ritonavir) + 2NRTI**

Listed below are antiretroviral component options for constructing a regimen for a treatment-naïve patient. Selection of a regimen should be individualized based on virologic efficacy, toxicities, pill burden, dosing frequency, drug-drug interaction potential, and comorbid conditions. Components are designated as preferred when clinical trial data suggest optimal and durable efficacy with acceptable tolerability and ease of use. Alternative components are those that clinical trial data show efficacy but that have disadvantages, such as antiviral activity or toxicities, compared with the preferred agent. In some cases, for an individual patient, a component listed as alternative may actually be the preferred component. When there is more than one component for a preferred or alternative option, the components are listed in alphabetical order. For management of an HIV-infected pregnant patient, please refer to ***"Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States,"*** at **http://aidsinfo.nih.gov/guidelines/**.

NNRTI Options:

Recommendation	NNRTI	Population in which to avoid or use with caution
Preferred NNRTI	**Efavirenz (AI)**	Do not use during 1st trimester of pregnancy or in those with high pregnancy potential. Use with caution in patients with unstable psychiatric disease.
Alternative NNRTI	Nevirapine **(BI)**	Do not use in patients with moderate to severe hepatic impairment (Child-Pugh score B or C). Do not use in women with pre-ARV CD4 >250 cells/mm^3 or in men with pre-ARV CD4 >400 cells/ mm^3 Use with caution in patients on tenofovir/emtricitabine (or lamivudine)—early virologic failure has been reported with this combination **(CIII)**.

PI Options:

Recommendation	PI	Population in which to avoid or use with caution
Preferred PIs	**Atazanavir + ritonavir—once daily (AI)**	Do not use in patients who require high-dose (>20 mg omeprazole equivalent/day) proton pump inhibitors (PPIs). Use with caution in patients on PPIs (any dose), H2 blockers, or antacids.
	Darunavir + ritonavir—once daily (AI)	
	Fosamprenavir + ritonavir—twice daily (BI)	
	Lopinavir/ritonavir—once or twice daily (AI)	Do not use once-daily lopinavir/ritonavir in pregnant women.
Alternative PIs	Atazanavir (unboosted)—once daily **(BI)**	Do not use in combination with tenofovir or didanosine/lamivudine.
	Fosamprenavir + ritonavir—once daily— or fosamprenavir (unboosted)—twice daily **(BI)**	
	Saquinavir + ritonavir (twice daily) **(BI)**	

Dual-NRTI Options:

Recommendation	2-NRTI	Population in which to avoid or use with caution
Preferred Dual NRTI	**Tenofovir + emtricitabine (AI)**	Do not use in combination with unboosted atazanavir. Use with caution: • with nevirapine due to reports of early virologic failure • in patients with underlying renal insufficiency
Alternative Dual NRTI	Abacavir + lamivudine **(BI)**	Do not use in patients who test positive for HLA-B*5701. Use with caution in the presence of the following: • HIV RNA >100,000 copies/mL—higher rate of virologic failure reported in ACTG 5202; or • High risk for cardiovascular disease.
	Didanosine + lamivudine (or emtricitabine) **(BI)**	Do not use in combination with unboosted atazanavir. Do not use in patients with a history of pancreatitis or peripheral neuropathy.
	Zidovudine + lamivudine **(BI)**	Use with caution in the presence of pretreatment anemia and/or neutropenia (may improve or worsen with zidovudine).

Table 7. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (Updated November 3, 2008)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
NNRTI (in alphabetical order)		**NNRTI Class Advantages:** • Save PIs for future use • Long half-lives	**NNRTI Class Disadvantages:** • Low genetic barrier to resistance (single mutation confers resistance for efavirenz, nevirapine, and delavirdine): greater risk for resistance with failure or treatment interruption • Potential for cross resistance • Skin rash • Potential for CYP450 drug interactions (See **Tables 14, 15b, and 16**) • Transmitted resistance to NNRTIs more common than resistance to PI
	Efavirenz (EFV)	• Virologic responses equivalent or superior to all comparators to date • Lowest pill burden; once-daily dosing • Fixed-dose combination with tenofovir + emtricitabine	• Neuropsychiatric side effects • Teratogenic in nonhuman primates, and several cases of neural tube defect reported in infants of women with first trimester exposure. EFV is contraindicated in first trimester of pregnancy; avoid use in women with pregnancy potential
	Nevirapine (NVP)	• No food effect • Less lipid effects than EFV	• Higher incidence of rash than with other NNRTIs, including rare but serious hypersensitivity reactions (Stevens-Johnson syndrome or toxic epidermal necrolysis) • Higher incidence of hepatotoxicity than with other NNRTIs, including serious and even fatal cases of hepatic necrosis • Contraindicated in patients with moderate or severe (Child Pugh B or C) hepatic impairment • Treatment-naïve patients with high pre-NVP CD4 counts (>250 cells/mm^3 females, >400 cells/mm^3 males) are at higher risk for symptomatic hepatic events. NVP not recommended in these patients unless benefit clearly outweighs risk • Early virologic failure of NVP + TDF + (FTC or 3TC) in small clinical trials • Less clinical trial data than with EFV
PI (in alphabetical order)		**PI Class Advantage:** • Save NNRTIs for future use • Higher genetic barrier to resistance • PI resistance uncommon with failure (boosted PIs)	**PI Class Disadvantages:** • Metabolic complications (e.g., dyslipidemia, insulin resistance, hepatotoxicity) • Gastrointestinal adverse effects • CYP3A4 inhibitors & substrates: potential for drug interactions (more pronounced w/ RTV-based regimens) (See **Tables 14–15a**)
	Atazanavir (unboosted) (ATV)	• Less adverse effect on lipids than other PI • Once-daily dosing • Low pill burden (two pills per day) • Good GI tolerability	• Indirect hyperbilirubinemia sometimes leading to jaundice or scleral icterus • PR interval prolongation: generally inconsequential unless combined with another drug with similar effect • Cannot be co-administered with tenofovir, efavirenz, or nevirapine (see ATV/r) • Nephrolithiasis • Skin rash • Food requirement • Absorption depends on food and low gastric pH (see **Table 15a** for detailed information regarding interactions with H2 antagonists, antacids, and PPI) • Preliminary data showed inferior virologic responses of ATV/ddI/FTC when compared to EFV/ZDV/3TC or EFV/TDF/FTC—combination of ATV/ddI/FTC should be avoided
	Atazanavir/ ritonavir (ATV/r)	• RTV-boosting: higher trough ATV concentration and greater antiviral effect • Once-daily dosing • Low pill burden (two pills per day)	• More adverse effects on lipids than unboosted ATV • More hyperbilirubinemia and jaundice than unboosted ATV • Food requirement • Absorption depends on food and low gastric pH (see **Table 15a** for interactions with H2 antagonists, antacids, and proton pump inhibitors) • RTV boosting required with TDF and EFV. - with EFV, use ATV 400 mg and RTV 100 mg once daily (PI-naïve patients only) • Should not be coadministered with NVP
	Darunavir/ ritonavir (DRV/r)	• Once-daily dosing	• Skin rash • Food requirement
	Fosamprenavir (unboosted) (FPV)	• No food effect	• Skin rash

Table 7. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (Updated November 3, 2008)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
PI (in alphabetical order)	**Fosamprenavir/ ritonavir (FPV/r)**	• Twice-daily dosing resulted in efficacy comparable to LPV/r • RTV-boosting: higher trough amprenavir concentration and greater antiviral effect • Once-daily dosing possible with RTV 100mg or 200mg daily • No food effect	• Skin rash • Hyperlipidemia • Once-daily dosing results in lower amprenavir concentrations than twice-daily dosing • Virologic failure with presence of amprenavir-resistant mutations may lead to suboptimal response to darunavir as salvage PI
	Lopinavir/ ritonavir (LPV/r)	• Coformulated • Once or twice-daily dosing in treatment-naïve patients • No food restriction • Recommended PI in pregnant women (twice daily only) • Greater CD4 T-cell count increase than with EFV-based regimens (ACTG 5142 and Mexican study	• Lower drug exposure in pregnant women – may need dose increase in third trimester; • Once-daily dosing not recommended in pregnant women • Once-daily dosing: lower trough concentration than twice-daily dosing
	Saquinavir + ritonavir (SQV/r)	• Efficacy similar to LPV/r with less hyperlipidemia • Alternative PI in pregnant women	• Highest pill burden among available PI regimens (6/day) • Food requirement
Dual NRTIs		**Dual NRTI Class Advantage:** Established backbone of combination antiretroviral therapy	**Dual NRTI Class Disadvantage:** Rare but serious cases of lactic acidosis with hepatic steatosis reported (d4T>ddI=ZDV>TDF=ABC=3TC=FTC)
Dual-NRTI pairs (in alphabetical order)	**Abacavir + lamivudine (ABC/3TC)**	• Non-inferior to ZDV+ 3TC with regard to virologic responses with better CD4 T-cell count response than with ZDV/3TC • Once-daily dosing • Coformulation • No food effect • No cumulative TAM-mediated resistance	• Potential for abacavir hypersensitivity reaction (HSR) in patients with HLA-B*5701 • Potential for increased cardiovascular events, especially in patients with cardiovascular risk factors • Inferior virologic responses when compared with TDF/FTC in patients with baseline HIV RNA >100,000 copies/mL in ACTG 5202 study
	Didanosine + lamivudine (ddI + 3TC) ***or*** **Didanosine + emtricitabine (ddI + FTC)**	• Once-daily dosing • No cumulative TAM-mediated resistance	• Peripheral neuropathy, pancreatitis • Food effect: must be taken on an empty stomach • Requires dosing separation from some PIs • Increase in toxicities when used with ribavirin, tenofovir, stavudine, or hydroxyurea • Preliminary data showed inferior virologic responses of ATV/ddI/FTC when compared with EFV/ZDV/3TC or EFV/TDF/FTC—combination of ATV/ddI/FTC should be avoided
	Tenofovir/ emtricitabine (or lamivudine) (TDF/FTC or TDF + 3TC)	• Better virologic responses than ZDV/3TC • Better virologic responses when compared with ABC/3TC in pts w/ baseline HIV RNA >100,000 copies/mL in ACTG 5202 study • Once-daily dosing • No food effect • Coformulated (TDF/FTC) and (EFV/TDF/FTC) • No cumulative TAM-mediated resistance	• Potential for renal impairment • Early virologic failure of NVP + TDF + (FTC or 3TC) in small clinical trials • Potential for decrease in bone mineral density
	Zidovudine/ lamivudine (ZDV/3TC)	• Coformulated (ZDV/3TC and ZDV/3TC/ABC) • No food effect (though better tolerated with food) • Preferred 2-NRTI in pregnant women	• Bone marrow suppression, especially anemia, with ZDV • Gastrointestinal intolerance • Mitochondrial toxicity, including lipoatrophy, lactic acidosis, hepatic steatosis • Inferior to TDF/FTC in combination with EFV • Diminished CD4 T-cell responses compared with ABC/3TC

Table 8. Antiretroviral Components Not Recommended as Initial Therapy
(Updated November 3, 2008)

Antiretroviral drugs or components (in alphabetical order)	**Reasons for not recommending as initial therapy**
Abacavir/lamivudine/zidovudine (coformulated) as triple-NRTI combination regimen **(BI)**	• Inferior virologic efficacy
Abacavir + didanosine **(BIII)**	• Insufficient data in treatment-naïve patients
Abacavir + tenofovir **(BIII)**	• Insufficient data in treatment-naïve patients
Darunavir (unboosted)	• Usage without ritonavir has not been studied
Delavirdine **(BII)**	• Inferior virologic efficacy • Inconvenient (three times daily) dosing
Didanosine + tenofovir **(BII)**	• High rate of early virologic failure • Rapid selection of resistance mutations • Potential for immunologic nonresponse/CD4 decline
Enfuvirtide **(BIII)**	• No clinical trial experience in treatment-naïve patients • Requires twice-daily subcutaneous injections
Etravirine **(BIII)**	• Insufficient data in treatment-naïve patients
Indinavir (unboosted) **(BIII)**	• Inconvenient dosing (three times daily with meal restrictions) • Fluid requirement
Indinavir (ritonavir-boosted) **(BIII)**	• High incidence of nephrolithiasis
Maraviroc **(BIII)**	• Insufficient data in treatment-naïve patients
Nelfinavir **(BI)**	• Inferior virologic efficacy
Raltegravir **(BIII)**	• Insufficient data in treatment-naïve patients
Ritonavir as sole PI **(BIII)**	• High pill burden • Gastrointestinal intolerance
Saquinavir (unboosted) **(BI)**	• Inferior virologic efficacy
Stavudine + lamivudine **(BI)**	• Significant toxicities including lipoatrophy, peripheral neuropathy, and hyperlactatemia, including symptomatic and life-threatening lactic acidosis, hepatic steatosis, and pancreatitis
Tipranavir (ritonavir-boosted) **(BI)**	• Inferior virologic efficacy

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What Not to Use (Table 9) (Updated November 3, 2008)

Some antiretroviral regimens or components are not generally recommended because of suboptimal antiviral potency, unacceptable toxicities, or pharmacologic concerns. These are summarized below.

ANTIRETROVIRAL REGIMENS NOT RECOMMENDED

Monotherapy with NRTI. Single-NRTI therapy does not demonstrate potent and sustained antiviral activity and **should not be used (AII)**. For prevention of mother-to-child transmission, zidovudine monotherapy might be considered in certain unusual circumstances in women with HIV RNA < 1,000 copies/mL. Even though the use of a potent combination regimen is generally recommended. See ***"Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States,"*** available at **http://aidsinfo.nih.gov**.

Single-drug treatment regimens with a ritonavir-boosted PI, either lopinavir *[1]* or atazanavir *[2]*, are under investigation with mixed results, and **cannot be recommended** outside of a clinical trial at this time.

Dual-nucleoside regimens. These regimens **are not recommended**, because they have not demonstrated potent and sustained antiviral activity compared with triple-drug combination regimens **(AI)** *[3]*.

Triple-NRTI regimens. Except for abacavir/lamivudine/zidovudine and possibly zidovudine/lamivudine + tenofovir, triple-NRTI regimens **should NOT be used routinely** because of suboptimal virologic activity *[4-6]* or lack of data **(AI)**.

ANTIRETROVIRAL COMPONENTS NOT RECOMMENDED

Atazanavir + indinavir. Both of these PIs can cause grade 3 to 4 hyperbilirubinemia and jaundice. Additive or worsened adverse effects may be possible when these agents are used concomitantly. Therefore, these two PIs **are not recommended** to be used in combination **(AIII)**.

Didanosine + stavudine. The combined use of didanosine and stavudine as a dual-NRTI backbone can result in a high incidence of toxicities, particularly peripheral neuropathy, pancreatitis, and lactic acidosis *[7-10]*. This combination has been implicated in several deaths of HIV-infected pregnant women secondary to severe lactic acidosis with or without hepatic steatosis and pancreatitis *[11]*; thus, it **is not recommended for use (AII)**.

Two-NNRTI combination. In the 2NN trial, treatment-naïve participants were randomized to receive once- or twice-daily nevirapine versus efavirenz versus efavirenz plus nevirapine, all combined with stavudine and lamivudine *[12]*. A higher frequency of clinical adverse events that led to treatment discontinuation was reported in participants randomized to the two-NNRTI arm. Both efavirenz and nevirapine may induce metabolism of etravirine, which leads to reduction in etravirine drug exposure *[13]*. Based on these findings, the Panel **does not recommend using two NNRTIs in combination in any regimen (AI)**.

Efavirenz in first trimester of pregnancy and in women with significant childbearing potential. Efavirenz use was associated with significant teratogenic effects in primates at drug exposures similar to those representing human exposure. Several cases of congenital anomalies have been reported after early human gestational exposure to efavirenz *[14, 15]*. Efavirenz **should be avoided** in pregnancy, particularly during the first trimester, and in women of childbearing potential who are trying to conceive or who are not using effective and consistent contraception **(AIII)**. If no other antiretroviral options are available for the woman who is pregnant or at risk of becoming pregnant, consultation should be obtained with a clinician who has expertise in both HIV infection and pregnancy. See ***"Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States,"*** available at **http://aidsinfo.nih.gov**.

Emtricitabine + lamivudine. Both of these drugs have similar resistance profiles and have minimal additive antiviral activity. Inhibition of intracellular phosphorylation may occur *in vivo* as seen with other dual–cytidine analog combinations *[16]*. These two agents **should not be used** as a dual-NRTI combination **(AIII)**.

Etravirine + Unboosted PI. Etravirine may induce the metabolism and significantly reduce the drug-exposure of these PIs. Appropriate doses of the PIs have not been established *[13]* **(AII)**.

Etravirine + ritonavir-boosted atazanavir, fosamprenavir, or tipranavir. Etravirine may alter the concentrations of these PIs. Appropriate doses of the PIs have not been established *[13]* **(AII)**.

Nevirapine initiated in treatment-naïve women with CD4 counts >250 cells/mm^3 or in treatment-naïve men with CD4 counts >400 cells/mm^3. Greater risk of symptomatic, including serious and life-threatening, hepatic events have been observed in these patient groups. Nevirapine **should not be initiated** in these patients **(BI)** unless the benefit clearly outweighs the risk *[17-19]*.

Unboosted darunavir, saquinavir, or tipranavir. The virologic benefit of these PIs has been demonstrated only when they were used with concomitant ritonavir. Therefore, use of these agents as part of a combination regimen **without ritonavir is not recommended (AII)**.

Stavudine + zidovudine. These two NRTIs **should not be used** in combination because of the demonstration of antagonism *in vitro [20]* and *in vivo [21]* **(AII)**.

Table 9. Antiretroviral Regimens or Components That Should Not Be Offered At Any Time
(Updated January 29, 2008)

	Rationale	Exception
Antiretroviral Regimens Not Recommended		
Monotherapy with NRTI (AII)	• Rapid development of resistance • Inferior antiretroviral activity when compared with combination of three or more antiretrovirals	• No exception (see footnote below regarding the pregnant patient)
Dual-NRTI regimens (AI)	• Rapid development of resistance • Inferior antiretroviral activity when compared with combination of three or more antiretrovirals	• No exception (see footnotes below regarding the pregnant patient and postexposure prophylaxis)
Triple-NRTI regimens (AIII) except for abacavir/zidovudine/lamivudine (BI) or possibly tenofovir + zidovudine/lamivudine (BII)	• High rate of early virologic nonresponse seen when triple-NRTI combinations, including ABC/TDF/3TC or TDF/ddI/3TC, were used as initial regimen in treatment-naïve patients • Other triple-NRTI regimens have not been evaluated	• Abacavir/zidovudine/lamivudine **(BII)**; and possibly tenofovir + zidovudine/lamivudine **(BII)** in selected patients in whom other combinations are not desirable
Antiretroviral Components Not Recommended as Part of an Antiretroviral Regimen		
Atazanavir + indinavir (AIII)	• Potential additive hyperbilirubinemia	• No exception
Didanosine + stavudine (AIII)	• High incidence of toxicities: peripheral neuropathy, pancreatitis, and hyperlactatemia • Reports of serious, even fatal, cases of lactic acidosis with hepatic steatosis with or without pancreatitis in pregnant women	• When no other antiretroviral options are available and potential benefits outweigh the risks **(BIII)**
2-NNRTI combination (AII)	• When EFV combined with NVP, higher incidence of clinical adverse events seen when compared to either EFV- or NVP-based regimen • Both EFV and NVP may induce metabolism and may lead to reductions in etravirine (ETV) exposure; thus, they should not be used in combination	• No exception
Efavirenz in first trimester of pregnancy or in women with significant child-bearing potential (AIII)	• Teratogenic in nonhuman primates	• When no other antiretroviral options are available and potential benefits outweigh the risks **(BIII)** (see footnote below regarding the pregnant patient)
Emtricitabine + lamivudine (AIII)	• Similar resistance profile • No potential benefit	• No exception
Etravirine + Unboosted PI (AII)	• Etravirine may induce metabolism of these PIs, appropriate doses not yet established.	• No exception
Etravirine + ritonavir-boosted atazanavir, fosamprenavir, or tipranavir (AII)	• Etravirine may induce metabolism of these PIs, appropriate doses not yet established.	• No exception
Nevirapine in treament-naïve women with CD4 >250 or men with CD4 >400 (BI)	• High incidence of symptomatic hepatotoxicity	• If no other antiretroviral option available, if used patients should be closely monitored
Stavudine + zidovudine (AII)	• Antagonistic effect on HIV-1	• No exception
Unboosted darunavir, saquinavir, or tipranavir (AII)	• Inadequate bioavailability	• No exception

When constructing an antiretroviral regimen for an HIV-infected pregnant woman, please consult ***"Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States"*** at **http://www.aidsinfo.nih.gov/guidelines.**

When considering an antiretroviral regimen to use in post-exposure prophylaxis, please consult *"Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis"* in ***CDC MMWR Recommendations and*** *Reports*. September 30, 2005/54 (RR 09); 1–17 and *"Management of Possible Sexual, Injection-Drug-Use, or Other Non-occupational Exposure to HIV, Including Considerations Related to Antiretroviral Therapy"* in ***CDC MMWR Recommendations and*** *Reports*. January 21, 2005/54 (RR 02); 1–19.

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Management of the Treatment-Experienced Patient

Panel's Recommendations:

- ***In treatment-experienced patients with suppressed viremia, assess adherence frequently and simplify the regimen as much as possible. Change individual antiretroviral drugs to reduce or manage toxicity, as needed.***
- ***Evaluation of antiretroviral treatment failure in a patient should include an assessment of the severity of HIV disease of the patient; the antiretroviral treatment history, including the duration, drugs used, antiretroviral potency, adherence history, and drug intolerance/toxicity; HIV RNA and CD4 T-cell count trends over time; and the results of prior drug resistance testing.***
- ***Virologic failure on treatment can be defined as a confirmed HIV RNA level >400 copies/mL after 24 weeks, >50 copies/mL after 48 weeks, or a repeated detectable HIV RNA level after prior suppression of viremia.***
- ***Drug resistance testing should be obtained while the patient is taking the failing antiretroviral regimen (or within 4 weeks of treatment discontinuation) (AI).***
- ***The goal of treatment for patients with prior drug exposure and drug resistance is to re-establish maximal virologic suppression, HIV RNA <50 copies/mL (AI).***
- ***Use the treatment history and the past and current resistance test results to identify fully active agents to design a new regimen (AII). A fully active agent is one that is likely to have antiretroviral activity on the basis of both the treatment history and susceptibility on drug resistance testing. Adding at least 2 (preferably 3) fully active agents to an optimized background antiretroviral regimen can provide significant antiretroviral activity (BII).***
- ***Immunologic failure can be defined as a failure to achieve and maintain an adequate CD4 response despite virologic suppression.***
- ***For immunologic failure, current medications, untreated coinfection, and serious medical conditions should be assessed.***
- ***There is no consensus for when and how to treat immunologic failure.***
- ***Assessing and managing a patient who has antiretroviral experience, who exhibits drug resistance, and who is experiencing treatment failure is complex and expert advice is critical.***

THE TREATMENT-EXPERIENCED PATIENT (Updated December 1, 2007)

Most patients benefit from antiretroviral therapy regimens. In clinical trials of effective combination regimens, a majority of study participants maintained virologic suppression for 3–7 years *[1-4]*.

In a patient on antiretroviral therapy with virologic suppression, adherence to antiretroviral drugs should be assessed on an ongoing basis (See **Adherence** section.) In such patients, antiretroviral regimens should be simplified as much as possible to ensure maximal adherence (See **Regimen Simplification** section). The use of newer formulations or coformulations of antiretroviral drugs will reduce dosing frequency and pill counts. Changing antiretroviral drugs to reduce or manage toxicity also is reasonable.

Antiretroviral treatment failure is not uncommon, and it increases the risk for HIV disease progression; therefore, it should be addressed aggressively.

MANAGEMENT OF PATIENTS WITH ANTIRETROVIRAL TREATMENT FAILURE
(Updated December 1, 2007)

Definitions and Causes of Antiretroviral Treatment Failure

Antiretroviral treatment failure can be defined as a suboptimal response to therapy. Treatment failure is often associated with virologic failure, immunologic failure, and/or clinical progression. Many factors are associated with an increased risk of treatment failure, including:

- Baseline patient factors, such as:
  - earlier calendar year of starting therapy, in which less potent regimens or less well-tolerated antiretroviral drugs were used,
  - higher pretreatment or baseline HIV RNA level (depending on the specific regimen used),
  - lower pretreatment or nadir CD4 T-cell count,
  - prior AIDS diagnosis,
  - comorbidities (e.g., depression, active substance use),
  - presence of drug-resistant virus, and
  - prior treatment failure, with development of drug resistance or cross resistance;
- incomplete medication adherence and missed clinic appointments;
- drug side effects and toxicity;
- suboptimal pharmacokinetics (variable absorption, metabolism, and/or penetration into reservoirs, food/fasting requirements, adverse drug-drug interactions with concomitant medications);
- suboptimal potency of the antiretroviral regimen; and/or
- other, unknown reasons.

Data from some patient cohorts suggest that suboptimal adherence and toxicity accounted for 28%–40% of treatment failure and regimen discontinuations *[5, 6]*. Multiple reasons for treatment failure can occur in one patient. Some factors that have not been associated with treatment failure include gender, pregnancy, and history of past substance use.

Assessment of Antiretroviral Treatment Failure and Changing Therapy

In general, the cause of treatment failure should be explored by:

- Reviewing the medical history, including:
  - change in HIV RNA and CD4 T-cell count over time;
  - occurrence of HIV-related clinical events;
  - antiretroviral treatment history;
  - results of prior resistance testing (if any);
  - medication-taking behavior, including adherence to recommended drug doses, dosing frequency, and food/fasting requirements;
  - tolerability of the medications;
  - concomitant medications (with consideration of adverse drug-drug interactions); and
  - comorbidities (including substance use) and
- Performing a physical examination to assess for signs of clinical progression.

In many cases the cause(s) of treatment failure will be readily apparent. In some cases, no obvious cause may be identified.

Initial Assessment of Treatment Failure. In conducting the assessment of treatment failure, it is important to distinguish among the reasons for treatment failure, because the approaches to subsequent therapy will differ. The following assessments should be undertaken initially:

- **Adherence.** Assess the patient's adherence to the regimen. For incomplete adherence, identify and address the underlying cause(s) of nonadherence (e.g., access to medications, depression, active substance use), and simplify the regimen if possible (e.g., decrease pill count or dosing frequency) **(AIII)**. (See **Adherence** section.)
- **Medication Intolerance.** Assess the patient's side effects. Address and review the likely duration of side effects (e.g., the limited duration of gastrointestinal symptoms with some regimens). Management strategies for intolerance may include:
  - using symptomatic treatment (e.g., antiemetics, antidiarrheals);
  - changing one drug to another within the same drug class, if needed (e.g., change to tenofovir or abacavir for zidovudine-related gastrointestinal symptoms or anemia; change to nevirapine for efavirenz-related central nervous system symptoms**) (AII)**;
  - changing drug classes (e.g., from an NNRTI to a PI, from an injectable drug to an oral agent), if necessary **(AII)**.
- **Pharmacokinetic Issues.** Review food/fasting requirements for each medication. Review recent history of gastrointestinal symptoms (such as vomiting or diarrhea) to assess the likelihood of short-term malabsorption. Review concomitant medications and dietary supplements for possible adverse drug-drug interactions, and make appropriate substitutions for antiretroviral agents and/or concomitant medications, if possible **(AIII)**. (See also **Exposure Response Relationship and Therapeutic Drug Monitoring**.)
- **Suspected Drug Resistance.** Obtain resistance testing while the patient is taking the failing regimen or within 4 weeks after regimen discontinuation **(AII)**. (See **Drug Resistance Testing**.)

Further Assessment of Treatment Failure. When adherence, tolerability, and pharmacokinetic causes of treatment failure have been considered and addressed, make further assessments for virologic failure, immunologic failure, and clinical progression.

Virologic suppression can be defined as a sustained reduction in HIV RNA level below the assay limit of detection (e.g., 50 copies/mL). Virologic failure is best understood in the context of virologic success; that is, virologic failure is defined as the inability to achieve or maintain suppression of viral replication to levels below the limit of detection (<50 copies/mL) and may manifest as any of the following:

- ***Incomplete virologic response***: Two consecutive HIV RNA >400 copies/mL after 24 weeks or >50 copies/mL by 48 weeks in a treatment-naïve patient who is initiating therapy. Baseline HIV RNA may affect the time course of response, and some patients will take longer than others to suppress HIV RNA levels. The timing, pattern, and/or slope of HIV RNA decrease may predict ultimate virologic response *[7]*. For example, most patients with an adequate virologic response at 24 weeks had at least a 1 $\log_{10}$ decrease in HIV RNA copies/mL at 1–4 weeks after starting therapy *[8-10]*.
- ***Virologic rebound***: After virologic suppression, repeated detection of HIV RNA above the assay limit of detection (e.g., 50 copies/mL).

Assessment of Virologic Failure. There is no consensus on the optimal time to change therapy for virologic failure. The most aggressive approach would be to change for any repeated, detectable viremia (e.g., two consecutive HIV RNA >50 copies/mL after suppression to <50 copies/mL in a patient taking the regimen). Other approaches allow detectable viremia up to an arbitrary level (e.g., 1,000–5,000 copies/mL). However, ongoing viral replication in the presence of antiretroviral drugs promotes the selection of drug resistance mutations *[11]* and may limit future treatment options. Isolated episodes of viremia ("blips," e.g., single levels of 51–1,000 copies/mL) may simply represent laboratory variation *[12]* and usually are not associated with subsequent virologic failure, but rebound to higher viral load levels or more frequent episodes of viremia increase the risk of failure *[13, 14]*.

When assessing virologic failure, one should assess the degree of drug resistance and should take into account prior treatment history and prior resistance test results **(AII)**. Drug resistance tends to be cumulative for a given individual; thus, all prior treatment history and resistance test results should be taken into account.

Management of Virologic Failure.
General Approach. Ideally, one should design a regimen with at least two, and preferably three, fully active drugs on the basis of drug history, resistance testing, or new mechanistic class **(BII)** *[15-20]*. Some antiretroviral drugs (e.g.,

NRTIs) may contribute partial antiretroviral activity to an antiretroviral regimen, despite drug resistance. Because of the potential for drug-class cross resistance that reduces drug activity, using a "new" drug that a patient has not yet taken may not mean that the drug is fully active. Drug potency and viral susceptibility are more important than the number of drugs prescribed.

Several clinical trials illustrate effective therapeutic strategies for treatment-experienced patients *[17-21]*. In these studies, patients received an antiretroviral regimen optimized based on drug treatment history and resistance testing and then were randomized to receive a new active antiretroviral agent or placebo. Patients who received more active drugs (e.g., a ritonavir-boosted PI and a drug with activity against resistance viral strains with or without a new mechanism of action) had a better and more prolonged virologic response than those with fewer active drugs in the regimen. These studies illustrate and support the strategy of conducting resistance testing while a treatment-experienced patient is taking a failing regimen, designing a new regimen based on the treatment history and resistance testing results, and selecting active antiretroviral drugs for the new treatment regimen.

Early studies of treatment-experienced patients identified factors associated with better virologic responses to subsequent regimens *[22, 23]*.They included lower HIV RNA at the time of therapy change, using a new (i.e., not yet taken) class of drugs, and using ritonavir-boosted PIs in PI-experienced patients. More recent studies show that higher CD4 T-cell counts and higher genotypic and/or phenotypic susceptibility scores (indicating a greater number of active agents) are associated with better virologic responses *[19, 20]*.

In general, adding a single, fully active antiretroviral drug in a new regimen is not recommended because of the risk of development of rapid resistance **(BII)**. However, in patients with a high likelihood of clinical progression (e.g., CD4 T-cell count <100/mm^3) and limited drug options, adding a single drug may reduce the risk of immediate clinical progression, because even transient decreases in HIV RNA and or transient increases in CD4 T-cell counts have been associated with clinical benefits **(CI)** *[24]*. Weighing the risks (e.g., selection of drug resistance) and benefits (e.g., antiretroviral activity) of using a single active drug in the heavily treatment experienced patient is complicated, and consultation with an expert is advised.

Discontinuing or briefly interrupting therapy (even with ongoing viremia) may lead to a rapid increase in HIV RNA and a decrease in the CD4 T-cell count, and it increases the risk for clinical progression *[25, 26]*. Therefore, it is not recommended **(BIII)**.

Sequencing and Cross Resistance. The order of use of some antiretroviral agents may be important. Cross resistance among NRTIs is common but varies by drug. Most, if not all, mutations associated with efavirenz resistance cause cross resistance to nevirapine, and vice versa. Etravirine demonstrates activity against some NNRTI-resistant viruses both *in vitro* and in clinical trials *[27]*. The K103N substitution does not affect the activity of etravirine, while the presence of other NNRTI-associated resistance mutations (e.g., Y181C, G190A), particulary when there are three or more, are associated with decreased activity of etravirine. Novel early mutations to some PIs (e.g., unboosted fosamprenavir, atazanavir, nelfinavir, saquinavir) that do not confer cross resistance to other PIs may occur initially, but subsequent accumulation of additional mutations confers broad cross resistance to the entire PI class. Pharmacologic boosting of PIs with ritonavir markedly reduces the likelihood of PI resistance with failure in patients without pre-existing PI mutations.

Tipranavir and darunavir are the two newest PIs approved for patients who are highly treatment-experienced or have HIV-1 strains resistant to multiple PIs based on demonstrated activity against PI-resistant viruses *[19, 21]*. However, with ongoing viremia and the accumulation of additional mutations, antiretroviral activity is time limited unless the regimen contains other active drugs (e.g., enfuvirtide, a CCR5 inhibitor, or an integrase inhibitor).

Newer Agents.
Maraviroc, the first approved CCR5 inhibitor, is an antiretroviral drug that specifically binds to the CCR5 receptor of the CD4 T-cell, thereby inhibiting HIV strains that use this coreceptor for cellular entry. Phase III clinical studies enrolled triple-class, treatment-experienced patients who experienced failure on their current antiretroviral regimens with detectable viremia with only CCR5-tropic (R5) viral strains (documented using a tropism assay). In these studies, maraviroc resulted in significantly better virologic responses over 48 weeks compared with placebo when added to an antiretroviral regimen that was optimized based on treatment history and drug resistance testing *[28, 29]*. In another study, maraviroc did not demonstrate significant virologic activity in treatment-experienced patients with viremia with

only X4 virus, a dual/mixed population of X4 and R5 viruses, or an indeterminate tropism result, although CD4 increases were seen *[30]*. Maraviroc was generally safe and well tolerated, although theoretical concerns about the longer-term safety of CCR5 inhibitors require additional assessment. With a unique mechanism of action and documented short-term efficacy and safety, maraviroc should be considered a fully active antiretroviral agent in treatment-experienced patients who have only R5 virus and who are naïve to CCR5 inhibitors.

Raltegravir, the first approved HIV integrase inhibitor, specifically inhibits the final step in integration, strand transfer of viral DNA to host cell DNA. Phase III clinical studies enrolled triple-class, treatment-experienced patients who experienced failure on their current antiretroviral regimens with detectable viremia. In these studies, raltegravir resulted in significantly better virologic responses over 24 weeks compared with placebo when added to an antiretroviral regimen that was optimized based on treatment history and drug resistance testing *[20]*. Raltegravir was generally safe and well tolerated. With a unique mechanism of action and documented short-term efficacy and safety, raltegravir should be considered a fully active antiretroviral agent in treatment-experienced patients who are naïve to HIV integrase inhibitors.

Etravirine, an NNRTI, has activity *in vitro* against viral strains with mutations that confer resistance to efavirenz and nevirapine *[29]*. Phase III studies enrolled triple-class, treatment-experienced patients who had at least one NNRTI-associated drug resistance mutation and who had detectable viremia on their current antiretroviral regimen. All subjects also received darunavir/ritonavir as part of the optimzed background regimen. In these studies, subjects in the etravirine arm experienced significantly better virologic responses over 24 weeks compared with placebo *[31, 32]*. In a phase II clinical study, patients who had failed a regimen containing NRTIs and an NNRTI (and who had NNRTI resistance) were randomized to receive either etravirine or an investigator selected PI in combination with 2 NRTIs. A lower virologic response was seen in patients randomized to etravirine arm *[33]*. Based on these results, etravirine should not be used with 2-NRTIs without additional active agents, especially in patients with pre-treatment NNRTI resistance mutations. Etravirine is a substrate and inducer of CYP 3A4, as well as being a substrate and inhibitor of 2C9, and 2C19, with complex drug interaction potential. Based on pharmacokinetic studies, either etravirine or the coadministered antiretroviral's drug exposure may be significantly affected when used in combination. As a result, etravirine is not recommended to be used with any unboosted PI, ritonavir-boosted atazanavir, fosamprenavir, or tipranavir (See **Tables 14** and **16b**). With activity against some NNRTI-resistant viral strains, etravirine may provide increased virologic activity in treatment-experienced patients, depending on the amount of NNRTI-resistance.

Other investigational drugs with newer mechanisms of action demonstrate short-term antiretroviral activity in patients with resistance to reverse transcriptase inhibitors and PIs *[34-36]* and are also under investigation in clinical trials.

Clinical Scenarios in Management of Patients with Antiretroviral Treatment Failure

- ***Prior treatment with no resistance identified.*** Consider the timing of the drug resistance test (e.g., Was the patient off antiretroviral medications for >4 weeks?) and/or nonadherence. Consider resuming the same regimen or starting a new regimen and then repeating genotypic testing early (e.g., in 2–4 weeks) to determine whether a resistant viral strain emerges **(CIII)**. Consider intensifying with one drug (e.g., tenofovir) **(BII)** *[37]* or pharmacokinetic enhancement (ritonavir boosting for an unboosted PI, e.g. atazanavir, fosamprenavir) **(BII)** *[38]*.
- ***Prior treatment and drug resistance.*** The goals in this situation are to resuppress HIV RNA levels maximally (e.g., to <50 copies/mL) and to prevent further selection of resistance mutations. With virologic failure, consider changing the treatment regimen sooner, rather than later, to minimize continued selection of resistance mutations. Discontinuing an NNRTI in a patient with ongoing viremia and evidence of NNRTI resistance to decrease the risk of selecting additional NNRTI resistance mutations is particularly important, because newer NNRTIs with activity against some NNRTI-resistant strains are available. A new regimen should include at least two, and preferably three, fully active agents **(BII)**.
- ***Extensive prior treatment and drug resistance.*** The goal is to resuppress the HIV RNA levels maximally (e.g., to <50 copies/mL). With the availability of multiple new antiretroviral drugs, including some with new mechanisms of action, this goal is now possible in many patients, including those with extensive treatment experience and drug resistance. In some cases, however, viral suppression may be difficult to achieve. If maximal virologic suppression cannot be achieved, the goals are to preserve immunologic function and to prevent clinical progression (even with ongoing viremia). Even partial virologic suppression of HIV RNA >0.5 $\log_{10}$ copies/mL

from baseline correlates with clinical benefits *[24]*; however, this must be balanced with the ongoing risk for accumulating additional resistance mutations.

- ***New regimen that contains at least two fully active agents cannot be identified.*** It is reasonable to observe a patient on the same regimen, rather than changing the regimen, depending on the stage of HIV disease **(BII)**. There is evidence from cohort studies that continuing therapy, even in the presence of viremia and the absence of CD4 T-cell count increases, decreases the risk of disease progression *[39]*. Other cohort studies suggest continued immunologic and clinical benefits if the HIV RNA level is maintained <10,000–20,000 copies/mL *[40, 41]*.

Immunologic Failure can be defined as a failure to achieve and maintain an adequate CD4 T-cell response despite virologic suppression. There is no specific definition for immunologic failure, although some studies have focused on patients who fail to increase CD4 T-cell counts above a specific threshold (e.g. >350 or 500 cells/mm^3) over a specific period of time (e.g. 4–7 years). Others have focused on an inability to increase CD4 T-cell counts above pre-therapy levels by a certain threshold (e.g. >50 or 100 cells/mm^3) over a given time period. The former approach may be preferable because of recent data linking these thresholds with the risk of non-AIDS clinical events *[42]*.

The proportion of patients experiencing immunologic failure depends on how failure is defined, the observation period, and the CD4 T-cell count when treatment was started. In the longest study conducted to date, the percentage of patients with suppressed viremia who reached a CD4 T-cell count >500 cells/mm^3 through 6 years of treatment was 42% (starting treatment with a CD4 <200 cells/mm^3), 66% (starting with CD4 200–350 cells/mm^3), and 85% (starting with CD4 >350 cells/mm^3) *[43]*; increases in CD4 T-cell counts in treatment-naïve patients with initial antiretroviral regimens are approximately 150 cells/mm^3 over the first year *[44]*. A CD4 T-cell count plateau may occur after 4–6 years of treatment with suppressed viremia *[43, 45-48]*.

A persistently low CD4 T-cell count while on suppressive antiretroviral therapy is associated with a small, but appreciable, risk of AIDS- and non–AIDS-related morbidity and mortality *[49, 50]*. For example, in the FIRST study *[51]*, a low CD4 T-cell count on therapy was associated with an increased risk for AIDS-related complications (adjusted hazard ratio of 0.57 for CD4 T-cell count 100 cells/mm^3 higher). Similarly, a low CD4 T-cell count was associated with an increased risk for non-AIDS events, including cardiovascular, hepatic, renal, and cancer events. Other studies support these associations *[52-54]*.

Factors associated with immunologic failure:

- CD4 count <200/mm^3 when starting ART;
- Older age;
- Coinfection (e.g., HCV);
- Medications, both antiretrovirals (ZDV *[55]*, TDF + ddI *[56-58]*) and other medications;
- Persistent immune activation; and
- Loss of regenerative potential of the immune system.

Assessment of Immunologic Failure: CD4 T-cell count should be confirmed by repeat testing. Concomitant medications should be reviewed carefully, with a focus on those known to decrease white blood cells or, specifically, CD4 T-cells (e.g., interferon, cancer chemotherapy, prednisone, zidovudine, combination of tenofovir and didanosine). Untreated coinfections (e.g., HIV-2, HTLV-1, HTLV-2) and serious medical conditions (e.g., malignancy) also should be considered. In many cases, no obvious cause for immunologic failure can be identified.

Management of Immunologic Failure: There is no consensus on when or how to treat immunologic failure. Given the risk of clinical events, it is reasonable to focus on patients with CD4 T-cell counts <200/mm^3. Patients with higher CD4 T-cell counts have a low risk of clinical events. It is not clear that immunologic failure in the setting of virologic suppression should prompt a change in the antiretroviral drug regimen. Because ongoing viral replication occurs in some patients with suppressed HIV RNA levels, some have suggested adding a drug to an existing regimen. However, this strategy does not result in clear virologic or immunologic benefit *[59]*. Others suggest changing the regimen (e.g., to a more suppressive regimen or from an NNRTI-based regimen to a PI-based regimen, based on some evidence that suggests improved CD4 T-cell count responses); however, these strategies have not been formally tested.

Immune-based therapies, such as interleukin-2, demonstrated robust and sustained CD4 T-cell count increases in some studies *[60, 61]*. However, controversy persists as to how much enhancement of immune function occurs. With this

controversy, drug-associated side effects, and the need for parenteral administration, this strategy cannot be recommended unless with enrollment into a clinical trial **(BIII)**. Other immune-based therapies (e.g., growth hormone, cyclosporine, interleukin-7) are currently under investigation. Currently, immune-based therapies should not be used unless it is in the context of a clinical trial **(BIII)**.

Clinical Progression can be defined as the occurrence or recurrence of HIV-related events (after at least 3 months on an antiretroviral regimen), excluding immune reconstitution syndromes *[62, 63]*. In one study, clinical progression (a new AIDS event or death) occurred in 7% of treated patients with virologic suppression, 9% of treated patients with virologic rebound, and 20% of treated patients who never achieved virologic suppression in 2.5 years *[64]*.

Management of Clinical Progression. Consider the possibility of immune reconstitution syndrome *[62, 63]*, which typically occurs within the first 3 months after starting effective antiretroviral therapy and which may respond to anti-inflammatory treatment(s) rather than changing antiretroviral therapy. Clinical progression may not warrant a change in therapy in the setting of suppressed viremia and adequate immunologic response **(BIII)**.

Relationship Among Virologic Failure, Immunologic Failure, and Clinical Progression: Some patients demonstrate discordant responses in virologic, immunologic, and clinical parameters *[65]*. In addition, virologic failure, immunologic failure, and clinical progression have distinct time courses and may occur independently or simultaneously. In general, virologic failure occurs first, followed by immunologic failure, and finally by clinical progression. These events may be separated by months to years *[66]*.

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REGIMEN SIMPLIFICATION **(Updated November 3, 2008)**

Regimen simplification can be defined broadly as a change in established effective therapy to reduce pill burden and dosing frequency, to enhance tolerability, or to decrease specific food and fluid requirements. Many patients on suppressive antiretroviral therapy may be considered candidates for this strategy, especially if (1) they are receiving treatments that are no longer recommended as preferred or alternative choices for initial therapy, (2) if they were prescribed a regimen in the setting of treatment failure at a time when there was an incomplete understanding of resistance or drug-drug interaction data, or (3) if they were prescribed a regimen prior to the availability of newer options that might be easier to administer and/or more tolerable.

This section will review situations in which clinicians might consider simplifying treatment in a patient with virologic suppression. Importantly, this section will not be considering changes in treatment for reducing ongoing adverse effects. Regimens used in simplification strategies generally should be those that have proven high efficacy in treatment-naïve patients (See **What to Start** section.) or that would be predicted to be highly active for a given patient based on their past treatment history and resistance profile.

Rationale

The major rationales behind regimen simplification are to improve the patient's quality of life, improve medication adherence, avoid long-term toxicities, and reduce the risk of virologic failure. Systematic reviews in the non-HIV literature have shown that adherence is inversely related to the number of daily doses *[1]*. Some prospective studies in HIV-infected individuals have shown that those on regimens with reduced dosing frequency have higher levels of adherence *[2, 3]*. Patient satisfaction with regimens that contain fewer pills and reduced dosing frequency is also higher *[4]*.

Candidates for Regimen Simplification

Many antiretroviral medications that have been approved in the United States in recent years have a sufficiently long half-life to allow for once-daily dosing, and most also do not have dietary restrictions. Patients who receive regimens

initiated earlier in the era of potent combination antiretroviral therapy with drugs that involve a large pill burden and/or frequent dosing requirements are often good candidates for regimen simplification.

Patients without suspected drug-resistant virus. Patients on first (or modified) treatment regimens without a history of treatment failure are ideal candidates for regimen simplification. These patients are less likely to harbor drug-resistant virus, especially if a pretreatment genotype did not detect drug resistance. Prospective clinical studies have demonstrated that the likelihood of treatment failure after simplification is relatively low, and indeed may be lower than in those who do not simplify treatment *[5]*. However, some patients may have undetected drug-resistant HIV, either acquired at the time of infection or as a consequence of prior treatment, such as those who were treated with presumably non-suppressive mono- or dual-NRTI regimens before the widespread availability of HIV RNA monitoring and resistance testing.

Patients with documented or suspected drug resistance. Treatment simplification may also be appropriate for selected individuals whose virus is suppressed after having had documented or suspected drug resistance. Often, these patients are on regimens selected at a time when management of drug resistance, understanding of potentially adverse drug-drug interactions, and understanding of treatment options were relatively limited. Additional patients for whom to consider regimen simplification are those on two ritonavir-boosted protease inhibitors. Despite suppressive treatment, these patients may be on regimens that are cumbersome and associated with potential long-term adverse events. The ability to simplify regimens in this setting often reflects the availability of recently approved agents that have activity against drug-resistant virus and that are easier-to-take without sacrificing antiviral activity. Specific situations in which drug simplification could be considered in treatment-experienced patients with viral drug resistance are outlined below. Simplifying regimens in patients who have extensive prior treatment histories is complicated. In these cases, designing a new regimen should be done after a thorough review of treatment history, treatment responses, and resistance tests. Expert consultation should be considered whenever possible.

Types of Treatment Simplification

Within-Class Simplifications. Within-class substitutions offer the advantage of not exposing patients to still-unused drug classes, which potentially preserves other classes for future regimens. In general, within-class substitutions use a newer agent, coformulated drugs, or a formulation that has a lower pill burden, has a lower dosing frequency, or would be less likely to cause toxicity.

- ***NRTI Substitutions*** *(e.g., changing from zidovudine or stavudine to tenofovir or abacavir)**:*** For a patient who has no history of viral resistance on an NRTI-containing regimen can substitute for other NRTIs to create a regimen with lower dosing frequency (e.g., once-daily) that takes advantage of coformulated agents and potentially avoids some long-term toxicity (e.g., pancreatitis, peripheral neuropathy, lipoatrophy).
- ***Switching of NNRTIs*** *(e.g., from nevirapine to efavirenz)**:*** This may be considered to reduce dosing frequency or to take advantage of coformulated agents.
- ***Switching of PIs*** This switch can be from one PI to another PI or to the same PI at a lower dosing frequency or, in the case of atazanavir, to administration without ritonavir boosting. (Note: Unboosted atazanavir is presently not a preferred PI component. It is not recommended if the patient is taking tenofovir or if the patient has HIV with reduced susceptibility to atazanavir and it must be taken with caution when the patient requires acid-reducing agents.) Such changes can reduce dosing frequency, pill count, drug-drug or drug-food interactions, or dyslipidemia or can take advantage of coformulation. These switches can be done with relative ease in those patients without PI-resistant virus, but the switches are not recommended in patients who have a history of documented or suspected PI resistance, because of a lack of convincing data in that setting.

Out-of-Class Substitutions. The most common out-of-class substitutions for regimen simplification involve a change from a PI-based to an NNRTI-based regimen. One important study in this regard was the NEFA trial, which evaluated substitution of a PI-based regimen in virologically suppressed patients with nevirapine, efavirenz, or abacavir *[6]*. Although the baseline regimens in the study are no longer in widespread use, the NEFA findings are still relevant, and they provide information about the risks and benefits of switching treatment in patients with virologic suppression. In this study, 460 patients on stable, PI-based regimens with virologic suppression (<200 copies/mL for the previous 6 months) were switched to their randomized treatment arms. After 36 months of follow-up, virologic failure occurred more frequently in patients switched to abacavir than in those switched to efavirenz or nevirapine. The increased risk of

treatment failure was particularly high in those who had previous suboptimal treatment with mono- and dual-NRTI therapy. This emphasizes the need to consider the potential for drug-resistant virus prior to attempting simplification *[7]*.

Newer agents that target different sites in the HIV life cycle, such as raltegravir and maraviroc, also offer opportunities for out-of-class substitutions, particularly in those patients who have a history of virus resistant to older HIV drugs. However, results of substitution studies involving these agents are limited. In addition, it is not currently feasible to measure viral tropism in patients who are virologically suppressed; hence, the use of maraviroc in this context is not recommended. One situation in which substitution of novel agents has been increasingly described is for the use of newer agents to replace enfuvirtide. Because enfuvirtide requires twice-daily injections, may cause injection-site reactions, and is more expensive than other available antiretroviral agents, patients who are virologically suppressed on enfuvirtide-containing regimens may wish to substitute it with another active agent. In one report, 35 patients on enfuvirtide who substituted raltegravir for enfuvirtide maintained suppressed HIV RNA for a median of 7 months of follow-up. Only one patient had low-level viremia after the switch, which suggests that this strategy is likely safe and efficacious *[8]*. A recent report described four patients who experienced depression after substituting different antiretroviral drugs with raltegravir, which highlights that substitution of new drugs in a suppressive regimen may introduce unexpected adverse effects, even with treatments that are generally well tolerated *[9]*. There is also concern when novel combinations of antiretrovirals for which there are limited drug interaction data are used, as illustrated by a recent report of liver toxicity after raltegravir was substituted for enfuvirtide in three patients who received ritonavir-boosted tipranavir *[10]*. Although a similar substitution can be considered with etravirine or maraviroc, this strategy can be limited by the inability to assess etravirine resistance or viral tropism in virologically suppressed patients. In addition, there are no data currently available that evaluate that simplification strategy.

Reducing the number of active drugs in a regimen: This approach to treatment simplification involves switching a patient from a suppressive regimen to fewer active drugs. Early studies of this approach were associated with a higher risk of treatment failure than continuation of standard treatment with two NRTIs plus a PI *[11]*. More recently, studies have evaluated the use of a ritonavir-boosted PI as monotherapy after virologic suppression with a 2 NRTI + boosted-PI regimen *[12, 13]*. The major motivations for this approach are a reduction in NRTI-related toxicity and a lower cost. In the largest of these studies *[13]*, low-level viremia was more common in those on maintenance ritonavir-boosted lopinavir alone than on a three-drug combination regimen. Viral suppression was achieved by resuming the NRTIs. In aggregate, boosted-PI monotherapy as initial *[14]* or as simplification treatment have been somewhat less effective in achieving complete virologic suppression and avoiding resistance. Therefore, this strategy cannot be recommended currently.

Monitoring After Treatment Simplification

After treatment simplification, patients should be evaluated in 2–6 weeks to assess tolerance and to undergo laboratory monitoring, including HIV RNA, CD4 cell count, and markers of renal function and hepatotoxicity. Assessment of fasting cholesterol subsets and triglycerides should be performed within 3 months after the switch. In the absence of any specific complaints, laboratory abnormalities, or viral rebound at that visit, patients may resume regularly scheduled clinical and laboratory monitoring.

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EXPOSURE-RESPONSE RELATIONSHIP AND THERAPEUTIC DRUG MONITORING (TDM) FOR ANTIRETROVIRAL AGENTS (Updated November 3, 2008)

Panel's Recommendation:

- ***Therapeutic drug monitoring (TDM) for antiretroviral agents is not recommended for routine use in the management of the HIV-infected adult (CIII).***

Knowledge of the relationship between systemic exposure (or concentration) and drug responses (beneficial and/or adverse) is key to selection of a dose for a drug, to understanding the variability in the response of patients to a drug, and to design strategies to optimize response and tolerability.

Therapeutic drug monitoring (TDM) is a strategy applied to certain antiarrhythmics, anticonvulsants, antineoplastics, and antibiotics that utilizes drug concentrations to design regimens that are safe and that will achieve a desired therapeutic outcome. The key characteristic of a drug that is a candidate for TDM is knowledge of the exposure-response relationship and a therapeutic range of concentrations. The therapeutic range is a range of concentrations established through clinical investigations that are associated with a greater likelihood of achieving the desired therapeutic response and/or reducing the frequency of drug-associated adverse reactions.

Current antiretroviral agents meet most of the characteristics of agents that can be considered candidates for a TDM strategy *[1]*. The rationale for TDM in managing antiretroviral therapy arises because of the following:

- data showing that considerable interpatient variability in drug concentrations exists among patients who take the same dose;
- data indicating that relationships exist between the concentration of drug in the body and anti-HIV effect—and, in some cases, toxicities; and
- data from small prospective studies demonstrating that TDM improved virologic response and/or decreased the incidence of concentration-related drug toxicities *[2, 3]*.

However, TDM for antiretroviral agents is not recommended for routine use in the management of the HIV-infected adult (CIII).

There are multiple factors that limit the routine use of TDM in adults *[4, 5]*. They include the following:

- lack of large prospective studies demonstrating that TDM improves clinical and virologic outcomes. This is the most important limiting factor for the implementation of TDM at present;
- lack of established therapeutic range of concentrations associated with achieving the desired therapeutic response and/or reducing the frequency of drug-associated adverse reactions;
- intrapatient variability in antiretroviral drug concentrations; and
- lack of widespread availability of laboratories that perform quantitation of antiretroviral drug concentrations under rigorous quality assurance/quality control standards, and the shortage of experts to assist with interpretation of antiretroviral concentration data and application of such data to revise patients' dosing regimens.

TDM with Different Antiretroviral Classes

PIs and NNRTIs. Data that describe relationships between antiretroviral agents and treatment response have been reviewed in various publications *[4-7]*. Although there are limitations and unanswered questions, the consensus among U.S. and European clinical pharmacologists is that the data provide a framework for the potential implementation of TDM for PIs and NNRTIs. This is because exposure-response data exist for these agents. Information on relationships between concentrations and drug-associated toxicities are sparse. Clinicians who use TDM as a strategy to manage either antiretroviral response or toxicities should consult the most current data on the proposed therapeutic concentration range. Exposure-response data for darunavir and etravirine are accumulating but are not sufficient for a recommendation at this time.

CCR5 Antagonists. Trough maraviroc concentrations have been shown to be an important predictor of virologic success in studies conducted in treatment-experienced persons *[8, 9]*. Clinical experience in the use of TDM for maraviroc, however, is very limited. Nonetheless, as with PIs and NNRTIs, the exposure-response data provide a framework for TDM, and that information is presented in these guidelines (**Table 10**).

Integrase Inhibitors. Exposure-response data for raltegravir are accumulating but are not sufficient for a recommendation at this time.

NRTIs. Relationships between plasma concentrations of NRTIs and their intracellular pharmacologically active moieties have not yet been established. Therefore, monitoring of plasma or intracellular NRTI concentrations for an individual patient largely remains a research tool. Measurement of plasma concentrations, however, is routinely used for studies of drug-drug interactions.

Scenarios for Use of TDM. There are multiple scenarios in which both data and expert opinion indicate that information on the concentration of an antiretroviral agent may be useful in patient management. Consultation with a clinical pharmacologist may be advisable. These scenarios include the following:

- **with clinically significant drug-drug or drug-food interactions** that may result in reduced efficacy or increased dose-related toxicities;
- **with changes in pathophysiologic states** that may impair gastrointestinal, hepatic, or renal function, thereby potentially altering drug absorption, distribution, metabolism, or elimination;
- **in pregnant women,** who may be at risk for virologic failure as a result of changes in their pharmacokinetic parameters during the later stage of pregnancy, which may result in plasma concentrations lower than those achieved in the earlier stages of pregnancy and in the nonpregnant patient;
- **in treatment-experienced persons** who may have viral isolates with reduced susceptibility to antiretroviral agents;
- **with use of alternative dosing regimens** in which safety and efficacy have not been established in clinical trials;
- **with concentration-dependent, drug-associated toxicities**; and
- **with lack of expected virologic response** in medication-adherent persons.

TDM in different patient populations

- **Patients who have drug-susceptible virus**. **Table 10** presents a synthesis of recommendations *[2-7]* for minimum target trough PI and NNRTI concentrations in persons with drug-susceptible virus.

- **Treatment-experienced patients**. Fewer data are available to formulate suggestions for minimum target trough concentrations in treatment-experienced patients who have viral isolates with reduced susceptibility to these agents. Concentration recommendations for tipranavir and maraviroc were derived only from studies in treatment-experienced persons. It is likely that use of PIs and NNRTIs in the setting of reduced viral susceptibility may require higher trough concentrations than those needed for wild-type virus. The inhibitory quotient (IQ), which is the ratio of antiretroviral drug concentration to a measure of susceptibility (genotype or phenotype) of the patient's strain of HIV to that drug, may additionally improve prediction of virologic response—as has been shown, for example, with darunavir in treatment-experienced persons *[10]*.

Monitoring Drug Concentrations. There are several challenges and considerations for implementation of TDM in the clinical setting. Use of TDM to monitor drug concentrations in a patient requires multiple steps:

- quantification of the concentration of the drug, usually in plasma or serum;
- determination of the patient's pharmacokinetic characteristics;
- integration of information on patient adherence;
- interpretation of the concentrations; and
- adjustment of the drug dose to achieve concentrations within the therapeutic range, if necessary.

Guidelines for the collection of blood samples and other practical suggestions can be found in a position paper by the Adult AIDS Clinical Trials Group Pharmacology Committee *[4]*.

A final caveat to the use of measured drug concentrations in patient management is a general one—drug concentration information cannot be used alone; it must be integrated with other clinical and patient information. In addition, as knowledge of associations between antiretroviral concentrations and virologic response continues to accumulate, clinicians who employ a TDM strategy for patient management should consult the most current literature.

Table 10. Suggested Minimum Target Trough Concentrations *[2-9]*

(Updated November 3, 2008)

Drug	Concentration (ng/mL)
Fosamprenavir	400 (measured as amprenavir concentration)
Atazanavir	150
Indinavir	100
Lopinavir	1,000
Nelfinavir[a]	800
Saquinavir	100–250
Efavirenz	1,000
Nevirapine	3,000
Recommendations applicable only to treatment-experienced persons who have resistant HIV-1 strains	
Maraviroc	>50
Tipranavir	20,500

a. Measurable active (M8) metabolite.

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DISCONTINUATION OR INTERRUPTION OF ANTIRETROVIRAL THERAPY

(Updated November 3, 2008)

Discontinuation of antiretroviral therapy may result in viral rebound, immune decompensation, and clinical progression. Unplanned interruption of antiretroviral therapy may become necessary because of severe drug toxicity, intervening illness, surgery that precludes oral therapy, or antiretroviral medication nonavailability. Planned treatment discontinuations have been proposed by some in situations such as: in patients who achieve viral suppression aiming to enhance adherence; reduce inconvenience, long-term toxicities, and costs for patients; or in extensively-treated patients who experience treatment failure due to resistant HIV, to allow reversion to wild-type virus. Potential risks and benefits of interruption vary according to a number of factors, including the clinical and immunologic status of the patient, the reason for the interruption, the type and duration of the interruption, and the presence or absence of resistant HIV at the time of interruption. Below are brief discussions on what is currently known about the risks and benefits of treatment interruption in some of these circumstances.

Short-Term Therapy Interruptions

Reasons for short-term interruption (days to weeks) of antiretroviral therapy vary and may include drug toxicity; intercurrent illnesses that preclude oral intake, such as gastroenteritis or pancreatitis; surgical procedures; or nonavailability of drugs. Stopping antiretroviral drugs for a short time (i.e., <1 to 2 days) due to medical/surgical procedures can usually be done by holding all drugs in the regimen. Recommendations for some other scenarios are listed below:

Unanticipated Need for Short-Term Interruption:

- **When a patient experiences a severe or life-threatening toxicity or unexpected inability to take oral medications** – all components of the drug regimen should be stopped simultaneously, regardless of drug half-life.

Planned Short Term Interruption (>2–3 days):

- **When all regimen components have similar half-lives and do not require food for proper absorption** – all drugs may be given with a sip of water, if allowed; otherwise, should be stopped simultaneously or. All discontinued regimen components should be restarted simultaneously.
- **When all regimen components have similar half-lives and require food for adequate absorption, and the patient is required not to take anything by mouth for a sustained period of time** – temporary discontinuation of all drug components is indicated. The regimen should be restarted as soon as the patient can resume oral intake.
- **When the antiretroviral regimen contains drugs with differing half-lives –** stopping all drugs simultaneously may result in functional monotherapy with the drug with the longest half-life (typically an NNRTI). Options in this circumstance are discussed below. (See **Discontinuation of efavirenz, etravirine, or nevirapine**.)

Interruption of Therapy After Pregnancy

During pregnancy, HIV-infected pregnant women who otherwise do not meet current CD4 count or clinical criteria for starting treatment may initiate antiretroviral therapy primarily for the purpose of preventing mother-to-child HIV transmission. After delivery, these women may desire to stop therapy. Discontinuation recommendations are in the current guidelines for pregnant women *[1]* and in the **HIV-Infected Women** section.

Planned Long-Term Therapy Interruptions

Planned therapy interruptions have been contemplated in various scenarios, listed below. Research is ongoing in several of the scenarios. None of the therapy interruptions can be recommended at this time outside of controlled clinical trials **(AI)**.

- **In patients who initiated therapy during acute HIV infection and achieved virologic suppression**—the optimal duration of treatment and the consequences of treatment interruption are not known at this time. (See **Acute HIV Infection** section.)
- **In patients who have had exposure to multiple antiretroviral agents, have experienced antiretroviral treatment failure, and have few treatment options available because of extensive resistance mutations**—interruption is **not** recommended unless it is done in a clinical trial setting **(AI)**. Several clinical trials largely yielding negative results, but some with conflicting results have been conducted to better understand the role of treatment interruption in these patients *[2-5]*. The largest of these studies showed negative clinical impact of treatment interruption in these patients *[2]*. The Panel notes that partial virologic suppression from combination therapy has been associated with clinical benefit *[6]*; therefore, interruption of therapy is not recommended.
- **In patients on antiretroviral therapy who have maintained a CD4 count above the level currently recommended for treatment initiation and irrespective of whether their baseline CD4 count was either above or below that recommended threshold**—interruption is also **not recommended** unless it is done in a clinical trial setting **(BI)**. (See discussion below highlighting potential adverse outcomes seen in some treatment interruption trials.)

Temporary treatment interruption to reduce inconvenience, potential long-term toxicity, and/or overall treatment cost has been considered as a strategy for patients on antiretroviral therapy who have maintained CD4 counts above those currently recommended for initiating therapy. Several clinical trials have been designed to determine the safety of such interruptions, in which reinitiation is triggered by predetermined CD4 count thresholds. In these trials, various CD4 count levels have been set to guide both treatment interruption and reinitiation. Two separate, randomized clinical trials of CD4 count-guided treatment interruption have been reported. In the SMART study, the largest of such trials with over 5,000 subjects, interrupting treatment with CD4 counts >350 cells/mm^3 and reinitiating when <250 cells/mm^3 was associated with an increased risk of disease progression and death compared with the trial arm of continuous antiretroviral therapy *[7]*. In the TRIVACAN study, the same CD4 count thresholds were used for stopping and restarting treatment *[8]*. This study also showed that interruption was an inferior strategy; the interventions in both trials were stopped early because of these findings. Data from the DART trial reported a two-fold increase in rates of WHO stage 4 events/deaths in the 12-week ART cycling group among African patients achieving a CD4 count >300/mm^3 compared to the continuous ART group *[9]*. Observational data from the EuroSIDA cohort noted a 2-fold increase in risk of death after a treatment interruption of $\geq$3 months. Factors linked to increased risk of death or progression included lower CD4 counts, higher viral loads, and a prior history of AIDS *[10]*. Other studies have reported no major safety concerns *[11-13]*, but these studies had smaller sample sizes. Results have been reported from several small observational studies evaluating treatment interruption in patients doing

well with nadir CD4 counts >350/mm^3, but further studies are needed to determine the safety of treatment interruption in this population *[14, 15]*. There is concern that CD4 counts <500 cells/mm^3 are associated with a range of non-AIDS clinical events (e.g., cancer, heart, liver, and kidney disease) *[7, 16, 17]*.

Planned long-term therapy interruption strategies **cannot** be recommended at this time outside of controlled clinical trials **(BI)** based on available data and a range of ongoing concerns.

If therapy has to be discontinued, patients should be counseled about the need for close clinical and laboratory monitoring. They should also be aware of the risks of viral rebound, acute retroviral syndrome, increased risk for HIV transmission, decline of CD4 count, HIV disease progression or death, development of minor HIV-associated manifestations such as oral thrush, development of serious non-AIDS complications, development of drug resistance, and the need for chemoprophylaxis against opportunistic infections depending on the CD4 count. Treatment interruptions often result in rapid reductions in CD4 counts.

Prior to any planned treatment interruption, a number of antiretroviral-specific issues should be taken into consideration. These include:

- **Discontinuation of efavirenz, etravirine, or nevirapine.** The optimal interval between stopping efavirenz, etravirine, or nevirapine and other antiretroviral drugs is not known. The duration of detectable levels of efavirenz or nevirapine after discontinuation ranges from less than 1 week to more than 3 weeks *[18, 19]*. Simultaneously stopping all drugs in a regimen containing these agents may result in functional monotherapy with the NNRTIs, because their half-lives are much longer than other agents. This may increase the risk of selection of NNRTI-resistant mutations. It is further complicated by evidence that certain host genetic polymorphisms may result in slower rates of clearance. Such polymorphisms may be more common among specific ethnic groups, such as African Americans and Hispanics *[19, 20]*. Some experts recommend stopping the NNRTI but continuing the other antiretroviral drugs for a period of time. The optimal time sequence for staggered component discontinuation has not been determined. A study in South Africa demonstrated that giving four or seven days of zidovudine + lamivudine after a single dose of nevirapine reduced the risk of postnatal nevirapine resistance from 60% to 10%–12% *[21]*. Use of nucleosides with a longer half-life such as tenofovir plus emtricitabine has also been shown to decrease nevirapine resistance after single dose treatment *[22]*. The findings may however differ in patients on chronic nevirapine treatment. An alternative strategy is to substitute a PI for the NNRTI and to continue the PI with dual NRTIs for a period of time. In a post-study analysis of the patients who interrupted therapy in the SMART trial, patients who were switched from NNRTI to a PI based regimen prior to interruption had a lower rate of NNRTI-resistant mutation after interruption and a greater chance of re-suppression of HIV-RNA after restarting therapy than those who stopped all the drugs simultaneously or stopping the NNRTI before the 2-NRTI *[23]*. The optimal duration needed to continue the PI-based regimen after stopping the NNRTI is not known. Given the potential of prolonged detectable NNRTI concentrations for more than 3 weeks, some suggest that the PI-based regimen may need to be continued for up to 4 weeks. Further research to determine the best approach to discontinuing NNRTIs is needed. Clinical data on etravirine and treatment interruption is lacking but its long half-life of approximately 40 hours suggests that stopping etravirine needs to be done carefully using the same suggestions for nevirapine and efavirenz for the time being.
- **Discontinuation and reintroduction of nevirapine**. Because nevirapine is an inducer of the drug-metabolizing hepatic enzymes, administration of full therapeutic doses of nevirapine without a 2-week, low-dose escalation phase will result in excess plasma drug levels and potentially increase the risk for toxicity. Therefore, in a patient who has interrupted treatment with nevirapine for more than 2 weeks, nevirapine should be reintroduced with a dose escalation period of 200mg once daily for 14 days, then a 200mg twice-daily regimen **(AII)**.
- **Discontinuation of emtricitabine, lamivudine, or tenofovir in patients with hepatitis B coinfection**. Patients with hepatitis B coinfection (hepatitis B surface antigen or HBeAg positive) and receiving one or a combination of these NRTIs may experience an exacerbation of hepatitis upon drug discontinuation *[24, 25]*. (See **Hepatitis B (HBV)/HIV Coinfection** section.)

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Considerations for Antiretroviral Use in Special Patient Populations

ACUTE HIV INFECTION (Updated January 29, 2008)

Panel's Recommendations:

- ***Whether treatment of acute HIV infection results in long-term virologic, immunologic, or clinical benefit is unknown; treatment should be considered optional at this time (CIII).***
- ***Therapy should also be considered optional for patients in whom HIV seroconversion has occurred within the previous 6 months (CIII).***
- ***If the clinician and patient elect to treat acute HIV infection with antiretroviral therapy, treatment should be implemented with the goal of suppressing plasma HIV RNA to below detectable levels (AIII).***
- ***For patients with acute HIV infection in whom therapy is initiated, testing for plasma HIV RNA levels and CD4 count and toxicity monitoring should be performed as described for patients with established, chronic HIV infection (AII).***
- ***If the decision is made to initiate therapy in a person with acute HIV infection, genotypic resistance testing at baseline will likely optimize virologic response; this strategy is therefore recommended (AIII). If therapy is deferred, genotypic resistance testing should still be performed, because the result may be useful in optimizing the virologic response when therapy is ultimately initiated (AIII).***
- ***Since clinically significant resistance to PIs is less common than resistance to NNRTIs in treatment-naïve persons who harbor drug-resistant virus, consideration should be given to using a PI-based regimen if therapy is initiated before drug resistance test results are available (BIII).***

This section focuses on diagnosis and treatment of acute HIV-1 infection.

An estimated 40%–90% of patients acutely infected with HIV will experience symptoms of acute retroviral syndrome characterized by fever, lymphadenopathy, pharyngitis, skin rash, myalgias/arthralgias, and other symptoms *[1-6]*. However, acute HIV infection is often not recognized by primary care clinicians because of the similarity of the symptoms to those of influenza, infectious mononucleosis, or other illnesses. Additionally, acute infection can occur asymptomatically. **Table 11** provides guidance to practitioners on the recognition, diagnosis, and management of acute HIV infection.

Diagnosis of Acute HIV Infection

Health care providers should maintain a high level of suspicion of acute HIV infection in patients who have a compatible clinical syndrome and who report recent high-risk behavior *[7]*. However, in some settings, patients may not always disclose or admit to high risk behaviors, or might not perceive their behaviors as high-risk. Thus, symptoms and signs consistent with acute retroviral syndrome should motivate consideration of this diagnosis even in the absence of reported high risk behaviors.

When acute retroviral syndrome is suspected, a plasma HIV RNA test should be used in conjunction with an HIV antibody test to diagnose acute infection **(BII)**. Acute HIV infection is often defined by detectable HIV RNA in plasma in the setting of a negative or indeterminate HIV antibody test. A low-positive HIV RNA level (<10,000 copies/mL) may represent a false-positive test, since values in acute infection are generally very high (>100,000 copies/mL) *[5, 6]*. A qualitative HIV RNA test can also be used in this setting. Patients diagnosed with acute HIV infection on the basis of either a quantitative or a qualitative HIV RNA test should have confirmatory serologic testing performed at a subsequent time point **(AI)**. (**Table 11**)

Data from the United States and Europe demonstrate that transmitted virus may be resistant to at least one antiretroviral drug in 6%–16% of patients. If the decision is made to initiate therapy in a person with acute HIV infection, resistance testing at baseline will likely optimize virologic response; this strategy is therefore recommended **(AIII)**. (See **Drug Resistance Testing** section.) If therapy is deferred, resistance testing should still be performed because the result may be useful in optimizing the virologic response when therapy is ultimately initiated **(AIII)**.

Treatment for Acute HIV Infection

Clinical trials information regarding treatment of acute HIV infection is limited. Ongoing trials are addressing the question of the long-term benefit of potent treatment regimens initiated during acute infection. Potential benefits and risks of treating acute infection are as follows:

- **Potential Benefits of Treating Acute Infection.** Preliminary data indicate that treatment of acute HIV infection with combination antiretroviral therapy has a beneficial effect on laboratory markers of disease progression *[8-12]*.Theoretically, early intervention could decrease the severity of acute disease; alter the initial viral setpoint, which can affect disease-progression rates; reduce the rate of viral mutation as a result of suppression of viral replication; preserve immune function; and reduce the risk for viral transmission. Additionally, although data are limited and the clinical relevance is unclear, the profound loss of gastrointestinal lymphoid tissue that occurs during the first weeks of infection may be mitigated by the early initiation of antiretroviral therapy *[13, 14]*.
- **Potential Risks of Treating Acute HIV Infection.** The potential disadvantages of initiating therapy include exposure to antiretroviral therapy without a known clinical benefit, which could result in drug toxicities, development of antiretroviral drug resistance, the need for continuous therapy with strict adherence, and adverse effect on quality of life.

The above risk and benefit considerations are similar to those for initiating therapy in the chronically infected asymptomatic patient with high CD4 T-cell count. The health care provider and the patient should be fully aware that the rationale for therapy for acute HIV infection is based on theoretical considerations, and the potential benefits should be weighed against the potential risks. For these reasons, treatment of acute HIV infection should be considered optional at this time **(CIII)**. Providers should consider enrolling patients with acute HIV infection in a clinical trial to evaluate the natural history of acute HIV and to determine the role of antiretroviral therapy in this setting. Information regarding such trials can be obtained at **www.clinicaltrials.gov** or from local HIV treatment experts.

Treatment of Recent but Nonacute HIV Infection or Infection of Undetermined Duration

Besides patients with acute HIV infection, experienced clinicians also recommend consideration of therapy for patients in whom seroconversion has occurred within the previous 6 months **(CIII)**. Although the initial burst of viremia among infected adults usually resolves in 2 months, rationale for treatment during the 2- to 6-month period after infection is based on the probability that virus replication in lymphoid tissue is still not maximally contained by the immune system during this time *[15]*.

Treatment Regimen for Acute or Recent HIV Infection

If the clinician and patient have made the decision to use antiretroviral therapy for acute or recent HIV infection, treatment should be implemented in an attempt to suppress plasma HIV RNA levels to below detectable levels **(AIII)**. Data are insufficient to draw firm conclusions regarding specific drug recommendations to use in acute HIV infection. Potential combinations of agents should be those used in established infection (**Table 6**). However, since clinically significant resistance to PIs is less common than resistance to NNRTIs in treatment-naïve persons who harbor drug resistant virus, consideration should be given to using a PI-based regimen if therapy is initiated before drug resistance test results are available **(BIII)**.

Patient Follow-up

Testing for plasma HIV RNA levels and CD4 count and toxicity monitoring should be performed as described in **Initial Assessment and Monitoring While on Antiretroviral Therapy** (i.e., HIV RNA on initiation of therapy, after 2–8 weeks, then every 4–8 weeks until viral suppression, then every 3–4 months thereafter) **(AII)**.

Duration of Therapy for Acute or Recent HIV Infection

The optimal duration of therapy for patients with acute or recent HIV infection is unknown, but ongoing clinical trials may provide relevant data regarding these concerns. Difficulties inherent in determining the optimal duration and

therapy composition for acute or recent infection (and the potential need for lifelong treatment) should be considered when first counseling the patient regarding therapy.

Table 11. Identifying, Diagnosing, and Managing Acute HIV-1 Infection (Updated January 29, 2008)

- **Suspecting acute HIV infection:** Signs or symptoms of acute HIV infection with recent (within 2-6 weeks) high HIV risk exposure*
  - Signs/symptoms/laboratory findings may include but are not limited to one or more of the following: fever, lymphadenopathy, skin rash, myalgia/arthralgia, headache, diarrhea, oral ulcers, leucopenia, thrombocytopenia, transaminase elevation
  - High risk exposures include sexual contact with a person infected with HIV or at risk for HIV, sharing of injection drug use paraphernalia, or contact of potentially infectious blood with mucous membranes or breaks in skin*

- **Differential diagnosis:** EBV- and non-EBV (e.g., CMV)-related infectious mononucleosis syndromes, influenza, viral hepatitis, streptococcal infection, syphilis

- **Evaluation/diagnosis of acute/primary HIV infection**
  - HIV antibody EIA (rapid test if available)
    - Reactive EIA must be followed by Western blot
    - Negative EIA or reactive EIA with negative or indeterminate Western blot should be followed by a virologic test**
  - Positive virologic test in this setting is consistent with acute HIV infection
  - Positive quantitative or qualitative HIV RNA test should be confirmed with subsequent documentation of seroconversion

- **Patient management:**
  - Treatment of acute HIV infection is considered optional **(CIII)**.
  - Enrollment in clinical trial should be considered.

* In some settings, behaviors conducive to acquisition of HIV infection might not be ascertained, or might not be perceived as "high-risk" by the health care provider or the patient or both. Thus, symptoms and signs consistent with acute retroviral syndrome should motivate consideration of this diagnosis even in the absence of reported high risk behaviors.
** p24 antigen or HIV RNA assay. P24 antigen is less sensitive but more specific than HIV RNA tests; HIV RNA tests are generally preferred. HIV RNA tests include quantitative bDNA or RT-PCR, or qualitative transcription-mediated amplification (APTIMA, GenProbe).

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HIV-INFECTED ADOLESCENTS (Updated November 3, 2008)

Older children and adolescents now make up the largest percentage of HIV-infected children cared for at U.S. sites. The CDC estimates that 15% of the 35,314 new HIV diagnoses reported among the 33 states that participated in confidential, name-based HIV infection reporting in 2006 were among youth aged 13–24 years old *[1]*. Recent trends in HIV prevalence among 13–19 year olds reveal racial minority youth to be more disproportionately affected than analogous disparities seen in adults *[2]*. HIV-infected adolescents represent a heterogeneous group in terms of sociodemographics, mode of HIV infection, sexual and substance abuse history, clinical and immunologic status, psychosocial development, and readiness to adhere to medications. Many of these factors may influence decisions concerning when to start and what antiretroviral medications should be used.

Most adolescents have behavioral acquisition of their HIV infection. Many of them have recent acquisition of infection and may not yet know their HIV infection status. Thus, many youths are in an early stage of HIV infection, which makes them ideal candidates for early interventions, such as prevention counseling, linkage, and engagement to care. A recent study conducted by the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) that enrolled HIV-infected adolescents and young adults who presented for care identified primary genotypic resistance mutations to antiretroviral medications in up to 18% of the evaluable sample of recently infected youth, as determined by the detuned antibody testing assay strategy that defined recent infection as occurring within 180 days of testing *[3]*. In addition, a limited but increasing number of HIV-infected adolescents are long-term survivors of HIV infection acquired perinatally or through blood products as infants. Such adolescents are usually heavily treatment-experienced and may have a unique clinical course that differs from that of adolescents infected later in life *[4]*. If they harbor resistant virus, optimal antiretroviral regimens should be based on the same guiding principles as for heavily treatment-experienced adults.

Antiretroviral Therapy Considerations in Adolescents

Adult guidelines for antiretroviral therapy are usually appropriate for postpubertal adolescents, because HIV-infected adolescents who were infected sexually or through injection drug use during adolescence follow a clinical course that is more similar to that of adults than to that of children.

Dosage of medications for HIV infection and opportunistic infections should be prescribed according to Tanner staging of puberty and not solely on the basis of age *[5, 6]*. Adolescents in early puberty (i.e., Tanner Stages I and II) should be administered doses on pediatric schedules, whereas those in late puberty (i.e., Tanner Stage V) should follow adult dosing schedules. However, Tanner stage and age are not necessarily directly predictive of drug pharmacokinetics. Because puberty may be delayed in perinatally HIV-infected children *[7]*, continued use of pediatric doses in puberty-delayed adolescents can result in medication doses that are higher than the usual adult doses. Because data are not available to predict optimal medication doses for each antiretroviral medication for this group of children, issues such as toxicity, pill or liquid volume burden, adherence, and virologic and immunologic parameters should be considered in determining when to transition from pediatric to adult doses. Youth who are in their growth spurt period (i.e., Tanner Stage III in females and Tanner Stage IV in males) and who are using adult or pediatric dosing guidelines and those adolescents

whose doses have been transitioned from pediatric to adult doses should be closely monitored for medication efficacy and toxicity. Therapeutic drug monitoring can be considered in selected circumstances to help guide therapy decisions under this context. Pharmacokinetic studies of drugs in youth are needed to better define appropriate dosing. For a more detailed discussion, see **Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection** *[8]*.

Adherence Concerns in Adolescents

HIV-infected adolescents have specific adherence problems. Comprehensive systems of care are required to serve both the medical and psychosocial needs of HIV-infected adolescents, who are frequently inexperienced with health care systems and who lack health insurance. Many HIV-infected adolescents face challenges in adhering to medical regimens for reasons that include:

- denial and fear of their HIV infection;
- misinformation;
- distrust of the medical establishment;
- fear and lack of belief in the effectiveness of medications;
- low self-esteem;
- unstructured and chaotic lifestyles;
- lack of familial and social support; and
- unavailable or inconsistent access to care or health insurance and incumbent risks of inadvertent parental disclosure of the youth's HIV infection status if parental health insurance is used.

Treatment regimens for adolescents must balance the goal of prescribing a maximally potent antiretroviral regimen with realistic assessment of existing and potential support systems to facilitate adherence. Adolescents benefit from reminder systems (e.g., beepers, timers, and pill boxes) that are stylish and do not call attention to themselves. It is important to make medication adherence as user friendly and as little stigmatizing as possible for the older child or adolescent. The concrete thought processes of adolescents make it difficult for them to take medications when they are asymptomatic, particularly if the medications have side effects. Adherence to complex regimens is particularly challenging at a time of life when adolescents do not want to be different from their peers. Directly observed therapy, although considered impractical for all adolescents, might be important for selected HIV-infected adolescents *[9-13]*.

Difficult Adherence Problems

Because adolescence is a period that is characterized by rapid changes in physical maturation, cognitive processes, and life style, predicting long-term adherence in an adolescent can be very challenging. The ability of youth to adhere to therapy needs to be included as part of therapeutic decision making concerning the risks and benefits of starting treatment. Erratic adherence may result in the loss of future regimens because of the development of resistance mutations. Clinicians who care for HIV-infected adolescents frequently manage youth in whom therapy is needed but in whom significant concerns exist regarding the ability to adhere to therapy. In these cases, alternative considerations to initiation of therapy can be the following: (1) a short-term deferral of treatment until adherence is more likely or while it is aggressively addressed; (2) an adherence testing period in which a placebo (e.g., vitamin pill) is administered; and (3) the avoidance of any regimens with low genetic resistance barriers. Such decisions are ideally individualized to each patient and should be taken carefully in context with the clinical status. For a more detailed discussion on specific therapy and adherence issues for HIV-infected adolescents, see **Guidelines for Use of Antiretroviral Agents in Pediatric HIV Infection** *[8]*.

Special Considerations in Adolescents

Sexually transmitted infections (STIs), in particular human papilloma virus (HPV), should also be addressed among every adolescent. For a more detailed discussion on STIs, see the most recent CDC guidelines *[14]* and the pediatric opportunistic infection treatment guidelines on HPV among HIV-infected adolescents *[15]*. Family planning counseling, including a discussion of the risks of perinatal HIV transmission and methods to reduce them, should be provided to all youth. Gynecologic care is especially important to provide for the HIV-infected female adolescent. Contraception, including the interaction of specific antiretroviral drugs on hormonal contraception, and the potential for pregnancy also

may alter choices of antiretroviral therapy. As an example, efavirenz should be used with caution in females of childbearing age and should only be prescribed after intensive counseling and education about the potential effects on the fetus, the need for close monitoring—including periodic pregnancy testing—and a commitment on the part of the teen to use effective contraception. For a more detailed discussion, see **HIV-Infected Women** *[16]*.

Transitioning Care

Given the lifelong infection with HIV and the need for treatment through several stages of growth and development, HIV care programs and providers need flexibility to appropriately transition care for HIV-infected children, adolescents, and young adults. A successful transition requires an awareness of some fundamental differences between many adolescent and adult HIV care models. In most adolescent HIV clinics, care is more "teen-centered" and multidisciplinary, with primary care being highly integrated into HIV care. Teen services, such as sexual and reproductive health, substance use treatment, mental health, treatment education, and adherence counseling are all found in one clinic setting. In contrast, many adult HIV clinics may rely more on referral of the patient to separate subspecialty care settings, such as gynecology. Transitioning the care of an emerging young adult includes considerations of areas such as medical insurance, independence, autonomy, decisional capacity, confidentiality, and consent. Also, adult clinic settings tend to be larger and can easily intimidate younger, less motivated patients. As an additional complication to this transition, HIV-infected adolescents belong to two epidemiologically distinct subgroups: (1) those who acquired their infection perinatally—who would likely have more disease burden history, complications, and chronicity; less functional autonomy; greater need for antiretroviral treatment; and higher mortality risk; and (2) those who are behaviorally infected. Thus, these subgroups have unique biomedical and psychosocial considerations.

To maximize the likelihood of a successful transition, facilitators to successful transitioning are best implemented early on. These include the following: (1) optimizing provider communication between adolescent and adult clinics; (2) addressing patient/family resistance caused by knowledge deficits, stigma or disclosure concerns, and differences in practice styles; (3) preparing youth for life skills development, including counseling them on the appropriate utilization of a primary care provider and appointment management, the importance of prompt symptom recognition and reporting, and of the importance of self-efficacy with medication management, insurance, and entitlements; (4) identifying an optimal clinic model for a given setting (i.e., simultaneous transition of mental health and/or case management versus a gradual phase-in); (5) implementing ongoing evaluation to measure the success of a selected model; (6) engaging in regular multidisciplinary case conferences between adult and adolescent care providers; (7) implementing interventions that may be associated with improved outcomes, such as support groups and mental health consultation; and (8) incorporating a family planning component into clinical care. Attention to these key areas will likely improve adherence to appointments and avert the potential for a youth to "fall through the cracks", as it is commonly referred to in adolescent medicine.

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HIV AND ILLICIT DRUG USERS (IDUs) (Updated November 3, 2008)

Treatment Challenges of HIV-Infected IDUs and Other Illicit Substance Users

Injection drug use is the second-most common mode of HIV transmission in the United States. In addition, non-injection illicit drug use may facilitate sexual transmission of HIV. Injection and non-injection illicit drugs include the following: heroin, cocaine, marijuana, and club drugs (i.e., methamphetamine, ketamine, gamma-hydroxybutyrate [GHB], and amyl nitrate). The most commonly used illicit drugs associated with HIV infection are heroin and cocaine; however, the use of club drugs has increased substantially in the past several years and is common among those who have HIV infection or who are at risk for HIV infection. Methamphetamine and amyl nitrate (i.e., poppers) have been the most strongly associated with high-risk sexual behavior in men who have sex with men (MSM), and the association is less consistent with the other club drugs *[1]*.

All illicit drugs have been associated with depression and anxiety, either as part of the withdrawal process or as a consequence of repeated use. This is particularly relevant in the treatment of HIV infection, as depression is one of the strongest predictors of poor adherence and poor treatment outcomes *[2]*. Although treatment of HIV disease in this population can be successful, IDUs who have HIV disease present special treatment challenges. These may include the following: (1) an array of complicating comorbid medical and mental health conditions, (2) limited access to HIV care, (3) inadequate adherence to therapy, (4) medication side effects and toxicities, (5) the need for substance abuse treatment, and (6) drug interactions that can complicate HIV treatment *[3]*.

Underlying health problems among IDUs result in increased morbidity and mortality, either independent of or accentuated by HIV disease. Many of these problems are the consequence of prior exposures to infectious pathogens and from nonsterile needle and syringe use. Such problems can include hepatitis B or C virus infection, tuberculosis, skin and soft tissue infections, recurrent bacterial pneumonia, endocarditis, and neurologic and renal disease. Furthermore, the high prevalence of underlying mental health illness in this population, which antedates and/or is exacerbated by illicit substance

use, results in both morbidity and difficulties in providing clinical care and treatment *[4-6]*. Successful HIV therapy for IDUs often rests upon acquiring familiarity with and providing care for these comorbid conditions.

IDUs have less access to HIV care and are less likely to receive antiretroviral therapy than other populations *[7, 8]*. Factors associated with low rates of antiretroviral therapy use among IDU have included active drug use, younger age, female gender, suboptimal health care, lack of access to illicit drug treatment programs, recent incarceration, and lack of expertise among health care providers *[7, 8]*. The typically unstable chaotic life patterns of many IDU, the powerful pull of addictive substances; and common misperceptions about the dangers, impact, and benefits of antiretroviral therapy all contribute to decreased adherence *[9]*. The chronic and relapsing nature of substance abuse as a biologic and medical disease, compounded by the high rate of mental illness, additionally complicates the relationship between health care workers and IDU. The first step in provision of care and treatment for these individuals is the recognition of the existence of a substance abuse problem. Whereas this is often open and obvious, patients may hide such behaviors from clinicians. Assessment of the patient for the presence of substance abuse should be part of routine medical history taking and should be done in a clinical, straightforward, and nonjudgmental manner.

Treatment Efficacy in HIV-Infected Illicit Drug Use Populations

Although IDUs are underrepresented in HIV therapy clinical trials, available data indicate that—when they are not actively using drugs— efficacy of antiretroviral therapy in the IDU is similar to that seen in other populations *[10]*. Furthermore, therapeutic failure in this population generally correlates with the degree that drug use disrupts daily activities rather than with drug use *per se [11]*. Providers need to remain attentive to the possible impact these factors have upon the patient before and during prescription of antiretroviral therapy. Although many IDUs can sufficiently control their drug use over long enough periods of time to benefit from care**,** substance abuse treatment is often necessary for successful HIV management.

Close collaboration with substance abuse treatment programs and proper support and attention to this population's special multidisciplinary needs are critical components of successful HIV treatment. Essential to this end are accommodating and flexible, community-based HIV care sites that are characterized by familiarity with and nonjudgmental expertise in management of drug users' wide array of needs and in development of effective strategies to promote medication adherence *[5, 6]*, including, if available, the use of adherence support mechanisms, such as modified directly observed therapy, which has shown promise in this population *[12]*.

Antiretroviral Agents and Illicit Drugs: Toxicities and Interactions

IDUs are more likely to experience an increased frequency of side effects and toxicities of antiretroviral therapy. Although not systematically studied, this is likely because underlying hepatic, renal, neurologic, psychiatric, gastrointestinal, and hematologic diseases are highly prevalent among IDUs. Selection of antiretroviral agents in this population should be made with consideration of these comorbid conditions and risks.

Methadone and Antiretroviral Therapy. Methadone, an orally administered, long-acting opiate agonist, is the most common pharmacologic treatment for opiate addiction. Its use is associated with decreased heroin addiction, decreased needle sharing, and improved quality of life. Because of its opiate-induced effects on gastric emptying and the metabolism of cytochrome P450 isoenzymes 3A4 and 2D6, pharmacologic effects and interactions with antiretroviral agents may commonly occur. These may diminish the effectiveness of either or both therapies by causing opiate withdrawal or overdose, increased methadone toxicity, and/or decreased antiretroviral efficacy.

Methadone and NRTIs

Most of the currently available antiretroviral agents have been examined in terms of potential significant pharmacokinetic interactions with methadone. (See **Table 15c**.) No NRTIs appear to have a clinically significant effect on methadone metabolism. Abacavir may increase methadone clearance, but the clinical significance is unknown *[13]*. Conversely, methadone is known to increase the area under the curve of zidovudine by 40% *[14]*, with a possible increase in zidovudine related side effects. Methadone decreases didanosine levels when didanosine is in the tablet formulation *[15]* but not when in the EC formulation. Recent data indicate a lack of significant interaction between methadone and lamivudine or tenofovir *[16, 17]*.

Methadone and NNRTIs
Pharmacokinetic interactions between NNRTIs and methadone are well described and clinically problematic *[18, 19]*. (See **Table 15b**.) Both efavirenz and nevirapine, potent inducers of CYP450 enzymes, have been associated with significant decreases in methadone levels, which results in the potential for opiate withdrawal. It is necessary to inform patients and substance abuse treatment facilities of the likelihood of this interaction if either drug is prescribed to those receiving methadone. The clinical effect is usually seen after 7 days of coadministration and may be managed by increasing the methadone dosage, usually in 5-mg to10-mg increments daily until the desired effect is achieved. Delavirdine, a CYP450 isoenzyme inhibitor, increases methadone levels moderately but is not likely to be of clinical significance *[20]*. Etravirine does not affect methadone level *[21]*.

Methadone and PIs
Limited information indicates that PI levels are generally not affected by methadone. However, many PIs have significant effects on methadone metabolism. Lopinavir and nelfinavir administration result in a significant decrease in methadone levels *[22]*, although opiate withdrawal is less likely to occur with nelfinavir use. This is likely because of lack of effect on free rather than total methadone levels. Lopinavir/ritonavir-associated significant reductions in methadone levels and opiate withdrawal symptoms are the result of the lopinavir, not the ritonavir, component *[23]*. There is no pharmacokinetic interaction between atazanavir and methadone *[24]*, and saquinavir does not significantly affect free unbound methadone levels *[25]*. **Table 15a** provides updated information regarding interactions between PIs and methadone.

Buprenorphine and Antiretroviral Drugs. Buprenorphine, a partial μ-opiate agonist, is administrated sublingually and is coformulated with naloxone. It is being increasingly used for opiate abuse treatment. The lower risk of respiratory depression and overdose compared with methadone allows it to be prescribed by physicians for the treatment of opiate dependency. This flexible treatment setting could be of significant value to opiate-addicted HIV-infected patients who require antiretroviral therapy, as it enables one physician or program to provide both medical and substance abuse services.

Limited information is currently available about interactions between buprenorphine and antiretroviral agents *[26]*. Findings from available studies show a more favorable drug interaction profile than that of methadone. In contrast to methadone, buprenorphine does not appear to increase zidovudine levels. Buprenorphine concentration is significantly reduced when administered with efavirenz, but opioid withdrawal has not been observed *[27]*. Buprenorphine/naloxone has also been studied in combination with several protease inhibitors (nelfinavir, lopinavir/ritonavir, and ritonavir). Findings from these studies indicate pharmacokinetic interactions that result in altered buprenorphine exposure, but these have not been of clinical significance *[28]*. In a small case series, over-sedation and probable opioid excess occurred in patients who received buprenorphine/naloxone with ritonavir-boosteed atazanavir *[29]*. A recent formal pharmacokinetic study suggested, but did not confirm, these findings *[30]*. Nevertheless, when atazanavir and buprenorphine/naloxone are coadministered, patients should be monitored carefully for opioid excess.

Methylenedioxymethamphetamine (MDMA), GHB, ketamine, and methamphetamine all have the potential to interact with antiretroviral agents as all are cleared, at least in part, by the cytochrome P450 system. Overdoses secondary to interactions between the party drugs (i.e., MDMA or GHB) and PI-based antiretroviral therapy have been reported *[31]*.

Summary

It is usually possible over time to support most active drug users, such that acceptable adherence levels with antiretroviral agents can be achieved *[32, 33]* Providers must work to combine all available resources to stabilize an active drug user to prepare them for antiretroviral therapy. This should include identification of concurrent medical and psychiatric illnesses, drug treatment, needle and syringe exchange, and harm reduction strategies. A history of drug use alone is insufficient reason to withhold antiretroviral therapy, as those with a history of prior drug use have adherence rates similar to non-drug users.

Important considerations in the selection of successful regimens and the provision of appropriate patient monitoring in this population include supportive clinical sites; linkage to substance abuse treatment; and awareness of the interactions between illicit drugs and antiretroviral agents, including the increased risk for side effects and toxicities. Simple regimens should be considered to enhance medication adherence. Preference should be given to antiretroviral

agents that have a lower risk for hepatic and neuropsychiatric side effects, simple dosing schedules, and minimal interaction with methadone.

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HIV-INFECTED WOMEN (Updated November 3, 2008)

Panel's Recommendations:

- ***When initiating antiretroviral therapy for HIV-infected women, the indications for initiation of therapy and the goals of treatment are the same as for other adults and adolescents (AI).***
- ***Women taking antiretroviral agents that have drug interactions with oral contraceptives should use an additional or alternative contraceptive method for prevention of uninintended pregnancy (AIII).***
- ***In pregnant women, an additional goal of therapy is prevention of mother-to-child transmission (PMTCT), with a goal of maximal viral suppression to reduce the risk of transmission of HIV to the fetus and newborn (AI).***
- ***Genotypic resistance testing is recommended for all HIV-infected patients, including pregnant women, prior to initiation of therapy (AIII) and for those entering pregnancy with detectable HIV RNA levels while on therapy (AII).***
- ***Selection of an antiretroviral combination in pregnant women should take into account known safety, efficacy, and pharmacokinetic data of each agent during pregnancy (AIII).***
- ***Efavirenz should be avoided in a pregnant woman during the first trimester or in a woman who desires to become pregnant or who does not or cannot use effective and consistent contraception (AIII).***
- ***Clinicians should consult the most current Public Health Service guidelines when designing a regimen for a pregnant patient (AIII).***

This section provides a brief discussion of some unique considerations and basic principles to follow when caring for HIV–infected women in general and for pregnant HIV–infected women. Clinicians who provide care for pregnant women should consult the latest guidelines of the ***Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States*** for in-depth discussion and management assistance *[1]*.

Gender Considerations in Antiretroviral Therapy

Adverse Effects:

- ***Nevirapine-associated hepatotoxicity***: Nevirapine has been associated with an increased risk of symptomatic, potentially fatal, and often rash-associated liver toxicity among antiretroviral-naïve individuals. These complications generally occur early in the course of treatment, and women with higher CD4 T-cell counts appear to be at greatest risk *[2-5]*. A meta-analysis of nevirapine-related clinical trials and observational studies found that a CD4 T cell count >250 cells/mm^3 at the time of nevirapine initiation was associated with a 9.8-fold increase in symptomatic hepatic events compared with lower CD4 T-cell counts in women *[2]*. Thus, it is generally recommended that nevirapine should not be prescribed to antiretroviral-naïve women who have CD4 T-cell counts >250 cells/mm^3 unless there is no other alternative and the benefit from the therapy outweighs the risk of hepatotoxicity **(AI)**.
- ***Lactic acidosis***: There appears to be a female predominance in the increased incidence of symptomatic and even fatal lactic acidosis associated with prolonged exposure to nucleoside analogues, particularly with stavudine and/or didanosine *[6]*. Although deaths as a result of lactic acidosis have been reported in HIV-infected pregnant women, it is unclear whether pregnancy increases the incidence of this disorder. However, because pregnancy itself can mimic some of the early symptoms of lactic acidosis and because pregnancy can also be associated with other significant disorders of liver metabolism (such as acute fatty liver of pregnancy and HELLP [hemolysis, elevated liver enzymes, and low platelet count] syndrome), early signs and symptoms of lactic acidosis related to antiretroviral use may be missed. Women receiving antiretroviral therapy should be warned about the signs and symptoms of lactic acidosis, and levels of liver enzymes and electrolytes should be monitored on a periodic basis *[6]*.
- ***Metabolic complications***: A few studies have compared women with men in terms of metabolic complications associated with antiretroviral therapy use. HIV-infected women are more likely to experience increases in central fat with antiretroviral therapy and are less likely to have triglyceride elevations on treatment *[7, 8]*. Women have an increased risk of osteopenia/osteoporosis, particularly after menopause, and this risk may be exacerbated by HIV and antiretroviral therapy *[9, 10]* At the present time, none of these differences require a change in recommendations regarding treatment or therapeutic monitoring.

Drug Interactions: Several PIs and NNRTIs have drug interactions with oral contraceptives. Interactions include either a decrease or an increase in blood levels of ethinyl estradiol and/or norethindrone levels (See **Tables 15a and b**), which potentially decrease contraceptive efficacy or increase estrogen- or progestin-related adverse effects (e.g., thromboembolic risk). In general, women who are on any of these antiretroviral agents should use an alternative or additional method of contraception **(AIII)**. Although there is minimal information about drug interactions with use of newer combined hormonal contraceptive methods (e.g., transdermal patch, vaginal ring), an additional or alternative contraceptive method should also be considered on the basis of established drug interactions between antiretroviral agents and oral contraceptives. There are limited data on drug interactions between antiretroviral agents and progestin-only contraceptive methods; however, recent data have found no significant changes in antiretroviral drug concentrations of nelfinavir, nevirapine, or efavirenz when used with depot medroxyprogesterone acetate (DMPA), and there is no evidence of reduced DMPA effectiveness *[11-13]*.

Women of Childbearing Potential

All women of childbearing potential should be offered preconception counseling and care as a component of routine primary medical care. Discussion should include special considerations with antiretroviral therapy use when trying to conceive and during pregnancy. (See ***Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States***.) Antiretroviral regimen selection should account for the possibility of planned or unplanned pregnancy. The most vulnerable period in fetal organogenesis is early in gestation, often before pregnancy is recognized. Sexual activity, reproductive plans, and use of effective contraception to prevent unintended pregnancy should be discussed with the patient. As part of the evaluation for initiating therapy, women should be counseled about the potential teratogenic risk of efavirenz-containing regimens, should pregnancy occur. These regimens should be avoided in women who are trying to conceive or who are not using effective and consistent contraception. Counseling should be provided on an ongoing basis.

Pregnant Women

The decision to use any antiretroviral drug during pregnancy should be made by the woman after counseling and discussion with her clinician regarding the benefits versus risks to her, her fetus, and the newborn. Her decision should be respected; coercive and punitive policies undermine provider-patient trust and could discourage women from seeking prenatal care and adopting health care behaviors that optimize personal, fetal, and neonatal well-being.

Prevention of Mother-to-Child Transmission (PMTCT). Antiretroviral therapy is recommended in all pregnant women, regardless of virologic, immunologic, or clinical parameters, for the purpose of PMTCT **(AI)**. Both reduction of HIV RNA levels and use of antiretroviral therapy appear to have an independent effect on reduction of perinatal transmission *[14-16]*. The goal with antiretroviral therapy in pregnancy, as in nonpregnant individuals, is to achieve maximal and sustained suppression of HIV RNA levels.

Genotypic resistance testing is recommended for all pregnant women prior to initiation of therapy **(AIII)** and for those entering pregnancy with detectable HIV RNA levels while on therapy **(AII)**. Optimal prevention of perinatal transmission may require initiation of antiretroviral therapy before results of resistance testing are available, in which case therapy should be modified if the result demonstrates the presence of significant mutation(s) that may confer resistance to the prescribed antiretroviral regimen.

Long-term follow-up is recommended for all infants born to women who have received antiretroviral drugs during pregnancy, regardless of the infant's HIV status.

Regimen Considerations. Pregnancy should not preclude the use of optimal therapeutic regimens. However, recommendations regarding the choice of antiretroviral drugs for treatment of HIV-infected pregnant women are subject to unique considerations, which may result in different specific recommendations regarding timing of initiation and choice of drugs. These considerations include the following:

- potential changes in pharmacokinetics, and thus dosing requirements, which result from physiologic changes associated with pregnancy,
- potential adverse effects of antiretroviral drugs in pregnant women,
- effect on the risk for perinatal HIV transmission, and
- potential short- and long-term effects of the antiretroviral drug on the fetus and newborn, all of which are unknown for many antiretroviral drugs.

Clinicians should review ***Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States*** for a detailed discussion of drug choices. Combination drug regimens are considered the standard of care for therapy, both for the treatment of HIV infection and for PMTCT. Zidovudine by intravenous infusion to the mother during labor and orally to the neonate for 6 weeks is recommended irrespective of antenatal regimen chosen.

There are some specific differences in treatment recommendations in pregnancy based on the above considerations:

- Zidovudine should be included in the antenatal antiretroviral regimen unless there is severe toxicity, there is documented resistance, or the woman is receiving a stavudine-containing regimen. Stavudine and zidovudine coadministration is contraindicated because of virologic antagonism. However, women well-controlled on a non–zidovudine-containing regimen have a very low risk of perinatal transmission, and substitution or addition of zidovudine may compromise adherence. Therefore, it is reasonable to continue a non–zidovudine-containing regimen as long as it is fully suppressive. Although controversial, the use of zidovudine alone might be an appropriate option for pregnant women who have CD4 T-cell counts >350 cells/mm3 and HIV RNA levels <1,000 on no treatment and who wish to restrict exposure of their fetus to antiretroviral drugs during pregnancy while still reducing the risk of HIV transmission to their infants. In this situation, time-limited use of zidovudine during the second and third trimesters of pregnancy is less likely to induce the development of resistance than it is in women with higher pre-treatment viral loads.

- Efavirenz-containing regimens should be avoided in the first trimester, because significant teratogenic effects were seen in primate studies at drug exposures similar to those achieved during human exposure **(AIII)**. In addition, several cases

of neural tube defects have now been reported after early human gestational exposure to efavirenz *[17, 18]*. Efavirenz may be considered for use after the first trimester if indicated because of toxicity, resistance, or drug interaction concerns (e.g., need for anti-tuberculosis therapy).

- Nevirapine has been associated with hepatic failure and death among a small number of pregnant patients *[19]*. Although there is no evidence that pregnancy additionally increases risk, pregnant women may receive combination antiretroviral regimens at higher CD4 T-cell counts for PMTCT, even if they would not otherwise meet indications for treatment. In antiretroviral-naïve pregnant women who have CD4 T-cell counts >250 cells/mm^3, nevirapine should not be initiated as a component of a combination regimen unless the benefit clearly outweighs the risk **(AII)**. Pregnant patients on chronic nevirapine prior to pregnancy are probably at a much lower risk for this toxicity. If nevirapine is used, close clinical and laboratory monitoring, particularly during the first 18 weeks of treatment, is advised, and nevirapine should be stopped immediately in all women who develop signs or symptoms of hepatitis. The use of single-dose nevirapine for prevention of perinatal transmission has not been associated with hepatotoxicity.

- Several small studies show that optimal levels of several PIs may not be achieved in pregnancy, especially in the third trimester, although the clinical relevance of this is unknown *[20-22]*. Once-daily lopinavir/ritonavir dosing is not recommended in pregnancy, because there are no data to address adequacy of blood levels with this dosing regimen **(BII)**.

- There are minimal data on the use of newer agents, such as enfurvitide, etravirine, maraviroc, or raltegravir, in pregnancy.

Clinicians who are treating HIV-infected pregnant women are strongly encouraged to report cases of prenatal exposure to antiretroviral drugs (either administered alone or in combinations) to the **Antiretroviral Pregnancy Registry** (**http://www.apregistry.com/**). The registry collects observational, nonexperimental data regarding antiretroviral exposure during pregnancy for the purpose of assessing potential teratogenicity. For more information regarding selection and use of antiretroviral therapy during pregnancy, please refer to ***Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States*** *[1]*.

Lastly, women should be counseled regarding the avoidance of breastfeeding. Continued clinical, immunologic, and virologic follow-up should be done as recommended for nonpregnant adults and adolescents.

Discontinuation of Antiretroviral Therapy Postpartum

For women who began antiretroviral therapy with a nadir CD4 T-cell count >350 cells/mm^3 for PMTCT, the decision on whether to continue therapy after delivery should take into account current recommendations for initiation of antiretroviral therapy, current and nadir CD4 T-cell counts and trajectory, HIV RNA levels, and patient preference. A recent study from the Women and Infants Transmission Study (WITS) of women who were antiretroviral-naïve prior to pregnancy and had CD4 T-cell counts >350/mm^3 *[23]* found no significant differences in CD4 T-cell count, viral load, or disease progression among those who did or did not continue antiretroviral treatment after delivery through 12 months postpartum. In most cases, when drugs are discontinued postnatally, all drugs should be stopped simultaneously. However, if therapy includes an NNRTI, stopping all regimen components simultaneously may result in functional monotherapy because of the long half-life of the NNRTI, which may increase risk of resistance. Nevirapine resistance mutations have been identified postpartum in women taking nevirapine-containing combination regimens only for PMTCT. In one study, nevirapine resistance was identified in 16% of women despite continuation of the nucleoside backbone for 5 days after stopping nevirapine *[24]*. The current recommendation in women receiving NNRTI-based regimens is to continue the dual NRTI backbone for a short period of time after stopping the NNRTI to decrease the risk of NNRTI resistance. However, the optimal interval between stopping an NNRTI and the other antiretroviral drugs is unknown. An alternative strategy is to substitute the NNRTI with a PI for a period of time while continuing the NRTIs, then to discontinue all the drugs at the same time. Additional research is needed to assess appropriate strategies for stopping NNRTI-containing combination regimens after delivery in situations when ongoing maternal treatment is not indicated, as well as to assess the effect of limited-duration, fully suppressive antiretroviral prophylaxis in pregnancy on future treatment efficacy. (See **Discontinuation or Interruption of Antiretroviral Therapy** section.)

In HIV and hepatitis B virus (HBV) coinfected pregnant women who are receiving antiretroviral therapy only for perinatal prophylaxis and who are stopping therapy after delivery, careful clinical and laboratory monitoring for HBV flare should be performed postpartum when antiretroviral agents active against HBV are discontinued. However, if treatment for HBV is indicated, a full combination regimen for both HIV and HBV infection should be continued. (See **When to Start** section.)

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Antiretroviral Considerations in Patients with Coinfections

HEPATITIS B (HBV)/HIV COINFECTION (Updated December 1, 2007)

It is not clear that treatment of HBV improves the course of HIV infection, nor is there evidence that treatment of HIV alters the natural history of chronic HBV. However, several liver-associated complications that are ascribed to flares in HBV activity or to toxicity of antiretroviral agents can affect the treatment of HIV in patients with HBV coinfection. These include the following:

- Emtricitabine, lamivudine, and tenofovir have activity against both HIV and HBV. Discontinuation of these drugs may potentially cause serious hepatocellular damage resulting from reactivation of HBV *[1-3]*;
- Lamivudine-resistant HBV is observed in approximately 40% of patients after 2 years of lamivudine monotherapy for chronic HBV and in approximately 90% after 4 years when it is used as the only active drug for HBV in coinfected patients *[4, 5]*;
- Entecavir has activity against HIV, and its use in patients with dual infection has been associated with selection of the M184V mutation that confers resistance to lamivudine and emtricitabine *[6, 7]*. Therefore, entecavir should be used only with a fully suppressive antiretroviral regimen in HIV/HBV–coinfected patients.
- Immune reconstitution can be associated with elevation in transaminases, possibly because HBV is primarily an immune-mediated disease *[8]*; and
- Many antiretroviral drugs can cause increases in transaminase levels. The rate and magnitude of these increases are higher with HBV coinfection *[9, 10]*. The etiology and consequences of these changes in liver function tests are unclear, because continuation of therapy may be accompanied by resolution of the changes. Nevertheless, some experts suspend the implicated agent(s) when the ALT is increased to 5–10 times the upper limit of normal. However, in HIV/HBV–coinfected persons, increases in transaminase levels can herald HBeAg seroconversion, so the cause of the elevations should be investigated prior to the decision to discontinue medications. HBeAg seroconversion can be evaluated by checking HBeAg and anti-HBe as well as HBV DNA levels.

Treatment Recommendations for HBV/HIV Coinfected Patients

- All patients with HBV should be advised to abstain from alcohol; should receive hepatitis A vaccine if found not to be immune at baseline (i.e., absence of hepatitis A total or IgG antibody); should be advised on methods to prevent HBV transmission (which do not differ from those to prevent HIV transmission); and should be evaluated for the severity of HBV infection.
- **If neither HIV nor HBV infection requires treatment**: Monitor the progression of both infections. If treatment becomes necessary for either infection, follow the guidelines listed in the scenarios below.
- **If treatment is needed for HIV but not for HBV**: The combination of tenofovir and emtricitabine or tenofovir and lamivudine should be used as the NRTI backbone of an antiretroviral regimen, which will result in treatment of both infections. To avoid development of HBV-resistant mutants, none of these agents should be used as the only agent with anti-HBV activity in an antiretroviral regimen.
- **If treatment for HBV is needed**: Patients who need treatment for HBV infection should also be started on a fully suppressive antiretroviral regimen that contains NRTIs with activity against both viruses: for example, tenofovir plus either emtricitabine or lamivudine. The use of lamivudine, emtricitabine, or tenofovir as the only active anti-HBV agent should be avoided because of the risk for resistance. If tenofovir cannot be used, another agent with anti-HBV activity should be used in combination with lamivudine or emtricitabine for treatment of HBV infection. Management of HIV should be continued with a combination regimen to provide maximal suppression.
- **Treating only HBV**: In instances when HIV treatment is not an option or is not desirable, pegylated interferon-alpha may be used for the treatment of HBV infection, as it does not lead to the emergence of HIV or HBV resistance. Adefovir dipivoxil is active against HBV but not against HIV at the 10mg dose; however, there is a theoretical risk for development of HIV resistance, as it has anti-HIV activity at higher doses and is related to tenofovir. Because of

the risk for HIV drug resistance, the use of emtricitabine, lamivudine, tenofovir, or entecavir without a full combination antiretroviral regimen should be avoided.

- **Need to discontinue emtricitabine, lamivudine, or tenofovir**: Monitor clinical course with frequent liver function tests and consider the use of interferon, adefovir dipivoxil, or telbivudine to prevent flares, especially in patients with marginal hepatic reserve.

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HEPATITIS C (HCV)/HIV COINFECTION **(Updated October 29, 2004)**

Long-term studies of patients with chronic HCV infection show that approximately 33% of the patients progress to cirrhosis at a median time of less than 20 years *[1]*. This rate of progression increases with older age, alcoholism, male sex, and HIV infection *[1-3]*. A meta-analysis demonstrated that the rate of progression to cirrhosis with HCV/HIV coinfection was about threefold higher when compared with patients who are seronegative for HIV *[2]*. This accelerated rate is magnified in patients with low CD4 counts. Chronic HCV infection also complicates HIV treatment by the increased frequency of antiretroviral-associated hepatotoxicity *[4]*. Multiple studies show poor prognosis for HCV/HIV coinfection in the era of combination antiretroviral therapy. It is unclear if HCV adversely affects the rate of HIV progression *[5, 6]* or if this primarily reflects the impact of injection drug use, which is strongly linked to HCV infection *[7, 8]*. It is also unclear if antiretroviral therapy improves the attributable morbidity/mortality for untreated HCV.

Assessment of HCV/HIV Coinfection

Patients with HCV/HIV coinfection should be advised to avoid or limit alcohol consumption, use appropriate precautions to prevent transmission of both viruses to others, and should be given hepatitis A and B vaccine if found susceptible. All patients with HCV, including those with HIV coinfection, should be evaluated for HCV therapy.

Standard indications for HCV therapy in the absence of HIV infection are detectable plasma HCV RNA and a liver biopsy showing bridging or portal fibrosis. ALT levels may be elevated in association with HCV infection. However, ALT levels do not accurately reflect the severity of HCV-associated liver disease. Liver biopsy is important for HCV therapeutic decision making but is indicated only if the patient is considered a treatment candidate based on multiple other variables including severity and stability of HIV disease, other comorbidities, probability of adherence, and if there are contraindications to interferon-alpha, one of the drugs available for treatment of HCV.

Clinical trials in patients with HCV/HIV coinfection using pegylated interferon plus ribavirin for 48 weeks show sustained virologic response (SVR) rates of 60%–70% for HCV genotype 2/3 but only 15%–28% for genotype 1 *[9, 10]*.

These data are based on experience almost exclusively in carefully selected patients with CD4 counts >200 cells/mm^3 *[10-12]*.

Treatment of HCV/HIV Coinfection

Based on these observations, treatment of HCV is recommended according to standard guidelines *[13]* with preference for those with higher CD4 counts (>200 cells/mm^3). For some patients with lower CD4 counts, it may be preferable to initiate antiretroviral therapy and delay HCV therapy. Concurrent treatment is feasible but may be complicated by pill burden, drug toxicities, and drug interactions.

Scenarios for Treating HCV/HIV Coinfection

Differences in HCV therapy management in the presence of HIV coinfection include:

- Ribavirin should not be given with didanosine because of the potential for drug-drug interactions leading to pancreatitis and lactic acidosis *[14]*;
- Some NRTIs and all NNRTIs and PIs are potentially hepatotoxic, so monitoring of serum transaminase levels is particularly important *[15]*;
- Zidovudine combined with ribavirin is associated with higher rates of anemia suggesting this combination be avoided when possible;
- Growth factors to manage interferon-associated neutropenia and ribavirin-associated anemia may be required.

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MYCOBACTERIUM TUBERCULOSIS DISEASE OR LATENT TUBERCULOSIS INFECTION WITH HIV COINFECTION (Updated January 29, 2008)

Panel's Recommendations:

- ***The treatment of active tuberculosis (TB) disease in patients with HIV infection should follow the same principles for persons without HIV infection (AI).***
- ***Presence of active TB requires immediate initiation of treatment (AI).***
- ***The optimal timing of initiation of antiretroviral therapy in patients with active TB disease is not known. In antiretroviral-naïve patients, delay of antiretroviral therapy for 2 to 8 weeks after initiation of TB treatment may allow for easier identification of causes of adverse drug reactions, and may reduce the risk of Immune Reconstitution Inflammatory Syndrome (IRIS or a "paradoxical reaction") once antiretroviral therapy is initiated. However, delay may increase the risk of HIV-related complications and mortality, particularly in those with very low CD4 cell counts (BII).***
- ***Directly observed therapy of TB treatment is strongly recommended for HIV-infected patients with active TB disease (AII).***
- ***Despite pharmacokinetic drug interactions, a rifamycin should be included in regimens for patients receiving antiretroviral therapy, with dosage adjustment as necessary (AII).***
- ***Where available, rifabutin is the preferred rifamycin in HIV-infected patients with active TB disease due to its lower risk of substantial interactions with antiretroviral therapy (AII).***
- ***Rifampin/rifabutin-based regimens should be given at least three times weekly in HIV-infected patients with active disease and CD4 count <100 cells/mm^3; twice weekly is acceptable if CD4 count >100 cells/mm^3 (AII).***
- ***Once-weekly rifapentine is not recommended in the treatment of active TB disease in HIV-infected patients (AI).***
- ***The optimal management of IRIS is unknown; TB treatment and antiretroviral therapy should be continued, along with use of non-steroidal anti-inflammatory agents for milder cases and consideration of the use of high dose corticosteroids for 1 to 4 weeks in severe cases, with the length of treatment and taper based on control of symptoms (BIII).***
- ***Immune restoration as a result of antiretroviral therapy may be associated with conversion from a negative to a positive tuberculin skin test (TST) or IFN-γ release assay (IGRA) in response to M.TB-specific proteins; repeat TST or IGRA is recommended in previously TST-negative or IGRA-negative individuals after initiation of antiretroviral therapy when the CD4 cell count exceeds 200 cells/mm^3 (BII).***
- ***HIV-infected individuals found to have latent TB infection (LTBI), defined as ≥5 mm skin test induration or positive IGRA with no prior treatment for LTBI and after appropriate evaluation to rule out active TB disease and no prior treatment of LTBI, should commence treatment with isoniazid (with pyridoxine) for 6 to 9 months (AI).***

HIV infection significantly increases the risk of progression from latent to active tuberculosis (TB) disease. In HIV-negative individuals with latent TB infection (LTBI), the lifetime risk of developing active TB disease is 5%–10%, whereas in people living with HIV with latent TB, the risk is 10% *per year [1]*. The CD4 T-cell count influences both the frequency and clinical expression of active TB disease *[2, 3]*. Active TB also negatively affects HIV disease. It may be associated with a higher HIV viral load and more rapid progression of HIV disease *[1, 2]*. Important issues with respect to the use of antiretroviral therapy in patients with active TB disease are 1) the sequencing of treatments, 2) the value of directly observed therapy, 3) potential for significant pharmacokinetic drug interactions with rifamycins, 4) the additive toxicities including high rates of hepatotoxicity and neuropathy associated with drugs used for each condition, 5) development of Immune Reconstitution Inflammatory Syndrome (IRIS) with TB after initiation of antiretroviral therapy, 6) the effect of antiretroviral therapy on results of tuberculin skin testing, and 7) the need for integration of HIV and TB care and therapy.

Terminology: In this section, the terms "HIV infected with active TB disease" and "HIV/TB disease" are used synonymously to designate HIV-infected patients with active TB disease in need of TB treatment. The term "HIV/TB coinfection" may cause confusion because it can refer to either active TB or LTBI in the presence of HIV infection.

Sequencing of Treatments

The treatment of active TB disease should follow the general principles for TB treatment in persons without HIV **(AI)**. Below are two scenarios for sequencing the treatment of HIV-infected patients with active TB disease:

- **Patients Currently Receiving Antiretroviral Therapy.** Patients receiving antiretroviral therapy at the time of initiation of TB treatment will require assessment of the antiretroviral therapy regimen in order to adjust the doses to permit use of the optimal TB regimen with particular attention to pharmacokinetic interactions with rifamycins (discussed below).
- **Patients Not Receiving Antiretroviral Therapy at the Time of Active TB Diagnosis.** Active pulmonary or extrapulmonary TB disease requires prompt initiation of TB treatment. However, a delay in initiation of antiretroviral therapy for 2 to 8 weeks permits easier assessment of signs and symptoms related to adverse drug reactions and may reduce the risk of IRIS. Starting antiretroviral therapy within a few days or weeks after initiating TB treatment increases the risk of IRIS compared to waiting for longer periods of time *[4]*. However, in patients with CD4 counts <200 cells/mm^3, starting antiretroviral therapy within a few days or weeks of initiating TB treatment may reduce the risk of the development of opportunistic infections (OIs) and other HIV-related complications and may improve survival *[5]*. The optimal timing of initiation of antiretroviral therapy after starting TB treatment is not known. Although these guidelines and the OI Treatment and Prevention Guidelines *[6]* from the NIH, CDC, and HIVMA/IDSA recommend a delay of antiretroviral therapy for 2 to 8 weeks **(BII)**, the timing chosen for an individual patient depends on clinical judgment, taking into account factors such as immunologic and clinical parameters and the availability of health care.

Some experts base the timing of initiation of antiretroviral therapy in patients with active TB disease on CD4 cell counts at the start of TB treatment, as shown below:

- CD4 <100cells/mm^3: start antiretroviral therapy after 2 weeks of TB treatment
- CD4 =100–200 cells/mm^3: start antiretroviral therapy after 8 weeks of TB treatment
- CD4 = 200–350 cells/mm^3: start antiretroviral therapy after 8 weeks of TB treatment*
- CD4 >350cells/mm^3: start ART after 8 to 24 weeks or after end of TB treatment*

* On case-by-case basis in clinician's judgment.

It is important to carefully monitor patients in whom initiation of antiretroviral therapy is deferred through regular clinical and CD4 cell count assessments during TB treatment in order to promptly initiate antiretroviral therapy if there is evidence of HIV disease progression or of a drop in CD4 cell count. Individuals with CD4 cell counts <200 cells/mm^3 should be placed on PCP prophylaxis, regardless of timing of initiation of antiretroviral therapy.

Treatment of TB

Treatment of drug-susceptible active TB disease in HIV-infected individuals should include the standard short-course regimen outlined in treatment guidelines, which consists of isoniazid (INH), rifampin (RIF) or rifabutin (RFB), pyrazinamide (PZA), and ethambutol (EMB) or streptomycin (SM) given for 2 months, followed by INH + RIF for 4 to 7 months *[6, 7]* **(AI)**. Special attention should be given to the potential of drug-drug interactions with rifamycin as discussed below. A minimum of thrice weekly treatment with rifamycin-containing TB treatment regimens is recommended for patients with a CD4 cell count <100 cells/mm^3 **(AII)**. Once- or twice-weekly dosing has been associated with increased rates of development of rifamycin resistance in patients with advanced HIV, and once-weekly rifapentine is not recommended **(AI)** *[7-9]*.

Directly Observed Therapy (DOT)

DOT of TB treatment, in a manner supportive of the patients' needs is strongly recommended for patients with HIV/TB disease **(AII)**. In general, daily or thrice weekly DOT is recommended for the first 2 months and then three times weekly DOT for the continuation phase of 4 to 7 months **(BII)**.

Anti-Tuberculosis/Antiretroviral Drug Toxicities and Interactions

Almost all antiretroviral drugs are associated with the potential for hepatotoxicity. INH, RIF, and PZA may also cause drug-induced hepatitis. These first-line TB drugs should be used for treatment of active TB disease, if possible, even with coadministration of other potentially hepatotoxic drugs or in the presence of baseline liver disease **(AIII)**. Patients receiving drugs with potential hepatotoxicity should have frequent monitoring for clinical symptoms and signs of hepatitis and laboratory monitoring for hepatotoxicity, including serum aminotransferases, bilirubin, and alkaline phosphatase.

Rifamycins are essential drugs for the treatment of active TB disease. However, they are associated with significant drug interactions with PIs, NNRTIs, maraviroc, and raltegravir, because of their effects as inducers of the hepatic cytochrome P450 and UGT1A1 enzymes. Despite these interactions, a rifamycin should be included in the TB treatment regimen in patients receiving antiretroviral therapy *[6, 10]* **(AII)**. Rifampin is the most potent inducer of hepatic enzymes, and results in significant decreases in exposure to ritonavir-boosted or unboosted PIs, with resultant risk of antiretroviral treatment failure. Coadministration of rifampin and nevirapine or efavirenz is associated with lower NNRTI drug exposures and greater variability in plasma NNRTI drug levels. However, some clinical and pharmacologic data suggest that comparable virologic, immunologic, and clinical outcomes are achieved with either efavirenz *[11, 12]* or nevirapine *[13, 14]* in standard doses in combination with rifampin-containing regimens. Some experts recommend consideration of dose escalation of efavirenz in patients who weigh more than 60 kg; other experts suggest that no dosage adjustment is necessary (**Table 15b**). One large, observational study from South Africa evaluated virologic responses at 6 months in patients treated with an NNRTI-based regimen with or without TB treatment that contained rifampin. Among the nevirapine-treated patients, the rate of virologic failure was higher among those with TB compared with those without TB [16.3% vs. 8.3%; adjusted odd ratio, 2.1 (95% CI, 1.2–3.4). No difference in virologic response was seen when comparing TB vs. non-TB patients who were started on efavirenz-based regimens *[15]*. Rifabutin has fewer and less severe drug interactions with antiretroviral therapy drugs and is preferred in patients with HIV/TB disease when used in combination with appropriate dose adjustments, according to **Tables 15a** and **15b**. In the case of an antiretroviral therapy–experienced patient in whom NNRTI-based regimens are not an option and for whom rifabutin is not available, consultation with an HIV expert is recommended.

IRIS with TB: Clinical Disease

Some patients while on treatment for active TB will develop IRIS, which is characterized by findings such as fever, new or worsening lymphadenopathy, worsening of pulmonary infiltrates, and pleural effusion. These reactions may occur in the absence of HIV infection and in the absence of antiretroviral therapy, but are more common after initiation of antiretroviral therapy in patients with active TB disease as a consequence of immune reconstitution. IRIS has been reported in 8%–43% of patients with HIV/TB disease, and may contribute to the higher mortality from antiretroviral therapy in the first year of treatment. Predictors of IRIS include CD4 cell count <50 cells/mm^3, severe TB disease with high pathogen burden, and interval between initiation of TB and HIV treatment of less than 30 days *[4, 13, 16-19]*. Most IRIS in HIV/TB disease occurs within three months of the start of TB treatment. Delaying the start of antiretroviral therapy for 2 to 8 weeks may reduce the incidence and severity of IRIS but must be weighed against the potential benefit of earlier antiretroviral therapy in improving immune function and preventing progression of HIV disease. In mild to moderate cases of IRIS, treatment of TB and HIV should be continued and nonsteroidal anti-inflammatory agents may be used to alleviate specific symptoms **(AII)**. In severe cases of IRIS high-dose prednisone (1mg/kg for 1 to 4 weeks followed by tapering doses, with the duration and timing of tapering based on the control of symptoms) has been associated with clinical improvement *[19-21]* **(BIII)**, and additional measures, such as surgical decompression, also may be required.

Immune Reconstitution with Antiretroviral Therapy: Conversion to Positive TST and/or IGRA Test

Immune reconstitution with antiretroviral therapy may result in unmasking LTBI (i.e., conversion of a previously negative TST to a positive TST or a positive interferon-gamma [IFN-γ] release assay [IGRA] for *M.TB*–specific proteins). A positive IGRA, similar to a positive TST, is indicative of LTBI in the absence of evidence of active TB disease *[22]*. Because treatment for LTBI is indicated in the absence of evidence of active TB disease, clinicians should be aware of this phenomenon. In individuals with a negative TST or IGRA and advanced HIV disease (i.e., CD4 count <200 cells/mm^3), TST or IGRA should be repeated after they have started antiretroviral therapy and their CD4 count has increased to above 200 cells/mm^3 *[23]* **(BII)**.

A TST or IGRA should also be performed prior to the initiation of antiretroviral therapy regardless of the CD4 count. Individuals found to have LTBI by IGRA or TST—defined as >5 mm skin test induration without evidence of active TB disease and after appropriate evaluation for active TB disease—should commence treatment as recommended by the guidelines for treatment and prevention of OIs in HIV-infected patients *[6]*. Caution should be taken regarding use of rifamycins with certain antiretroviral drugs (see above).

A more complete discussion of the use of IGRAs and the diagnosis and treatment of TB disease and LTBI in patients with HIV infection will be available in *"**The Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents—2008**: Recommendations from the NIH, the CDC, and the HIVMA/IDSA"[6].*

Integration of TB and HIV Care

Due to the complexities described above, optimal management of HIV-infected individuals with active TB disease requires close collaboration between TB and HIV clinicians, health care institutions, and public health programs.

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Limitations to Treatment Safety and Efficacy

ADHERENCE TO ANTIRETROVIRAL THERAPY **(Updated November 3, 2008)**

Adherence to antiretroviral therapy has been strongly correlated with HIV viral suppression, reduced rates of resistance, an increase in survival, *and* improved quality of life *[1, 2]*. Because HIV treatment is a lifelong endeavor, and because many patients will initiate therapy when they are generally in good health, feel well, and demonstrate no obvious signs or symptoms of HIV disease, adherence poses a special challenge and requires commitment from the patient and the health care team. Adherence remains a challenging and complicated topic; the guidance put forth in this document provides a basis to guide clinicians in their approach.

Predictors of Adherence

Adherence is related to characteristics of the patient, the regimen, the clinical setting, and the strength of the provider/patient relationship *[3]*. The information given and the patient's understanding about HIV disease and the specific regimen to be taken is critical. A number of factors have been associated with poor adherence, including the following:

- low levels of literacy *[4]*;
- certain age-related challenges (e.g., vision loss, cognitive impairment) *[5]*;
- psychosocial issues (e.g., depression, homelessness, lower social support, stressful life events, dementia, or psychosis) *[6]*;
- active (but not history of) substance abuse, particularly for patients who have experienced recent relapse;
- stigma *[7];*
- difficulty with medication taking (e.g., trouble swallowing pills, daily schedule issues);
- complex regimens (e.g., pill burden, dosing frequency, food requirements);
- adverse drug effects; and
- treatment fatigue.

Adherence studies in the early era of combination therapy with unboosted PIs found that taking 95% or more of doses was required for full viral suppression *[8]*. More recent adherence studies that utilized boosted PIs and NNRTIs suggest that boosted PIs and efavirenz may be more forgiving of lapses in adherence because of their longer half-lives *[9, 10]*. Nonetheless, clinicians should encourage patients to adhere as closely as possible to the prescribed doses for all antiretroviral regimens.

Measurement of Adherence

There is no gold standard for the assessment of adherence *[1]*, but there are many validated tools and strategies to choose from. Although patient self-report of adherence predictably overestimates adherence by as much as 20% *[11]*, this measure still is associated with viral load responses *[12]*. Thus, a patient's report of suboptimal adherence is a strong indicator of nonadherence and should be taken seriously.

When ascertained in a simple, nonjudgmental, routine, and structured format that normalizes less-than-perfect adherence and minimizes socially desirable responses, patient self-report remains the most useful method for the assessment and longitudinal monitoring of a patient's adherence in the clinical setting. A survey of all doses during the past 3 days or the past week accurately reflects longitudinal adherence and is the most practical and readily available tool for adherence assessments in clinical trials and in clinical practice *[1]*. Other strategies may also be effective. One study found that asking patients to rate their adherence on a six-point scale during 1 month was more accurate than asking them how often they miss doses or asking about the percentage of doses taken during the previous 3 or 7 days *[13]*. Pharmacy records and pill counts can also be used as an adjunct to simply asking the patient *[14]*. Other methods of assessing adherence include the use of electronic measurement devices (e.g., bottle caps, dispensing systems). However, these methods may not be feasible in some clinical settings.

Interventions to Improve Adherence

Prior to writing the first prescriptions, the clinician should assess the patient's readiness to take medication; factors that might limit adherence (e.g., psychiatric illness, active drug use, etc) that may require additional support; understanding of the disease and the regimen; social support; housing; work and home situation; and daily schedules. Patients should understand that the first regimen is usually the best chance for a simple regimen with long-term treatment success and prevention of drug resistance. Resources should be identified to assist in achievement of good adherence that is individualized to each patient's schedule, competing psychosocial needs, learning needs, and literacy level.

Individualizing treatment with involvement of the patient in decision making is the cornerstone of any treatment plan *[14]*. The first principle of successful treatment is negotiation of an understandable plan to which the patient can commit *[15, 16]*. Establishing a trusting relationship over time and maintaining good communication will help to improve adherence and long-term outcomes. With the patient who is not critically ill, several office visits and the patience of clinicians are generally required before therapy can be started.

There is a growing menu of possible interventions that have demonstrated efficacy in improving adherence to antiretroviral therapy. For example, a meta-analysis of 19 randomized controlled trials of antiretroviral adherence interventions found that intervention participants were 1.5 times as likely to report 95% adherence and 1.25 times as likely to achieve an undetectable viral load compared with participants in comparison conditions *[17]*. Interventions that have been successful include those focused on the patient and those that work to improve the tolerability of the regimen. Successful support interventions of different modalities have included the following: adherence support groups, peer adherence counselors, behavioral interventions, cognitive-behavioral and reminder strategies, and use of community-based case managers and peer educators. Health care team members, such has nurses, nurse practitioners, pharmacists, medication managers, and social workers, have integral roles in successful adherence programs *[18-21]*. It is also important to address the competing needs of a patient, including active substance use, depression, and housing issues, to reduce the risk of nonadherence.

A number of advances during the past several years have dramatically simplified many regimens, particularly for treatment-naïve patients. Prescribing regimens that are simple to take, have a low pill burden and frequency of dosing, have no food requirements, and have low incidence and severity of adverse effects will facilitate adherence. Current treatment recommendations take regimen simplicity as well as efficacy into account.

Adherence assessment and counseling should be done at each clinical encounter and should be the responsibility of the entire health care team. Directly observed therapy (DOT) has been shown to be effective in provision of antiretroviral therapy to active drug users *[22]*. In resource-limited settings, the use of community-based DOT has been very successful, and programs have replicated this intervention with success in the United States *[23]*. Although DOT is labor intensive and programmatically complex, modification of traditional DOT methodologies may be feasible and can be adapted in a variety of clinical settings, in which DOT is given a few days each week *[24]*.

Conclusion

There has been significant progress made regarding determinants, measurements, and interventions to improve adherence to antiretroviral therapies. Given the various assessment strategies and potential interventions available, the challenge for the treatment team is to select the techniques that provide the best fit for their treatment setting, resources, and patient population. The complexity of this topic and the importance of adherence encourage clinicians to continue to seek novel, patient-centered ways to prevent nonadherence and to tailor adherence interventions. Early detection of nonadherence and prompt intervention can greatly reduce the development of viral resistance and the likelihood of virologic failure.

Table 12. Strategies to Improve Adherence to Antiretroviral Therapy

Strategies	Examples
Utilize a multidisciplinary team approach Provide an accessible, trusting healthcare team	• Nurses, social workers, pharmacists, and medications managers
Establish a trusting relationship with the patient	
Establish readiness to start ART	
Identify potential barriers to adherence prior to starting ART	• Psychosocial issues • Active substance abuse or at high risk for relapse • Low literacy level • Busy daily schedule and/or travel away from home • Lack of disclosure of HIV diagnosis • Skepticism about ART • Lack of prescription drug coverage
Provide resources for the patient	• Referrals for mental health and/or substance abuse treatment • Resources to obtain prescription drug coverage • Pillboxes
Involve the patient in ARV regimen selection	For each option, review potential side effects, dosing frequency, pill burden, storage requirements, food requirements, and consequences of nonadherence
Assess adherence at every clinic visit	• Simple checklist patient can complete in the waiting room • Assessment also by other members of the healthcare team • Ask the patient open-ended questions (e.g., *In the last three days, please tell me how you took your medicines?*)
Identify the type of nonadherence	• Failure to fill the prescription(s) • Failure to take the right dose(s) at the right time(s) • Nonadherence to food requirements
Identify reasons for nonadherence	• Adverse effects from medications • Complexity of regimen – pill burden, dosing frequency, etc. • Difficulty swallowing large pills • Forgetfulness • Failure to understand dosing instructions • Inadequate understanding of drug resistance and its relationship to adherence • Pill fatigue • Reassess other potential barriers listed above
Assess and simplify regimen, if possible	

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ADVERSE EFFECTS OF ANTIRETROVIRAL AGENTS **(Updated November 3, 2008)**

Adverse effects have been reported with all antiretroviral drugs and are among the most common reasons for switching or discontinuing therapy and for medication nonadherence *[1]*. Rates of treatment-limiting adverse events in treatment-naïve patients enrolled in randomized trials appear to be declining with newer antiretroviral regimens. Rates of discontinuation for adverse events ranged from 4% among patients randomized to the fixed-dose combination of tenofovir and emtricitabine combined with efavirenz to 9% for those assigned to zidovudine, lamivudine, and efavirenz and to 10%–12% among patients who received abacavir and lamivudine combined with either lopinavir/ritonavir or fosamprenavir. In the Swiss Cohort study, the presence of laboratory adverse events was associated with higher rates of mortality during 6 years of follow-up, which highlights the importance of adverse events in overall patient management *[2]*. Whereas some common adverse effects were identified during premarketing clinical trials, some less frequent toxicities (e.g., lactic acidosis with hepatic steatosis and progressive ascending neuromuscular weakness syndrome) and longer-term complications (e.g., dyslipidemia and fat maldistribution) were not recognized until after the drugs had been used for years. In rare cases, some drug-related events may result in significant morbidity and even mortality.

Several factors may predispose individuals to certain antiretroviral-associated adverse events. For example, women seem to have a higher propensity of developing Stevens-Johnson Syndrome and symptomatic hepatic events from nevirapine (especially in treatment-naïve women who have high CD4 counts) *[3-5]* or lactic acidosis from NRTIs *[6-8]*. Other factors may also contribute to the development of adverse events, such as use of concomitant medications with overlapping and additive toxicities; comorbid conditions that may increase the risk of or exacerbate adverse effects (e.g., alcoholism *[9]* or coinfection with hepatitis B or C, which may increase risk of hepatotoxicity *[10-12]*); drug-drug interactions that may lead to an increase in dose-related toxicities (e.g., concomitant use of ribavirin with didanosine, which may increase didanosine-associated toxicities *[13-15]*); or genetic factor predisposing patients to abacavir hypersensitivity reaction *[16, 17]*.

Although the therapeutic goals of antiretroviral therapy include achieving and maintaining viral suppression and improving patient immune function, an overarching goal should be to select a safe and effective regimen while taking into account individual patient underlying conditions, concomitant medications, and history of drug intolerance.

Information on adverse events is outlined in multiple tables in the guidelines:

Appendix Tables 2–7 summarize common adverse effects of individual antiretroviral agents; and
Table 13 provides clinicians with a list of antiretroviral-associated adverse events, common causative agents, estimated frequency of occurrence, timing of symptoms, clinical manifestations, potential preventive measures, and suggested management strategies.

Table 13. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations

Adverse Effects	Associated ARVs	Onset/Clinical Manifestation	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Bleeding events	TPV/r: reports of intracranial hemorrhage (ICH) PIs: ↑ bleeding in hemophiliac patients	Median time to ICH event: 525 days on TPV/r therapy Hemophiliac patients: ↑ spontaneous bleeding tendency – in joints, muscles, soft tissues, and hematuria	In 2006, 13 cases of ICH reported, w/ TPV/r use, including 8 fatalities *[18]* For hemophilia: frequency unknown	For ICH: • Patients with CNS lesions, head trauma, recent neurosurgery, coagulopathy, hypertension, alcohol abuse, or receiving anticoagulant or anti-platelet agents including vitamin E For hemophiliac patients: • PI use	Avoid Vitamin E supplements, particularly with the oral solution formulation of tipranavir For ICH: • Avoid use of TPV/r in patients at risk for ICH For hemophiliac patients: • Consider using NNRTI-based regimen • Monitor for spontaneous bleeding	For ICH: • Discontinue TPV/r ; manage ICH with supportive care For hemophiliac patients: • May require increased use of Factor VIII products
Bone marrow suppression	ZDV	Onset: few weeks to months Laboratory abnormalities: • anemia (usually macrocytic) • neutropenia Symptoms: fatigue because of anemia; potential for increased bacterial infections because of neutropenia	Severe anemia (Hgb <7 g/dL): 1.1%–4% Severe neutropenia (ANC <500 cells/mm^3): 1.8%–8%	• Advanced HIV • High dose • Pre-existing anemia or neutropenia • Concomitant use of bone marrow suppressants (e.g., cotrimoxazole, ganciclovir, valganciclovir, etc.) or drugs that cause hemolytic anemia (e.g., ribavirin)	• Avoid use in patients at risk • Avoid other bone marrow suppressants if possible • Monitor CBC with differential after the 1st few weeks, then at least every 3 months (more frequently in patients at risk)	• Switch to another NRTI if there is an alternative option; • Discontinue concomitant bone marrow suppressant if there is an alternative option; otherwise: For neutropenia: • Identify and treat other causes • Consider treatment with filgrastim For anemia: • Identify and treat other causes of anemia (if present) • Blood transfusion if indicated • Consider erythropoietin therapy
Cardiovascular effects [including myocardial infarction (MI)] and cerebrovascular accidents (CVA)	MI & CVA: associated with PI use MI only: Observational cohort found possible association of recent ABC & ddI use, and MI in pts with high risk for cardio-vascular events *[19]*	Onset: months to years after beginning of therapy Presentation: premature coronary artery disease or CVA	3–6 per 1,000 patient-years CVA: ~ 1 per 1,000 patient-years	Other risk factors for cardiovascular disease, such as smoking, age, hyperlipidemia, hypertension, diabetes mellitus, family history of premature coronary artery disease, and personal history of coronary artery disease	• Assess cardiac disease risk factors • Monitor & identify patients with hyperlipidemia or hyperglycemia • Consider regimen with less adverse lipid effects • Life style modification: smoking cessation, diet, and exercise	• Early diagnosis, prevention, and pharmacologic management of other cardiovascular risk factors, such as hyperlipidemia, hypertension, and insulin resistance/diabetes mellitus • Lifestyle modifications: diet, exercise, and/or smoking cessation • Switch to agents with less propensity for increasing cardiovascular risk factors
Central nervous system effects	EFV	Onset: begin with first few doses Symptoms: may include one or more of the following: drowsiness, somnolence, insomnia, abnormal dreams, dizziness, impaired concentration & attention span, depression, hallucination, exacerbation of psychiatric disorders, psychosis, suicidal ideation Most symptoms subside or diminish after 2–4 weeks	>50% of patients may have some symptoms	• Pre-existing or unstable psychiatric illnesses • Use of concomitant drugs with CNS effects • Higher plasma EFV concentrations in people with G-->T polymorphism at position 516 (516G-->T) of CYP2B6 *[20]*	• Take at bedtime or 2–3 hours before bedtime • Take on an empty stomach to reduce drug concentration & CNS effects • Warn patients regarding restriction of risky activities, such as operating heavy machinery during the 1st 2–4 weeks of therapy	• Symptoms usually diminish or disappear within 2–4 weeks • Consider switching to alternative agent if symptoms persist and cause significant impairment in daily function or exacerbation of psychiatric illness

Adverse Effects	Associated ARVs	Onset/Clinical Manifestation	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Gastrointestinal (GI) intolerance	All PIs, ZDV, ddI	Onset: within first doses Symptoms: • nausea, vomiting, abdominal pain with all listed agents • Diarrhea, most commonly seen with NFV	Varies with different agents	• All patients	•Taking with food may reduce symptoms (not recommended for ddI or unboosted IDV) • Some patients may require antiemetics or antidiarrheals pre-emptively to reduce symptoms	May spontaneously resolve or become tolerable with time; if not: For nausea & vomiting, consider: •Antiemetic prior to dosing •Switch to less emetogenic ARV For diarrhea, consider: • Bulk-forming agents, such as psyllium products • Antimotility agents, such as loperamide, diphenoxylate/atropine •Calcium tablets •Pancreatic enzymes •L-glutamate: may ↓ diarrhea, esp. when assoc. w/ NFV or LPV/r In case of severe GI loss: •Rehydration & electrolyte replacement as indicated
Hepatic failure	NVP	Onset: Greatest risk within first 6 weeks of therapy; can occur through 18 weeks Symptoms: Abrupt onset of flu-like symptoms (nausea, vomiting, myalgia, fatigue), abdominal pain, jaundice, or fever with or without skin rash; may progress to fulminant hepatic failure particularly in those with rash Approximately 1/2 of the cases have accompanying skin rash, some of which may present as part of DRESS syndrome (drug rash with eosinophilia and systemic symptoms)	Symptomatic hepatic events: • 4% overall (2.5%–11% from different trials) • In women: 11% in those w/ pre-NVP CD4 >250 cells/mm^3 vs. 0.9% w/ CD4 <250 cells/mm^3 • In men: 6.3% w/ pre-NVP CD4 >400 cells/mm^3 vs. 2.3% w/ CD4 <400 cells/mm^3	•Treatment-naive patients with higher CD4 count at initiation (>250 cells/mm^3 in women & >400 cells/mm^3 in men) •Females 3-fold higher risk than males •HIV (-) individuals when NVP is used for post-exposure prophylaxis •Possibly, high NVP concentrations	•Avoid initiation of NVP in women w/ CD4 >250 cells/mm^3 or men w/ CD4 >400 cells/mm^3 unless the benefit clearly outweighs the risk •Do not use NVP in HIV(-) individuals for post-exposure prophylaxis •Counsel patients re: signs & symptoms of hepatitis; stop NVP & seek medical attention if signs & symptoms of hepatitis, severe skin rash, or hypersensitivity reactions appear •Monitoring of ALT & AST (every 2 weeks x first month, then monthly x 3 months, then every 3 months) •Obtain AST & ALT in patients with rash •2-week dose escalation may reduce incidence of hepatic events	•Discontinue ARVs, including NVP (caution should be taken in discontinuation of 3TC, FTC, or TDF in HBV-coinfected patients) •Discontinue all other hepatotoxic agents if possible • Rule out other causes of hepatitis • Aggressive supportive care as indicated **Note:** Hepatic injury may progress despite treatment discontinuation. Careful monitoring should continue until symptom resolution. **Do not rechallenge patient with NVP.** The safety of other NNRTIs (e.g., EFV, ETR, or DLV) in patients who experienced significant hepatic event from NVP is unknown; use with caution.
Hepatotoxicity (clinical hepatitis or asymptomatic serum transaminase elevation)	All NNRTIs; all PIs; most NRTIs; maraviroc	Onset: NNRTIs: for NVP, 2/3 within 1st 12 weeks NRTIs: over months to years PIs: generally after weeks to months Symptoms/findings: **NNRTIs:** •Asymptomatic to non-specific symptoms, such as anorexia, weight loss, or fatigue. Approximately 1/2 of patients with NVP-associated symptomatic hepatic events present with skin rash. **NRTIs:** •ZDV, ddI, d4T: may cause hepatotoxicity associated with lactic acidosis with microvesicular or macrovesicular hepatic steatosis because of mitochondrial toxicity	Varies with the different agents	•HBV or HCV coinfection •Alcoholism •Concomitant hepatotoxic drugs, particularly rifampin •Elevated ALT &/or AST at baseline •For NVP-associated hepatic events: female w/ pre-NVP CD4 >250 cells/mm^3 or male w/ pre-NVP CD4 >400 cells/mm^3 •Higher drug concentrations for PIs, particularly TPV	•NVP: monitor liver-associated enzymes at baseline, at 2 & 4 weeks, then monthly for 1st 3 months; then every 3 months •TPV/RTV: contraindicated in patients with moderate to severe hepatic insufficiency; for other patients follow frequently during treatment •Other agents: monitor liver-associated enzymes at least every 3–4 months or more frequently in patients at risk	•Rule out other causes of hepatotoxicity, such as alcoholism, viral hepatitis, chronic HBV w/ 3TC, FTC, or TDF withdrawal, HBV resistance, etc. For symptomatic patients: •Discontinue all ARVs and other potential hepatotoxic agents •After symptoms subside & serum transaminases return to normal, construct a new ARV regimen without the potential offending agent(s) For asymptomatic patients: •If ALT >5–10x ULN, some may consider discontinuing ARVs, others may continue therapy with close monitoring unless direct bilirubin iw also elevated •After serum transaminases return to normal, construct a new ARV

Adverse Effects	Associated ARVs	Onset/Clinical Manifestation	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
		• 3TC, FTC, or TDF: HBV-coinfected patients may develop severe hepatic flare when these drugs are withdrawn or when resistance develops. **PIs:** • Clinical hepatitis & hepatic decompensation have been reported with TPV/r and also with other PIs to varying degrees. Underlying liver disease increases risk. • Generally asymptomatic, some with anorexia, weight loss, jaundice, etc.				regimen without the potential offending agent(s) **Note:** Refer to information regarding NVP-associated symptomatic hepatic events & NRTI-associated lactic acidosis with hepatic steatosis in this table
Hyperlipidemia	All PIs (except unboosted ATV); d4T; EFV; NVP (to a less extent)	Onset: weeks to months after beginning of therapy Presentation: All PIs (except unboosted ATV): ↑ in LDL & total cholesterol (TC), & triglyceride (TG). Also: ↑ HDL seen w/ ATV,DRV, FPV, LPV, SQV when boosted w/ RTV LPV/r *[21]* & FPV/r *[22]*: disproportionate ↑ in TG EFV & NVP (to a lesser extent): ↑ in LDL & TC, and slight ↑ TG; also ↑ HDL d4T & ZDV: ↑ in LDL, TC, & TG	Varies with different agents Swiss Cohort: ↑TC & TG: 1.7–2.3x higher in patients receiving (non-ATV) PI	• Underlying hyperlipidemia • Risk based on ARV therapy PI: All RTV-boosted PI may ↑ LDL& TG; ATV/r may produce less of an ↑ in LDL & TG NNRTI: EFV >NVP *[23]* NRTI: d4T >ZDV>ABC>TDF *[24, 25]*	• Assess cardiac disease risk factors • Use PIs and NNRTIs with less adverse effect on lipids and non–d4T-based regimen • Fasting lipid profile at baseline, at 3–6 months after starting new regimen, then annually or more frequently if indicated (in high-risk patients or in patients with abnormal baseline levels)	• Lifestyle modification: diet, exercise, and/or smoking cessation • Switching to agents with less propensity for causing hyperlipidemia Pharmacologic Management: • Per HIVMA/ACTG guidelines *[26]* & National Cholesterol Education Program ATP III guidelines *[27]* • For potential interactions between ARV and lipid lowering agents, refer to **Table 15**
Hypersensitivity reaction (HSR)	ABC	Onset of 1st reaction: median onset , 9 days; approximately 90% within 1st 6 weeks Onset of rechallenge reactions: within hours of rechallenge dose Usually >2–3 acute symptoms seen with HSR, in descending frequency): high fever, diffuse skin rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, respiratory symptoms (pharyngitis, dyspnea/tachypnea) With continuation of ABC, symptoms may worsen to include hypotension, respiratory distress, vascular collapse Rechallenge reactions: generally greater intensity than 1st reaction, can mimic anaphylaxis	Clinically suspected ≈ 8% in clinical trial (2%–9%); 5% in retrospective analysis; significantly reduced with pre-treatment HLA-B*5701screening *[16]*	• HLA-B*5701, HLA-DR7, HLA-DQ3 • Higher incidence of grade 3 or 4 HSR with 600mg once-daily dose than 300mg twice-daily dose in one study (5% vs. 2%)	• HLA-B*5701 screening prior to initiation of ABC • Those patients tested (+) for HLA-B*5701 should be labelled as allergic to abacavir in medical records • Educate patients about potential signs and symptoms of HSR and need for reporting of symptoms promptly • Wallet card with warning information for patients • Note multiple names for products containing abacavir (ABC, ZIAGEN, EPZICOM or KIVEXA, TRIZIVIR)	• Discontinue ABC and switch to another NRTI • Rule out other causes of symptoms (e.g., intercurrent illnesses such as viral syndromes, and other causes of skin rash) • Most signs and symptoms resolve 48 hours after discontinuation of ABC *More severe cases:* • Symptomatic support: antipyretic, fluid resuscitation, pressure support (if necessary) • **Do not rechallenge patients with ABC after suspected HSR, even in patients who are (-) for HLA-B*5701. There are cases of hypersensitivity in HLA-B*5701 (-) patients.**
Insulin resistance/ diabetes mellitus (DM)	Combination ART, thymidine analogs (ZDV, d4T), some PIs linked to insulin resistance and diabetes mellitus (but this may not be a class effect)	Onset: weeks to months after beginning of therapy Presentation: Polyuria, polydipsia, polyphagia, fatigue, weakness; exacerbation of hyperglycemia in patients with underlying DM	Up to 3%–5% of patients developed diabetes in some series; D:A:D cohort incidence rate of 5.72 per 1,000 pt-yr f/up (95% CI: 5.31-6.13) *[28]* Incidence of DM in HIV (+) women in WHIS (2.5–2.9 pt- yrs) not different	• Family history of DM	• Use non–-thymidine analog–containing regimens or NNRTIs • Fasting blood glucose 1–3 months after starting new regimen, then at least every 3–6 months	• Diet and exercise • Consider switching to non–thymidine analog–containing ART • Consider switching PI to an alternative PI and/or NNRTI • Pharmacotherapeutic management per American Diabetic Association and American Association of Clinical Endocrinologists guidelines *[30, 31]*

Adverse Effects	Associated ARVs	Onset/Clinical Manifestation	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
			from HIV(-) pts *[29]* and associated with NRTIs			
Lactic acidosis/ hepatic steatosis +/- pancreatitis (severe mitochondrial toxicities)	NRTIs, esp. d4T, ddI, ZDV	Onset: months after initiation of NRTIs Symptoms: • Insidious onset with nonspecific GI prodrome (nausea, anorexia, abdominal pain, vomiting), weight loss, and fatigue; • Subsequent symptoms may be rapidly progressive, with tachycardia, tachypnea, hyperventilation, jaundice, muscular weakness, mental status changes, or respiratory distress • Some may present with multi-organ failure (e.g., hepatic failure, acute pancreatitis, encephalopathy, and respiratory failure) Laboratory findings: • Increased lactate (often >5 mmol/L) • Low arterial pH (some as low as <7.0) • Low serum bicarbonate • Increased anion gap • Elevated serum transaminases, prothrombin time, bilirubin • Low serum albumin • Increase serum amylase & lipase in patients with pancreatitis • Histologic findings of the liver: microvesicular or macrovesicular steatosis Mortality up to 50% in some case series, esp. in patients with serum lactate >10 mmol/L	Rare Depends on regimen and patient sex: U.S.: 0.85 cases per 1,000 pt-yrs *[32]* South Africa: 16.1 per 1,000 pt-yrs in female & 1.2 cases per 1,000 pt-yrs in male patients[7]	• d4T + ddI • d4T, ZDV, ddI use (d4T most frequently implicated) • Long duration of NRTI use • Female gender • Obesity • Pregnancy (esp. with d4T + ddI) • ddI + hydroxyurea or ribavirin	• Routine monitoring of lactic acid not recommended • Consider obtaining lactate levels in patients with low serum bicarbonate or high anion gap and with complaints consistent with lactic acidosis • Appropriate phlebotomy technique for obtaining lactate level should be employed	• For mild cases, consider switching off offending drugs to safe alternatives • For severe lactic acidosis, discontinue all ARVs if this syndrome is highly suspected (diagnosis is established by clinical correlations, drug history, and lactate level) • Symptomatic support with fluid hydration • Some patients may require IV bicarbonate infusion, hemodialysis or hemofiltration, parenteral nutrition, or mechanical ventilation • IV thiamine and/or riboflavin, which resulted in rapid resolution of hyperlactatemia in some case reports **Note:** • Interpretation of high lactate level should be done in the context of clinical findings • The implication of asymptomatic hyperlactatemia is unknown at this point **ARV treatment options**: • Use NRTIs with less propensity for mitochondrial toxicity (e.g., ABC, TDF, 3TC, FTC) • Recommend close monitoring of serum lactate after restarting NRTIs • Consider NRTI-sparing regimens
Lipodystrophy	Lipo-atrophy: NRTIs (d4T > ZDV > TDF, ABC, 3TC, FTC), especially when combined with EFV *[33]* Lipo-hypertrophy: Abdominal fat gain seen with PI- or NNRTI-based regimens & with thymidine analogs (e.g., d4T, ZDV)	Onset: gradual: months after initiation of therapy Symptoms: • Lipoatrophy: peripheral fat loss manifested as facial thinning and as thinning of extremities and buttocks (d4T) • Lipohypertrophy: increase in abdominal girth, breast size, and dorsocervical fat pad (buffalo hump)	High: exact frequency uncertain and dependent on regimen; increases with duration on offending agents	• Both lipoatrophy & lipohypertrophy: low baseline body mass index	• Lipoatrophy: avoid thymidine analogs (esp. when combined with EFV), or switch from ZDV or d4T to ABC or TDF • Lipohypertrophy: pretreatment diet/exercise program may reduce incidence and extent	Lipoatrophy: • Switch from thymidine analogs to TDF or ABC: may slow or halt progression; however, may not fully reverse effects • Injectable poly-L-lactic acid or other injectable fillers for treatment of facial lipoatrophy Lipohypertrophy: • Liposuction for dorsocervical fat pad enlargement (recurrence common) • Diet/exercise • Recombinant human growth hormone, under investigation
Nephrolithiasis/ urolithiasis/ crystalluria	IDV, ATV	Onset: any time after beginning of therapy, especially at times of reduced fluid intake Laboratory abnormalities: pyuria, hematuria, crystalluria; rarely, rise	IDV: 12.4% of nephrolithiasis reported in clinical trials (4.7%–34.4% in different	• History of nephrolithiasis • Patients unable to maintain adequate fluid intake	• Drink at least 1.5–2 liters of non-caffeinated fluid (preferably water) per day • Increase fluid intake at	• Increase hydration • Pain control • May consider switching to alternative agent or therapeutic drug monitoring (IDV) if treatment option is limited

Adverse Effects	Associated ARVs	Onset/Clinical Manifestation	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
		in serum creatinine & acute renal failure Symptoms: flank pain and/or abdominal pain (can be severe), dysuria, frequency	trials) ATV: rare; case reports only	•High peak IDV concentration (↑ATV levels not found to correlate with risk) •↑duration of exposure •warmer climate	first sign of darkened urine •Monitor urinalysis and serum creatinine every 3–6 months	•Stent placement may be required
Nephrotoxicity	IDV, TDF	Onset: IDV: months after therapy TDF: weeks to months after therapy Laboratory and other findings: IDV: ↑ serum creatinine, pyuria; hydronephrosis or renal atrophy TDF: ↑ serum creatinine, proteinuria, hypophosphatemia, glycosuria, hypokalemia, non-anion gap metabolic acidosis Symptoms: IDV: asymptomatic; rarely progresses to end-stage renal disease TDF: asymptomatic to signs of nephrogenic diabetes insipidus, Fanconi syndrome with weakness and myalgias	Severe toxicity is rare	IDV and TDF: •History of renal disease; elevated creatinine at baseline •Concomitant use of nephrotoxic drugs •TDF: advanced age, low body weight, low CD4 count	•Avoid use of other nephrotoxic drugs •Adequate hydration if on IDV therapy •Monitor serum creatinine, urinalysis, serum potassium and phosphorus in patients at risk	•Stop offending agent, generally reversible •Supportive care •Electrolyte replacement as indicated
Neuro-muscular weakness syndrome (ascending)	Most frequently implicated ARV: d4T	Onset: months after initiation of ARV; then dramatic motor weakness occurring within days to weeks Symptoms: very rapidly progressive ascending demyelinating polyneuropathy, may mimic Guillain-Barré syndrome; some patients may develop respiratory paralysis requiring mechanical ventilation; has resulted in deaths in some patients Laboratory findings may include: •lactic acidosis reported in some cases •Markedly increased creatine phosphokinase	Rare	•Prolonged d4T use (found in 61 of 69 [88%] cases in one report) *[34]*	•Early recognition and discontinuation of ARVs may avoid further progression	•Discontinuation of ARVs •Supportive care, including mechanical ventilation if needed (as in cases of lactic acidosis listed previously) •Other measures attempted with variable success: plasmapheresis, high-dose corticosteroid, intravenous immunoglobulin, carnitine, acetylcarnitine •Recovery often takes months and ranges from complete recovery to substantial residual deficits •Symptoms may be irreversible in some patients **Do not rechallenge patient with offending agent.**
Osteonecrosis	Link to older PIs, but unclear whether it is caused by ARVs or by HIV	Clinical presentation (generally similar to non–HIV-infected population): •Insidious in onset, with subtle symptoms of mild to moderate periarticular pain •85% of cases involving one or both femoral heads, but other bones may also be affected •Pain may be triggered by weight bearing or movement	Symptomatic osteonecrosis: 0.08%–1.33%Asymptomatic osteonecrosis: 4% from MRI reports	•Diabetes •Advanced HIV disease •Prior steroid use •Old age •Alcohol use •Hyperlipidemia •Role of ARVs and osteonecrosis is still controversial	•Risk reduction (e.g., limit steroid and alcohol use) •Asymptomatic cases w/ <15% bony head involvement: follow with MRI every 3–6 months x 1 yr, then every 6 months x 1 yr, then annually to assess for disease progression	Conservative management**:** • ↓ weight bearing on affected joint; • Remove or reduce risk factors • Analgesics as needed Surgical Intervention: •Core decompression +/- bone grafting for early stages of disease •For more severe and debilitating disease. total joint arthroplasty
Osteopenia (defined as DEXA scan t-score of 1–2.5 SD from normal) or osteoporosis (t-score >2.5 SD from normal)	Some evidence for early but not progressive bone loss after starting variety of ARVs; Assoc/ with TDF or d4T; ↓ bone density and	Onset: months to years after starting ART Symptoms: generally asymptomatic, bone pain, increased risk of fractures	Wide range depending on methodology & patient population;rate appears much higher than seen in the general population: osteopenia: 20%–54%	General: low body weight, female, white, southeast Asian, older age, alcohol use, smoking, caffeine, hypogonadism, hyperthyroidism, corticosteroids, vitamin D deficiency, history of significant weight loss, TDF	•Consider assessment of bone mineral density with DEXA scan (baseline and f/u if abnormal; proper interval in setting of HIV(+) not determined) *[36]* •Weight-bearing exercise •Calcium & vitamin D supplementation	•Switch from potentially contributing ARVs (i.e., d4T or TDF) & stop other contributing drugs • Follow National Osteoporosis Foundation guidelines *[37]* • Increase exercise, improve diet, decrease alcohol & tobacco use, increase calcium & vitamin D supplementation • Bisphosphonate (e.g., once weekly alendronate) • Judicious hormone replacement

Adverse Effects	Associated ARVs	Onset/Clinical Manifestation	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
	markers of bone turnover with TDF observed in randomized clinical trials		*[35]*; osteoporosis: 2%–27% *[35]*	exposure HIV: low CD4 T-cell count, duration of HIV, lipoatrophy, increased lactic acid levels	• Hormone replacement	• Intranasal calcitonin
Pancreatitis	ddI alone; ddI + d4T, hydroxyurea (HU), ribavirin (RBV), or TDF	Onset: usually weeks to months Laboratory abnormalities: increased serum amylase and lipase Symptoms: postprandial abdominal pain, nausea, vomiting	ddI alone: 1%–7% ddI with HU: ↑ by 4–5-fold ↑ frequency if ddI use w/ d4T, TDF, or ribavirin	• High intraceullar and/or serum ddI concentrations • History of pancreatitis • Alcoholism • Hypertriglyceridemia • Concomitant use of ddI with d4T, HU, or RBV • Use of ddI + TDF without ddI dose reduction	• ddI should not be used in patients with history of pancreatitis • Avoid concomitant use of ddI with d4T, TDF, HU, or RBV • Reduce ddI dose when used with TDF • Monitoring of amylase/lipase in asymptomatic patients is generally not recommended • Treat hypertriglyceridemia	• Discontinue offending agent(s) • Symptomatic management of pancreatitis: bowel rest, IV hydration, pain control, then gradual resumption of oral intake • Parenteral nutrition may be necessary in patients with recurrent symptoms upon resumption of oral intake
Peripheral neuropathy	ddI, d4T, ddC	Onset: weeks to months after initiation of therapy (may be sooner in patients with pre-existing neuropathy) Symptoms: • Begins with numbness & paresthesia of toes and feet • May progress to painful neuropathy of feet and calf • Upper extremities less frequently involved • Can be debilitating for some patients • May be irreversible despite discontinuation of offending agent(s)	ddI: 12%–34% in clinical trials d4T: 52% in monotherapy trial ddC: 22%–35% in clinical trials Incidence increases with prolonged exposure	• Pre-existing peripheral neuropathy; • Combined use of these NRTIs or concomitant use of other drugs that may cause neuropathy • Advanced HIV disease • High dose or concomitant use of drugs that may increase ddI intracellular activities (e.g., HU or RBV)	• Avoid using these agents in patients at risk, if possible • Avoid combined use of these agents • Patient query at each encounter	• Discontinue offending agent if alternative is available; may halt further progression, but symptoms may be irreversible • Substitute alternative ART without potential for neuropathy Pharmacologic management (with variable successes): • Gabapentin (most experience), tricyclic antidepressants, lamotrigine, oxycarbamazepine (potential for CYP interactions), topiramate, tramadol • Narcotic analgesics • Topical capsaicin • Topical lidocaine
Stevens-Johnson syndrome (SJS)/ Toxic epidermal necrosis (TEN)	NVP > EFV, DLV, ETR Also reported with APV, FPV, ABC, DRV, ZDV, ddI, IDV, LPV/r, ATV	Onset: first few days to weeks after initiation of therapy but can occur later Symptoms: • Skin eruption with mucosal ulcerations (may involve orogingival mucosa, conjunctiva, anogenital area) • Can rapidly evolve with blister or bullae formation • May eventually evolve to epidermal detachment and/or necrosis • For NVP, may occur with hepatic toxicity • Systemic symptoms (e.g., fever, tachycardia, malaise, myalgia, arthralgia) may be present Complications: ↓ oral intake; fluid depletion; bacterial or fungal superinfection; multiorgan failure	NVP: 0.3%–1%; DLV & EFV: 0.1%; ETR: <0.1% 1–2 case reports for ABC, FPV, ddI, ZDV, IDV, LPV/r, ATV, DRV	• NVP: Female, Black, Asian, Hispanic	• For NVP: 2-week lead-in period with 200mg once daily, then escalate to 200mg twice daily • Educate patients to report symptoms as soon as they appear • Avoid use of corticosteroid during NVP dose escalation: may increase incidence of rash	• Discontinue all ARVs and any other possible agent(s) (e.g., cotrimoxazole) Aggressive symptomatic support may include: • Intensive care support • Aggressive local wound care (e.g., in a burn unit) • Intravenous hydration • Parenteral nutrition, if needed • Pain management • Antipyretics • Empiric broad-spectrum antimicrobial therapy if superinfection is suspected Controversial management strategies: • Corticosteroid • Intravenous immunoglobulin **Do not rechallenge patient with offending agent.** • It is unknown whether patients who experienced SJS while on one NNRTI are more susceptible to SJS from another NNRTI. Most experts would suggest avoiding use of this class unless no other options are available.

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DRUG INTERACTIONS (Updated November 3, 2008)

Potential drug-drug and/or drug-food interactions should be taken into consideration when selecting an antiretroviral regimen. A thorough review of current medications can help in designing a regimen that minimizes undesirable interactions. Moreover, review of drug interaction potential should be undertaken when any new drug, including over-the-counter agents, is added to an existing antiretroviral combination. **Tables 14–16b** list significant drug interactions with different antiretroviral agents and suggested recommendations on contraindications, dose modifications, and alternative agents.

PI and NNRTI Drug Interactions

Most drug interactions with antiretrovirals are mediated through inhibition or induction of hepatic drug metabolism *[1]*. All PIs and NNRTIs are metabolized in the liver by the CYP 450 system, particularly by the CYP3A4 isoenzyme. The

list of drugs that may have significant interactions with PIs or NNRTIs is extensive and is continuously expanding. Some examples of these drugs include medications that are commonly prescribed in HIV patients for non-HIV medical conditions, such as lipid-lowering agents (e.g., statins), benzodiazepines, calcium channel blockers, immunosuppressants (e.g., cyclosporine and tacrolimus), anticonvulsants, rifamycins, erectile dysfunction agents (e.g., sildenafil), ergot derivatives, azole antifungals, macrolides, oral contraceptives, and methadone. Herbal products, such as St. John's wort, can also cause negative interactions.

All PIs are substrates of CYP3A4, so their metabolic rates may be altered in the presence of CYP inducers or inhibitors. Some PIs may also be inducers or inhibitors of other CYP isoenzymes and of P-glycoprotein or other transporters. Tipranavir, for example, is a potent inducer of P-glycoprotein. The net effect of tipranavir/ritonavir on CYP3A *in vivo* appears to be enzyme inhibition. Thus, concentrations of drugs that are substrates for only CYP3A are likely to be increased if given with tipranavir/ritonavir. The net effect of tipranavir/ritonavir on a drug that is a substrate for both CYP3A and P-glycoprotein cannot be confidently predicted; significant decreases in saquinavir, amprenavir, and lopinavir concentrations have been observed *in vivo* when given with tipranavir/ritonavir.

The NNRTIs are also substrates of CYP3A4 and can act as an inducer (nevirapine), an inhibitor (delavirdine), or a mixed inducer and inhibitor (efavirenz). Etravirine is a substrate of CYPs 3A4, 2C9, and 2C19. It is also an inducer of CYP3A4 and an inhibitor of 2C9 and 2C19. Thus, these antiretroviral agents can interact with each other in multiple ways and with other drugs commonly prescribed for other concomitant diseases.

The use of a CYP3A4 substrate that has a narrow margin of safety in the presence of a potent CYP3A4 inhibitor may lead to markedly prolonged elimination half-life ($t_{1/2}$) and toxic drug accumulation. Avoidance of concomitant use or dose reduction of the affected drug, with close monitoring for dose-related toxicities, may be warranted.

The inhibitory effect of ritonavir, however, can be beneficial when added to a PI, such as atazanavir, fosamprenavir, or indinavir *[2]*. The PIs darunavir, lopinavir, saquinavir, and tipranavir require coadministration with ritonavir. Lower-than-therapeutic doses of ritonavir are commonly used in clinical practice as a pharmacokinetic enhancer to increase the trough concentration (C_{min}) and prolong the half-life of the active PIs *[3]*. The higher C_{min} allows for a greater C_{min}: IC_{50} ratio, which reduces the chance for development of drug resistance as a result of suboptimal drug exposure; the longer half-life allows for less frequent dosing, which may enhance medication adherence.

Coadministration of PIs or NNRTIs with a potent CYP3A4 inducer, on the other hand, may lead to suboptimal drug concentrations and reduced therapeutic effects of the antiretroviral agents. These drug combinations should be avoided if alternative agents can be used. If this is not possible, close monitoring of plasma HIV RNA, with or without antiretroviral dosage adjustment and therapeutic drug monitoring (TDM), may be warranted. For example, the rifamycins (i.e., rifampin and, to a lesser extent, rifabutin) are CYP3A4 inducers that can significantly reduce plasma concentrations of most PIs and NNRTIs *[4, 5]*. As rifabutin is a less potent inducer, it is generally considered a reasonable alternative to rifampin for the treatment of TB when it is used with a PI- or NNRTI-based regimen, despite wider experience with rifampin use *[6]*. **Table 15** lists dosage recommendations for concomitant use of rifamycins and other CYP3A4 inducers with PIs and NNRTIs.

NRTI Drug Interactions

Unlike PIs and NNRTIs, NRTIs do not undergo hepatic transformation through the CYP metabolic pathway. Some, however, do have other routes of hepatic metabolism. Significant pharmacodynamic interactions of NRTIs and other drugs have been reported. They include increases in intracellular drug levels and toxicities when didanosine is used in combination with hydroxyurea *[7, 8]* or ribavirin *[9]*; additive bone marrow suppressive effects of zidovudine and ganciclovir *[10]*; and antagonism of intracellular phosphorylation with the combination of zidovudine and stavudine *[11]*. Pharmacokinetic interactions have also been reported. However, the mechanisms of some of these interactions are still unclear. Examples of such interactions include increases of didanosine concentration in the presence of oral ganciclovir or tenofovir *[12, 13]* and decreases in atazanavir concentration when atazanavir is coadministered with tenofovir *[14, 15]*. **Table 15c** lists significant interactions with NRTIs.

CCR5 Antagonist Drug Interaction

Maraviroc, the first FDA-approved CCR5 antagonist, is a substrate of CYP3A enzymes and P-glycoprotein. As a consequence, the concentrations of maraviroc can be significantly increased in the presence of strong CYP3A inhibitors (such as ritonavir and other PIs, except for ritonavir-boosted tipranavir) and are reduced when used with CYP3A inducers, such as efavirenz or rifampin. Dose adjustment is necessary when used in combination with these agents (See **Appendix Table 6** for dosage recommendations.). Maraviroc is neither an inducer nor an inhibitor of the CYP3A system. It does not alter the pharmacokinetics of the drugs evaluated in interaction studies to date.

Fusion Inhibitor Drug Interaction

The fusion inhibitor enfuvirtide is a 36–amino acid peptide that does not enter human cells. It is expected to undergo catabolism to its constituent amino acids with subsequent recycling of the amino acids in the body pool. No clinically significant drug-drug interaction has been identified with enfuvirtide to date.

Integrase Inhibitor Drug Interaction

Raltegravir, an HIV integrase strand transfer inhibitor, is primarily eliminated by glucuronidation that is mediated by the UDP-glucuronosyltransferase (UGT1A1) enzymes. Strong inducers of UGT1A1 enzymes (e.g., rifampin) can significantly reduce the concentration of raltegravir. The significance of this interaction is unknown; thus, this combination should be used with caution or an alternative therapy should be considered. Other inducers of UGT1A1, such as efavirenz, tipranavir/ritonavir, or rifabutin, can also reduce raltegravir concentration. A pharmacokinetic interaction should be considered if optimal virologic response is not achieved when these drugs are used in combination.

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Table 14. Drugs That Should Not Be Used With PI, NNRTI, or CCR5 Antagonist Antiretrovirals
(Updated January 29, 2008)

Drug Category#	Calcium Channel Blockers	Cardiac Agents	Lipid Lowering Agents	Anti mycobacterials‡	Anti-histamines ∂	Gastro-intestinal Drugs∂	Neuro-leptics	Psychotropics	Ergot Alkaloids (vasoconstrictors)	Herbs	Others
Atazanavir	Bepridil	(none)	simvastatin lovastatin	rifampin rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam∑ triazolam	dihydroergotamine (D.H.E. 45) ergotamine† (various forms) ergonovine methylergonovine	St. John's wort	fluticasone indinavir irinotecan proton pump inhibitor (not recommended for unboosted ATV)
Darunavir/ ritonavir	(none)	(none)	simvastatin lovastatin	rifampin rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam∑ triazolam	as above	St. John's wort	carbamazepine phenobarbital phenytoin fluticasone⊗
Fosamprenavir	Bepridil	(none)	simvastatin lovastatin	rifampin rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam∑ triazolam	as above	St. John's wort	Delavirdine fluticasone oral contraceptives
Indinavir	(none)	amiodarone	simvastatin lovastatin	rifampin rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam∑ triazolam	as above	St. John's wort	atazanavir
Lopinavir/ ritonavir	(none)	flecainide propafenone	simvastatin lovastatin	rifampin∫ rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam∑ triazolam	as above	St. John's wort	fluticasone⊗
Nelfinavir	(none)	(none)	simvastatin lovastatin	rifampin rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam∑ triazolam	as above	St. John's wort	
Ritonavir	Bepridil	amiodarone flecainide propafenone quinidine	simvastatin lovastatin	rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam∑ triazolam	as above	St. John's wort	voriconazole (with RTV ≥400mg BID) fluticasone⊗ alfuzosin
Saquinavir/ ritonavir	(none)	(none)	simvastatin lovastatin	rifampin∫ rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam ∑ triazolam	as above	St. John's wort garlic supplements	fluticasone⊗
Tipranavir/ ritonavir	Bepridil	amiodarone flecainide propafenone quinidine	simvastatin lovastatin	rifampin rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam ∑ triazolam	as above	St. John's wort	fluticasone⊗
Delavirdine	(none)	(none)	simvastatin lovastatin	rifampin rifapentine‡ rifabutin	astemizole terfenadine	cisapride	(none)	alprazolam midazolam∑ triazolam	as above	St. John's wort	fosamprenavir carbamazepine phenobarbital phenytoin
Efavirenz	(none)	(none)	(none)	rifapentine‡	astemizole terfenadine	cisapride	(none)	midazolam∑ triazolam	as above	St. John's wort	
Etravirine	(none)	(none)	(none)	rifampin rifapentine‡	(none)	(none)	(none)	(none)	(none)	St John's wort	Unboosted PIs, ritonavir-boosted atazanavir, fosamprenavir, or tipranavir, other NNRTIs, carbamazepine, phenobarbital, phenytoin
Nevirapine	(none)	(none)	(none)	rifapentine‡	(none)	(none)	(none)	(none)	(none)	St. John's wort	
Maraviroc	•	•	•	rifapentine‡	•	•	•	•	•	St. John's wort	•

\# Certain listed drugs are contraindicated based on theoretical considerations. Thus, drugs with narrow therapeutic indices and suspected metabolic involvement with CYP450 3A, 2D6, or unknown pathways are included in this table. Actual interactions may or may not occur among patients.

‡ HIV patients treated with rifapentine have a higher rate of TB relapse than those treated with other rifamycin-based regimens; an alternative agent is recommended.

∫ A high rate of grade 4 serum transaminase elevation was seen when a higher dose of ritonavir was added to lopinavir/ritonavir or saquinavir or when double-dose lopinavir/ritonavir was used with rifampin to compensate for rifampin's induction effect, so these dosing strategies should not be used.

∑ Contraindicated with oral midazolam. Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation.

† This is likely a class effect.

∂ Astemizole and terfenadine are not marketed in the United States. The manufacturer of cisapride has a limited-access protocol for patients who meet specific clinical eligibility criteria.

⊗ Concomitant use of fluticasone and ritonavir results in significantly reduced serum cortisol concentrations. Coadministration of fluticasone and ritonavir or any ritonavir-boosted PI regimen is not recommended unless potential benefit outweighs risk of systemic corticosteroid adverse effects. Fluticasone should be used with caution, and alternatives should be considered, if given with an unboosted PI regimen.

Suggested Alternatives to:

Lovastatin, simvastatin: Pravastatin and fluvastatin have the least potential for drug-drug interactions (except for pravastatin with darunavir/ritonavir, see **Table 15a**); atorvastatin and rosuvastatin - use with caution, start with the lowest possible dose and titrate based on tolerance and lipid-lowering efficacy.

Rifampin: Rifabutin (with dosage adjustment – see **Tables 15a and b**)

Astemizole, terfenadine (no longer marketed in the United States): desloratadine, loratadine, fexofenadine, cetirizine

Midazolam, triazolam: temazepam, lorazepam

Table 15a. Drug Interactions Between Protease Inhibitors (PIs) and Other Drugs

This table provides information relating to pharmacokinetic interactions between PIs and non-antiretroviral drugs. When information is available, interactions with boosted and unboosted PIs are listed separately. For interactions among antiretroviral agents and dosing recommendations, please refer to **Table 16a**.

Concomitant Drug Class/Name	Protease Inhibitor (PI)	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Antacids	ATV ± RTV	No data	↓ ATV concentrations expected when given simultaneously. Give ATV at least 2 hrs before or 1 hr after antacids or buffered medications.
	FPV	APV AUC ↓ 18%; Cmin: no significant change	Can be given simultaneously or separated at least 2 hrs before or 1 hr after antacids.
	DRV/r, FPV/r, IDV ± RTV, LPV/r, NFV, SQV/r	No data	
	TPV/r	↓ TPV ~30%	Give TPV at least 2 hrs before or 1 hr after antacids.
H_2 Receptor Antagonists	**RTV-boosted PI**		
	ATV/r	↓ ATV	H_2 receptor antagonist dose should not exceed a dose equivalent to famotidine 40mg BID in treatment-naïve patients or 20mg BID in treatment-experienced patients. ATV 300mg + RTV 100mg should be administered simultaneously with and/or ≥10 hours after the H_2 receptor antagonist. In treatment-experienced patients, if TDF is used with H_2 receptor antagonists, ATV 400mg + RTV 100mg should be used.
	DRV/r, LPV/r	No effect	
	FPV/r, SQV/r, TPV/r	No data	
	PIs without RTV:		
	ATV	↓ ATV	H_2 receptor antagonist single dose should not exceed a dose equivalent of famotidine 20mg or total daily dose equivalent of famotidine 20mg BID in treatment-naïve patients. ATV should be administered ≥2 hours before and/or ≥10 hours after the H_2 receptor antagonist.
	FPV	APV AUC ↓ 30%; Cmin: unchanged	Separate administration if coadministration is necessary. Consider boosting with RTV.
	IDV, NFV	No data	
Proton Pump Inhibitors (PPIs)	ATV	↓ ATV	**PPIs are not recommended in patients receiving unboosted ATV.** In these patients, consider alternative acid-reducing agents, ritonavir-boosting, or alternative PIs.
	ATV/r	↓ ATV	PPIs should not exceed a dose equivalent to omeprazole 20mg daily in treatment-naïve patients. PPIs should be administered ≥ 12 hrs prior to ATV/r. **PPIs are not recommended in treatment-experienced patients**.
	DRV/r, FPV ± RTV, LPV/r,	No effect	
	IDV ± RTV	No data	
	NFV	NFV AUC ↓ 36% M8 AUC ↓ 92%	**Do not coadminister PPIs and NFV.**
	SQV/r	SQV AUC ↑ 82%	Monitor for SQV toxicities.
	TPV/r	↓ omeprazole, TPV: no effect	May need to increase omeprazole dose.

Concomitant Drug Class/Name	Protease Inhibitor (PI)	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antifungals			
Fluconazole	**RTV-boosted PI**		
	ATV/r	No effect	
	DRV/r, FPV/r, IDV/r, LPV/r	No data	
	SQV/r	No data with RTV-boosting; SQV AUC ↑ 50%, Cmax ↑ 56% with SQV 1200mg TID	
	TPV/r	TPV AUC ↑ 50%, Cmax ↑ 32%, Cmin ↑ 69%	Fluconazole >200mg daily not recommended.
	PIs without RTV		
	ATV, FPV, NFV	No data	
	IDV	No effect	
Itraconazole	**RTV-boosted PI**		
	ATV/r, DRV/r, FPV/r, IDV/r, TPV/r	No data	Potential for bi-directional inhibition between itraconazole and PIs. Consider monitoring itraconazole level to guide dosage adjustments. High doses (>200 mg/day) are not recommended.
	LPV/r	↑ itraconazole	Consider not exceeding 200mg itraconazole daily, or monitor itraconazole level.
	SQV/r	Bi-directional interaction has been observed.	Dose not established, but decreased itraconazole dosage may be warranted. Consider monitoring itraconazole level.
	PIs without RTV:		
	ATV, FPV, NFV	No data	Potential for bi-directional inhibition between itraconazole and PIs. Consider monitoring itraconazole level to guide dosage adjustments.
	IDV	↑ IDV IDV 600mg Q8H + itraconazole 200mg BID: AUC similar to IDV 800mg Q8H	Dose: IDV 600mg Q8H (without ritonavir); Do not exceed 200mg itraconazole BID. Dosing of IDV when used with ritonavir and itraconazole not established.
Ketoconazole	**RTV-boosted PI**:		
	ATV/r, FPV/r	↑ ketoconazole levels	Use with caution. Do not exceed 200mg ketoconazole daily. Potential for bidirectional interaction between ketoconazole & IDV/r, SQV/r, TPV/r.
	DRV/r	DRV AUC ↑ 42%, ketoconazole ↑ 3-fold	
	IDV/r	No data	
	LPV/r	May ↑ or ↓ LPV , ketoconazole ↑ 3-fold	
	SQV/r	SQV ↑ 3x (when ketoconazole used with unboosted SQV)	
	TPV/r	No data	
	PIs without RTV:		
	ATV, NFV		No dosage adjustment necessary.
	FPV	No data with FPV ↑ APV ↑ ketoconazole	Consider ketoconazole dose reduction if dose is >400mg/day. Presumably similar interaction as seen with APV: APV ↑ 31%; ketoconazole ↑ 44%
	IDV	↑ IDV	Dose: IDV 600mg Q8H. Levels: IDV ↑ 68% IDV dosage when used with ritonavir and ketoconazole has not been established.
Posaconazole	All PIs	No data	
Voriconazole	**RTV-boosted PI**		
	ATV/r, DRV/r, FPV/r, IDV/r, LPV/r, SQV/r, TPV/r	voriconazole AUC ↓ 82% with RTV 400mg BID and ↓ 39% with RTV 100mg BID	Administration of voriconazole and RTV 100mg once daily or BID is not recommended unless benefit outweighs risk. Consider monitoring voriconazole level. **Administration of voriconazole and RTV 400mg BID or higher is contraindicated.**
	PIs without RTV:		
	ATV FPV NFV	No data	Potential for bi-directional inhibition between voriconazole and PIs. Monitor for toxicities.
	IDV	No significant effect	No dose adjustment.

Concomitant Drug Class/Name	Protease Inhibitor (PI)	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anticonvulsants			
Carbamazepine Phenobarbital Phenytoin	**RTV-boosted PI**		
	ATV/r, DRV/r, IDV/r, LPV/r SQV/r, TPV/r	↑ carbamazepine ↓ PI level	Consider alternative anticonvulsant or monitor levels of both drugs.
	FPV/r	↓ phenytoin ↑ APV	Monitor anticonvulsant level, and adjust dose accordingly. No change in FPV/r dose recommended.
	LPV/r	↓ phenytoin ↓ phenobarbital ↓ LPV/r level May ↓ other PI levels	Consider alternative anticonvulsant or monitor levels of both drugs.
	PIs without RTV:		
	ATV FPV NFV	No data May ↓ PI levels substantially NFV ↓ phenytoin	Monitor anticonvulsant level and virologic response. Consider alternative anticonvulsant, RTV boosting for ATV and FPV, and/or monitoring PI level.
	IDV	↓ IDV	Consider alternative anticonvulsant, RTV boosting, and/or monitoring IDV level.
Anti-mycobacterials			
Clarithromycin	ATV ± RTV	clarithromycin AUC ↑ 94%	May cause QTc prolongation. Reduce clarithromycin dose by 50%. Consider alternative therapy.
	DRV/r IDV ± RTV LPV/r SQV/r TPV/r	DRV/r ↑ Clar AUC 57%; IDV ↑ Clar AUC 53%; LPV/r ↑ Clar AUC 77%; RTV ↑ Clar 77%; SQV ↑ Clar 45%; Clar ↑ SQV 177%; TPV/r ↑ Clar 19% and ↓ active metabolite 97%; Clar ↑ TPV 66%	Reduce clarithromycin dose by 50% in patients with CrCl 30-60mL/min. Reduce clarithromycin dose by 75% in patients with CrCl <30mL/min.
	FPV	↑ APV	No dose adjustment.
	NFV	No data	
	RTV-boosted PI:		
Rifabutin	ATV ± RTV FPV/r DRV/r IDV/r LPV/r SQVr TPV/r	ATV ↑ rifabutin AUC 2.5-fold; FPV/r, DRV/r, IDV/r: no PK data, expect ↑ rifabutin; RTV (500mg bid) ↑ rifabutin 4X; LPV/r ↑ rifabutin AUC 3-fold, ↑ 25-O-desacetyl metabolite 47.5-fold; Rifabutin ↓ unboosted SQV 40%; TPV/r ↑ rifabutin AUC 2.9-fold, ↑ 25-O-desacetyl metabolite 20.7-fold	Rifabutin 150mg QOD or 3x/week. Acquired rifamycin resistance has been reported in patients with inadequate rifabutin levels while on 150mg twice weekly and RTV-boosted PIs. May consider therapeutic drug monitoring and adjust dose accordingly.
	PIs without RTV:		
	FPV	↑ rifabutin	Rifabutin 150mg daily or 300mg 3x/week
	IDV	↑ rifabutin ↓ IDV	Rifabutin 150mg daily or 300mg 3x/week + IDV 1,000mg q8h or consider RTV boosting. Levels: rifabutin ↑ 2X, IDV ↓ 32%
	NFV	↑ rifabutin 2X; ↓ NFV 750mg Q8H 32%	Rifabutin 150mg daily or 300mg 3x/week
Rifampin	All PIs	Approximately >75% ↓ in PI concentrations	**Do not coadminister rifampin and PIs.**
Benzodiazepines			
Alprazolam Diazepam	All PIs	May ↑ benzodiazepine levels RTV 200mg BID x 2 days ↑ alprazolam half-life 200% and AUC 248%	Consider alternative benzodiazepines such as lorazepam, oxazepam, or temazepam
Lorazepam Oxazepam Temazepam	All PIs	No data	Metabolism of these benzodiazepines via non-CYP450 pathways decreases interaction potential compared with other benzodiazepines.

Concomitant Drug Class/Name	Protease Inhibitor (PI)	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Midazolam	All PIs	↑ midazolam SQV/r ↑ midazolam (oral) AUC 1144%, ↑ Cmax 327%	**Do not coadminister oral midazolam and PIs.** Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation.
Triazolam	All PIs	RTV 200mg BID: ↑ triazolam AUC by 20x; Other PIs: No data; may significantly ↑ triazolam concentration	**Do not coadminister triazolam and PIs.**
Calcium Channel Blockers			
Dihydropyridine	ATV ± RTV	No data	Caution warranted with ATV. Dose titration should be considered as well as ECG monitoring.
	DRV/r, FPV ± RTV, NFV, TPV/r	No data	
	IDV/r	↑ amlodipine	Monitor closely.
	LPV/r SQV/r	↑ dihydropyridine	Caution is warranted and clinical monitoring of patients is recommended.
Diltiazem	ATV ± RTV	↑ diltiazem AUC 125%	Decrease diltiazem dose by 50%. ECG monitoring is recommended.
	DRV/r, FPV ± RTV, IDV ± RTV, LPV/r, NFV, TPV/r	No data	Potential for ↑ diltiazem level.
	SQV/r	↑ diltiazem	Caution is warranted, and clinical monitoring of patients is recommended.
Herbal Products			
St. John's wort	All PIs	↓ PI	Administration of St. John's wort with PIs is not recommended.
Hormonal Contraceptives			
Hormonal Contraceptives	**RTV-boosted PI:**		
	ATV/r	↓ ethinyl estradiol ↑ progestin	Oral contraceptive should contain at least 35mcg of ethinyl estradiol. Oral contraceptives containing progestins other than norethindrone or norgestimate have not been studied.
	DRV/r, IDV/r	No data	Use alternative or additional method because of possible interaction.
	FPV/r	↓ ethinyl estradiol AUC 37%; ↓ norethindrone AUC 34%; APV: no change	Use alternative or additional method.
	LPV/r	↓ ethinyl estradiol 42%	Use alternative or additional method.
	SQV/r	↓ ethinyl estradiol	Use alternative or additional method.
	TPV/r	↓ ethinyl estradiol Cmax & AUC ↓ ~50%	Use alternative or additional method. Used as hormone replacement therapy, monitor clinically for signs of estrogen deficiency.
	PIs without RTV:		
	ATV	↑ ethinyl estradiol AUC 48%; ↑ norethindrone AUC 110%	Oral contraceptive should contain no more than 30mcg of ethinyl estradiol, or use alternate method. Oral contraceptives containing less than 25mcg of ethinyl estradiol or progestins other than norethindrone or norgestimate have not been studied.
	FPV	With APV: ↑ ethinyl estradiol, ↑ norethindrone, ↓ APV 20%	Use alternative method.
	IDV	↑ ethinyl estradiol; ↑ norethindrone	No dose adjustment.
	NFV	ethinyl estradiol ↓ 47%; norethindrone ↓ 18%	Use alternative or additional method.
HMG-CoA Reductase Inhibitors			
Atorvastatin	All PIs	↑ atorvastatin; DRV/r + atorvastatin 10mg similar to atorvastatin 40mg alone; FPV ↑ atorvastatin AUC 150%; LPV/r ↑ atorvastatin AUC 5.88-fold; NFV ↑ atorvastatin AUC 74%; SQV/r ↑ atorvastatin levels 450%; TPV/r ↑ atorvastatin AUC 9-fold	Use lowest possible starting dose with careful monitoring, or consider other HMG-CoA reductase inhibitors with less potential for interaction.

Concomitant Drug Class/Name	Protease Inhibitor (PI)	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Lovastatin	All PIs	Significant ↑ lovastatin level	**Contraindicated – do not coadminister.**
Pravastatin	DRV/r	Mean ↑ in pravastatin AUC 81% & up to 5-fold in some patients	Use lowest possible starting dose with careful monitoring.
	LPV/r	↑ pravastatin	No dose adjustment necessary.
	NFV, SQV/r	↓ pravastatin	No dose adjustment necessary.
	TPV/r ATV, FPV, IDV	No data	
Rosuvastatin	ATV +/- RTV, DRV/r, FPV +/- RTV, IDV +/- RTV, NFV, SQV/r	No data Potential for ↑ rosuvastatin level.	Use lowest possible starting dose with careful monitoring, or consider other HMG-CoA reductase inhibitors with less potential for interaction.
	LPV/r	rosuvastatin AUC ↑ 2.1-fold and Cmax ↑ 4.7-fold	Use lowest possible starting dose with careful monitoring for rosuvastatin toxicities, or consider other HMG-CoA reductase inhibitors with less potential for interaction.
	TPV/r	rosuvastatin AUC ↑ 37% and Cmax ↑ 123%	Use lowest possible starting dose with monitoring for rosuvastatin toxicities, or consider other HMG-CoA reductase inhibitors with less potential for interaction.
Simvastatin	All PIs	Significant ↑ simvastatin level; NFV ↑ simvastatin AUC 505%	**Contraindicated – do not coadminister**.
Methadone			
	RTV-boosted PI:		
Methadone	ATV/r, FPV/r, DRV/r, IDV/r, LPV/r, SQV/r, TPV/r	↓ methadone levels: ATV/r ↓ R-methadone AUC 16%; DRV/r ↓ R-methadone AUC 16%; FPV/r ↓ R-methadone AUC 18% ; LPV/r ↓ methadone AUC 26%–53%; SQV/r 1,000/100mg BID ↓ methadone AUC 19%; TPV/r ↓ R-methadone AUC 48%	Opiate withdrawal unlikely but may occur. No adjustment in methadone usually required but monitor for opiate withdrawal and increase methadone dose as clinically indicated. R-methadone is the active form of methadone.
	PIs without RTV:		
	ATV, IDV	No effect	
	FPV	No data with FPV ; with APV, R-methadone levels ↓ 13%	Monitor and titrate methadone as clinically indicated. The interaction with FPV is presumed to be similar.
	NFV	NFV ↓ methadone AUC 40%	Opiate withdrawal rarely occurs. Monitor and titrate dose as clinically indicated. May require ↑ methadone dose.
Phosphodiesterase Type 5 Inhibitors			
Sildenafil	All PIs	↑ sildenafil; APV ↑ sildenafil AUC 2- to 11-fold; DRV/r + sildenafil 25mg similar to sildenafil 100mg alone; IDV ↑ sildenafil AUC 3-fold; LPV/r ↑ sildenafil 11-fold; NFV ↑ sildenafil 2- to 11-fold; RTV ↑ sildenafil AUC 11-fold	Sildenafil: start with 25mg every 48 hours and monitor for adverse effects of sildenafil.
Tadalafil	All PIs	LPV/r ↑ tadalafil AUC 124%	Tadalafil: start with 5mg dose and do not exceed a single dose of 10mg every 72 hours. Monitor for adverse effects of tadalafil.
Vardenafil	All PIs	↑ vardenafil; IDV ↑ vardenafil AUC 16-fold, ↓ IDV AUC 30%; RTV ↑ vardenafil AUC 49-fold, ↓ RTV AUC 20%	Vardenafil: start with 2.5mg every 72 hours and monitor for adverse effects of vardenafil.

Drug-Specific Interactions

Protease Inhibitor (PI)	Concomitant Drug Class/Name	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
DRV/r	**Paroxetine** **Sertraline**	↓ paroxetine ↓ sertraline	Monitor closely for antidepressant response. Carefully titrate SSRI dose based on clinical assessment.
IDV	**Grapefruit juice** **Vitamin C >1 g/day**	↓ IDV ↓ IDV	Monitor for virologic responses.
RTV	**Desipramine**	RTV ↑ desipramine 145%	Reduce desipramine dose.
	Trazodone	RTV 200mg BID ↑ trazodone AUC 2.4-fold.	Use lowest dose of trazodone, and monitor for CNS and CV adverse effects.
	Theophylline	RTV ↓ theophylline 47%.	Monitor theophylline levels.
SQV	**Grapefruit juice**	↑ SQV	
	Dexamethasone	↓ SQV	

Abbreviations: APV = amprenavir, ATV = atazanavir, ATV/r = atazanavir + ritonavir, DRV/r = darunavir + ritonavir, FPV = fosamprenavir, FPV/r = fosamprenavir + ritonavir, IDV = indinavir, IDV/r = indinavir + ritonavir, LPV/r = lopinavir/ritonavir, NFV = nelfinavir, RTV = ritonavir, SQV/r = saquinavir + ritonavir, TPV/r = tipranavir + ritonavir.

Table 15b. Drug Interactions Between NNRTIs and Other Drugs

This table provides information relating to pharmacokinetic interactions between NNRTIs and non-antiretroviral drugs. For interactions among antiretroviral agents and dosing recommendations, please refer to **Table 16b**.

Concomitant Drug Class/Name	NNRTI	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comment
Antifungals			
Fluconazole	DLV, EFV	No significant effect	
	ETR	↑ ETR	No dosage adjustment necessary.
	NVP	NVP Cmax, AUC, and Cmin ↑ 100%	Increased risk of hepatotoxicity possible with this combination. Monitor NVP toxicity.
Itraconazole	DLV, NVP	No data, potential for bi-directional interactions	Consider monitoring NNRTI and itraconazole levels.
	EFV	itraconazole and OH-itraconazole AUC, Cmax, and Cmin ↓ 35%–44%	Dose adjustments for itraconazole may be necessary. Monitor itraconazole level.
	ETR	↑ ETR ↓ itraconazole	Dose adjustments for itraconazole may be necessary. Monitor itraconazole level.
Ketoconazole	DLV	↑ DLV	No dosage adjustment necessary.
	EFV	No data	
	ETR	↑ ETR ↓ ketoconazole	Dose adjustment for ketoconazole may be necessary depending on other coadministered drugs.
	NVP	ketoconazole ↓ 63%, NVP ↑ 15%–30%	**Coadministration not recommended.**
Posaconazole	DLV, NVP	No data	
	EFV	Posaconazole AUC ↓ 50%, Cmax ↓45% EFV Cmax ↑ 13%	Consider alternative antifungal if possible or consider monitoring posaconazole level if available
	ETR	↑ ETR	No dosage adjustment necessary.
Voriconazole	DLV	No data	Potential for bi-directional inhibition of metabolism. Monitor for toxicity.
	EFV	EFV ↑ 44% voriconazole ↓ 77%	**Contraindicated at standard doses**. Dose: voriconazole 400mg BID, EFV 300mg daily
	ETR	↑ ETR ↑ voriconazole	Dose adjustments for voriconazole may be necessary depending on other coadministered drugs. Monitor voriconazole level.
	NVP	No data	Potential for induction of voriconazole metabolism and inhibition of NVP metabolism. Monitor for toxicity and antifungal outcome.
Anticonvulsants			
Carbamazepine Phenobarbital Phenytoin	DLV	DLV Cmin ↓ 90% by phenytoin, phenobarbital, and carbamazepine	**Contraindicated – do not coadminister.**
	EFV	carbamazepine + EFV: AUCs ↓ 27% and 36%, respectively, when combined. EFV + phenytoin: ↓EFV concentrations (case report)	Monitor anticonvulsant levels, or if possible, use alternative anticonvulsant.
	ETR	No data. Potential for ↓ ETR and anticonvulsant concentrations.	**Do not coadminister.** Consider alternative anticonvulsants.
	NVP	No data	

Concomitant Drug Class/Name	NNRTI	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comment
Anti-mycobacterials			
Clarithromycin	DLV	clarithromycin ↑ 100% DLV ↑ 44%	Reduce clarithromycin dose by 50% in patients with CrCl 30–60mL/min and by 75% in patients with CrCl <30mL/min.
	EFV	clarithromycin ↓ 39%	Monitor for efficacy or consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
	ETR	ETR AUC ↑ 42%, clarithromycin AUC ↓ 39% and Cmin ↓ 53%, OH-clarithromycin AUC ↑ 21%	Consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
	NVP	NVP ↑ 26%, clarithromycin ↓ 30%	Monitor for efficacy or use alternative agent.
Rifabutin	DLV	DLV ↓ 80% rifabutin ↑ 100%	**Coadministration not recommended**.
	EFV	rifabutin ↓ 35%	Dose: rifabutin 450–600mg once daily or 600mg 3x/week if EFV is not coadministered with a PI.
	ETR	ETR AUC ↓ 37% & Cmin ↓ 35% rifabutin AUC ↓ 17% & Cmin ↓ 24%, 25-O-desacetylrifabutin AUC ↓ 17% & Cmin ↓ 22%	Dose: rifabutin 300mg once daily if ETR is not coadministered with a RTV-boosted PI. If ETR is coadministered with DRV/r or SQV/r and rifabutin is needed, consider alternative ARV agent to ETR. If ETR is coadministered with LPV/r, use rifabutin 150mg QOD or 3x/week. Acquired rifamycin resistance has been reported in patients with inadequate rifabutin levels while on 150mg twice weekly and RTV-boosted PIs. Consider therapeutic drug monitoring and adjust dose accordingly.
	NVP	↓ NVP ↑ Rifabutin	No dosage adjustment necessary.
Rifampin	DLV	DLV ↓ 96%	**Contraindicated—do not coadminister.**
	EFV	↓ EFV 25%	Maintain efavirenz dose at 600mg once daily and monitor for viral response. Some clinicians suggest EFV 800mg dose in patients >60kg.
	ETR	Potential for significant ↓ ETR levels	**Do not coadminister.**
	NVP	↓ NVP 20%–58%	**Do not coadminister.**
Benzodiazepines			
Alprazolam	DLV	No data May ↑ alprazolam	**Do not coadminister.** Consider alternative benzodiazepines, such as lorazepam, oxazepam, or temazepam.
	EFV, NVP, ETR	No data	Monitor for therapeutic efficacy of alprazolam.
Diazepam	DLV	No data May ↑ diazepam	Consider alternative benzodiazepines, such as lorazepam, oxazepam, or temazepam.
	EFV, NVP	No data	
	ETR	↑ diazepam	Decreased dose of diazepam may be necessary.
Lorazepam	DLV, ETR, NVP	No data	
	EFV	Lorazepam Cmax ↑ 16%, no significant effect on lorazepam AUC	No dosage adjustment necessary.
Midazolam	DLV, EFV	No data May ↑ midazolam	**Do not coadminister with oral midazolam.** Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation.
	ETR, NVP	No data	

Concomitant Drug Class/Name	NNRTI	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comment
Triazolam	DLV, EFV	No data May ↑ triazolam	**Do not coadminister.**
	ETR, NVP	No data	
Herbal Products			
St. John's wort	All NNRTIs	↓ NNRTI	Administration of St. John's wort with NNRTIs is not recommended.
Hormonal Contraceptives			
Hormonal Contraceptives	DLV	No data Potential for ↑ ethinyl estradiol levels.	Clinical significance unknown.
	EFV	↑ ethinyl estradiol	Use alternative or additional methods. No data on other components.
	ETR	↑ ethinyl estradiol No effect on norethindrone levels.	No dosage adjustment necessary.
	NVP	ethinyl estradiol ↓ 20%.	Use alternative or additional methods.
HMG-CoA Reductase Inhibitors			
Atorvastatin	DLV	No data Potential for inhibition of atorvastatin metabolism.	Use lowest possible dose and monitor for toxicity, or consider other HMG-CoA reductase inhibitors with less potential for interaction.
	EFV	atorvastatin AUC ↓ 37%–43%.	Adjust atorvastatin according to lipid responses, not to exceed the maximum recommended dose.
	ETR	↓ atorvastatin AUC 37%	Dose: standard, adjust dose according to response.
	NVP	No data Potential for induction of atorvastatin metabolism	Dose: standard, adjust dose according to response.
Fluvastatin	DLV, EFV, NVP	No data	
	ETR	↑ fluvastatin	Dose adjustments for fluvastatin may be necessary.
Lovastatin **Simvastatin**	DLV	No data Potential for large increase in statin levels.	**Avoid concomitant use.**
	EFV	simvastatin AUC ↓ 68%	Adjust simvastatin dose according to lipid responses, not to exceed the maximum recommended dose.
	ETR	↓ lovastatin ↓ simvastatin	Adjust lovastatin or simvastatin dose according to lipid responses, not to exceed the maximum recommended dose. If used with RTV-boosted PI, simvastatin and lovastatin should be avoided.
Pravastatin **Rosuvastatin**	DLV, NVP	No data	
	EFV	pravastatin AUC ↓ 44%.	Adjust pravastatin dose according to lipid responses, not to exceed the maximum recommended dose.
	ETR	No effect	Dose: standard
Methadone			
Methadone	DLV	No effect on DLV Potential for ↑ methadone	Monitor for methadone toxicity and need for dose reduction
	EFV	Methadone ↓ 60%	Potential for opiate withdrawal; increased methadone dose often necessary.
	ETR	No effect	Dose: standard
	NVP	↓ methadone No effect on NVP	Opiate withdrawal common; increased methadone dose often necessary.

Concomitant Drug Class/Name	NNRTI	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comment
Oral Anticoagulant			
Warfarin	DLV	No data	May increase warfarin levels. Monitor INR.
	EFV, NVP	No data	May increase or decrease warfarin levels. Monitor INR.
	ETR	↑ warfarin	Monitor INR and adjust warfarin dose accordingly.

Abbreviations: DLV = delavirdine, EFV = efavirenz, ETR = etravirine, NNRTI = non-nucleoside reverse transcriptase inhibitor, NVP = nevirapine, CBZ = carbamazepine.

Drug-Specific Interactions

NNRTI	Concomitant Drug Class/Name	Effect on NNRTI or Concomitant Drug Concentrations	Dosage Recommendations and Clinical Comment
DLV	**Fluoxetine**	↑ DLV	No dosage adjustment necessary.
	Quinidine	No data May increase quinidine levels.	Monitor quinidine level and toxicities.
	Sildenafil **Vardenafil** **Tadalafil**	No data Potential for increased phosphodiesterase inhibitor levels.	Use cautiously. Start with reduced dose of sildenafil 25mg Q48H, vardenafil 2.5mg Q24H, and tadalafil 5mg Q72H.
ETR	**Antiarrhythmics**	↓ antiarrhythmics	Use with caution with antiarrhythmic level monitoring if available.
	Dexamethasone	↓ ETR	Use systemic dexamethasone with caution or consider alternative corticosteroid for long-term use.
	Sildenafil	↓ sildenafil	May need to increase sildenafil dose based on clinical effect. Levels: sildenafil AUC ↓ 57%.

Table 15c. Drug Interactions Between NRTIs and Other Drugs (including antiretroviral agents)

Concomitant Drug Class/Name	NRTI	Effect on NRTI or Concomitant Drug Concentrations	Clinical Comment
Antivirals			
Ganciclovir (GCV) Valganciclovir	ddI	↑ ddI AUC ↑ 50%–111% ↓ GCV AUC ↓ 21% when ddI administered 2 hours prior to oral GCV. No change in IV GCV concentrations.	Appropriate doses for combination of ddI and GCV have not been established. Monitor for ddI associated toxicities.
	TDF	No data	Serum concentrations of these drugs and/or TDF may be increased. Monitor for dose-related toxicities.
	ZDV	No significant pharmacokinetic effects	Potential increase in hematologic toxicities.
Ribavirin	ddI	↑ intracellular ddI	**Coadministration not recommended**. May cause ddI-related serious toxicities.
	ZDV	Ribavirin inhibits phosphorylation of ZDV.	Avoid coadministration if possible, or closely monitor virologic response and hematologic toxicities.
Methadone			
Methadone	ABC	↓ methadone	Monitor for opiate withdrawal and titrate methadone as clinically indicated. May require ↑ methadone dose.
	d4T	↓ d4T	No dosage adjustment necessary.
	ZDV	↑ ZDV AUC 43%	Monitor for ZDV-related adverse effects.
NRTIs			
Didanosine	d4T	No significant effect	Avoid coadministration if possible. Peripheral neuropathy, lactic acidosis, and pancreatitis seen with this combination.
	TDF	↑ ddI-EC AUC and Cmax 48%–60%	Dose if CrCl >60mL/min: ddI-EC 250mg/day if patient weighs >60kg and ddI-EC 200mg if patient weighs <60kg. Monitor for ddI-associated toxicity.
PIs			
Atazanavir (ATV)	ddI	Simultaneous ddI-EC + ATV (with food) ↓ ddI AUC 34%. ATV no change.	ATV with food should be administered 2 hours before or 1 hour after didanosine.
	TDF	↓ ATV AUC 25% and Cmin 23%–40% (higher Cmin with RTV than without) ↑ TDF AUC 24%–30%	Dose: ATV/r 300/100mg daily coadministered with TDF 300mg daily. Avoid concomitant use without ritonavir. Monitor for TDF-associated toxicity.
	ZDV	↓ ZDV Cmin 30%, no change in AUC	Clinical significance unknown.
Darunavir (DRV)	TDF	↑ TDF AUC 22%, Cmax 24%, Cmin 37%	Clinical significance unknown. Monitor for TDF toxicity.
Indinavir (IDV)	TDF	↑ IDV	No dosage adjustment necessary.
Lopinavir/ritonavir (LPV/r)	TDF	↓ LPV/r AUC 15% ↑ TDF AUC 34%	Clinical significance unknown. Monitor for TDF toxicity.
Tipranavir/ritonavir (TPV/r)	ABC	↓ ABC 35%–44% with TPV/r 1,250/100mg BID	Appropriate doses for this combination have not been established.
	ddI	↓ ddI-EC 10% and ↓ TPV Cmin 34% with TPV/r 1,250/100mg BID	Separate doses by at least 2 hours.
	TDF	↓ TPV AUC 9%–18% and Cmin 12%–21% with TPV/r 1,250/100mg BID	Clinical significance is unknown.
	ZDV	↓ ZDV AUC 31%–43% and Cmax 46%–51% with TPV/r 1,250/100mg BID	Appropriate doses for this combination have not been established.

Abbreviations: ABC = abacavir, ddI = didanosine, d4T = stavudine, TDF = tenofovir, ZDV = zidovudine.

Table 15d. Drug Interactions Between CCR5 Antagonists and Other Drugs

This table provides information relating to pharmacokinetic interactions between maraviroc and non-antiretroviral drugs. For interactions among antiretroviral agents and dosing recommendations, please refer to **Table 16b.**

Concomitant Drug Class/Name	CCR5 Antagonist	Effect on CCR5 Antagonist or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comment
Antifungals			
Fluconazole **Posaconazole**	MVC	No data	
Itraconazole	MVC	No data possible ↑ MVC levels	Dose: MVC 150mg BID
Ketoconazole	MVC	↑ MVC AUC 5x	Dose: MVC 150mg BID
Voriconazole	MVC	No data possible ↑ MVC levels	Consider dose reduction to MVC 150mg BID.
Anticonvulsants			
Carbamazepine **Phenobarbital** **Phenytoin**	MVC	No data possible ↓ MVC levels	If used without a strong CYP3A inhibitor: MVC 600mg BID or use alternative antiepileptic agent.
Anti-mycobacterials			
Clarithromycin	MVC	No data possible ↑ MVC levels	Dose: MVC 150mg BID
Rifabutin	MVC	No data possible ↓ MVC levels	If used without a strong CYP3A inducer or inhibitor: MVC 300mg BID. If used with a strong CYP3A inhibitor: MVC 150mg BID.
Rifampin	MVC	↓ MVC AUC 64%	If used without a strong CYP3A inhibitor: MVC 600mg BID. If used with a strong inhibitor: 300mg BID
Herbal Products			
St. John's wort	MVC	No data possible ↓ MVC levels	Administration of St. John's wort with MVC is not recommended.
Hormonal Contraceptives			
Hormonal Contraceptives	MVC	No significant effect.	Safe to use in combination.

Abbreviation: MVC = maraviroc.

Table 15e. Drug Interactions Between Antiretrovirals and Other Drugs: Integrase Inhibitors

Concomitant Drug Class/Name	Integrase Inhibitors	Effect on Integrase Inhibitor or Concomitant Drug Concentrations	Clinical Comment
Anti-mycobacterials			
Rifampin	RAL	↓ RAL AUC 40%, Cmin 61%	Clinical significance unknown. Should consider using rifabutin as alternative. If rifampin is to be used, monitor for antiretroviral efficacy.

Abbreviation: RAL = raltegravir.

Table 16a. Interactions Among Protease Inhibitors

Drug Affected	Fosamprenavir	Atazanavir	Lopinavir/ Ritonavir	Nelfinavir	Ritonavir	Saquinavir*	Tipranavir
Protease Inhibitors							
Darunavir (DRV)	No data.	Levels: ATV 300mg once daily + DRV/r -- similar to ATV/r 300/100mg once daily. DRV was unchanged. Dose: Administer ATV 300mg once daily with DRV/r for exposure similar to ATV/r 300/100mg once daily.	Levels: DRV AUC and Cmin ↓ 53% and 65%, respectively. LPV AUC and Cmin ↑ 37% and 72%, respectively. **Dose: Should not be coadministered, as doses are not established.**	No data.	Levels: 14-fold ↑ in DRV exposure in combination with RTV 100mg BID. Dose: DRV should only be used in combination with RTV 100mg BID to achieve sufficient DRV exposure.	Levels: DRV AUC and Cmin ↓ 26% and 42%, respectively. SQV exposure similar to when administered with RTV 1,000/100mg BID.‡ **Dose: Should not be coadministered, as doses are not established.**	No data.
Fosamprenavir (FPV)	•	Levels: With FPV/ATV 1,400/400 once daily, ATV AUC & Cmin ↓ 33% and 57%, resp. APV AUC & Cmin ↑ 78% and 283%, respectively. With FPV/r 700/100mg BID + ATV 300mg once daily, ATV AUC and Cmax ↓ 22% and 24%, resp; APV unchanged. Dose: Insufficient data.for dose recommendation.	Levels: With coadministration of FPV 700mg BID and LPV/r capsules 400/100mg BID, FPV Cmin ↓64% and LPV Cmin ↓53%. An increased rate of adverse events was seen with coadministration. **Dose: Should not be coadministered, as doses are not established.**	See FPV + NFV cell	Levels: APV AUC and Cmin ↑100% and 400%, respectively, with 200mg RTV. Dose: (FPV 1,400mg + RTV 200mg) once daily; or FPV 700mg + RTV 100mg BID.	Levels: APV AUC ↓ 32%. Dose: Insufficient data.for dose recommendation	Levels: APV AUC and Cmin ↓44% and 55%, respectively, when given as APV/r 600/100 BID with TPV/r. No data with FPV, but a ↓ in AUC is expected. **Dose: Should not be coadministered, as doses are not established.**
Indinavir (IDV)	Levels: APV AUC ↑33%. Dose: Not established.	Coadministration of these agents is not recommended because of potential for additive hyperbilirubinema.	Levels: IDV AUC and Cmin↑. Dose: IDV 600mg BID.	Levels: IDV ↑50%; NFV ↑80%. Dose: Limited data for IDV 1,200mg BID + NFV 1,250mg BID.	Levels: IDV ↑ 2–5 times. Dose: IDV/RTV 800/100mg, 800/200mg, or 400/400mg BID Caution: Renal events may ↑ with ↑ IDV concentrations.	Levels: IDV-No effect. SQV ↑ 4-7 times.† Dose: Insufficient data.	No data. **Should not be coadministered, as doses are not established.**
Lopinavir/ Ritonavir (LPV/r)	see LPV/r + FPV cell	Levels: With ATV 300 once daily + LPV/r 400/100 BID, ATV Cmin ↑45%; ATV AUC and Cmax were unchanged. LPV PK similar to historic data.	•	see LPV/r + NFV cell	Additional ritonavir is generally not recommended.	see LPV/r + SQV cell	Levels: LPV AUC and Cmin ↓ 55% & 70%, respectively. **Dose: Should not be coadministered, as doses are not established.**
Nelfinavir (NFV)	Levels: APV AUC ↑ 1.5-fold. Dose: Insufficient data.	No data	Levels: With LPV/r capsules, LPV ↓27%; NFV ↑ 25%. Dose: No data with LPV/r tablets. No dosing recommendation.	•	see NFV + RTV cell	see NFV+SQV cell	No data. **Should not be coadministered, as doses are not established.**
Ritonavir (RTV)	see RTV + FPV cell	Levels: ATV AUC ↑238%. Dose: ATV 300mg QD + RTV 100mg QD.	Lopinavir is coformulated with ritonavir as Kaletra®. Additional ritonavir is generally not recommended.	Levels: RTV - No effect. NFV ↑ 1.5 times. Dose: not established	•	Levels: RTV no effect SQV ↑ 20 times.†‡ Dose: 1,000/ 100mg SQV/RTV BID	Levels: TPV AUC ↑ 11-fold.
Saquinavir (SQV)	Levels: APV AUC ↓32%. Dose: Insufficient data.	Levels: SQV AUC ↑60% with SQV/ATV/RTV 1,600/300/100 once daily, compared with SQV/ RTV 1,600/100 once daily Dose: No dose recommendations can be made.	Levels: SQV† AUC and Cmin ↑ Dose: SQV 1,000mg BID; LPV/r standard.	Levels: SQV ↑ 3–5 times; NFV ↑ 20%.†	see SQV + RTV cell	•	Levels: SQV AUC & Cmin ↓ 76% & 82%, respectively, when given as SQV/r 600/100 BID with TPV/r. **Dose: Should not be coadministered, as doses are not established.**

* Several drug interaction studies have been completed with saquinavir given as Invirase (old hard-gel capsule formulation) or Fortovase (soft-gel capsule formulation. Currently, only Invirase (as 500mg tablet or 200mg hard-gel capsule) is available.
† Study conducted with Fortovase.
‡ Study conducted with Invirase

Table 16b. Interactions between NNRTIs, Maraviroc, and PIs

Drug Affected	Delavirdine	Efavirenz	Etravirine	Nevirapine	Maraviroc
Atazanavir (ATV)	No data.	Levels: With unboosted ATV, ATV AUC ↓ 74%. EFV no change. ATV 300 + RTV 100mg QD with food - ATV concentrations similar to unboosted ATV Dose: in treatment-naïve patients, ATV 400mg + RTV 100mg: EFV dose = standard. Do not coadminister in treatment-experienced patients.	Levels: With unboosted ATV, ETR AUC, Cmax and Cmin ↑ 50%, 47% and 58%, respectively ATV AUC ↓ 17%, Cmin ↓ 47% With ATV/RTV, ETR AUC, Cmax and Cmin ↑ approx 30%: ATV AUC ↓ 14% and Cmin ↓ 38% **Do not coadminister with unboosted ATV or ATV/RTV**	Levels: ↓ ATV, ↑ NVP **Coadministration of NVP is not recommended with ATV + RTV.**	Levels: With unboosted ATV, MVC AUC ↑ 3.6x. With ATV/r, MVC AUC ↑ 5x. Dose: With unboosted ATV or ATV/r, 150mg BID.
Darunavir (DRV)	No data.	Levels: DRV AUC and Cmin ↓ 13% and 31%, respectively. EFV AUC and Cmin ↑ 21% and 17%, respectively. Dose: Clinical significance unknown. Use standard doses and monitor closely. Consider monitoring levels.	Levels: ETR AUC ↓ 37% Cmin ↓ 49% DRV no change Dose: Standard for ETR and DRV. Despite decrease in ETR, safety and efficacy established with this combination	Levels: NVP AUC and Cmin ↑ 27% and 47%, respectively. DRV unchanged.† Dose: Standard.	Levels: With DRV/r, MVC AUC ↑ 4x. Dose: 150mg BID.
Delavirdine (DLV)	•	no data	•	•	Levels: Unknown, possibly ↑ MVC conc. Dose: 150mg BID.
Efavirenz (EFV)	no data	•	Potential for ↓ ETR concentration. **Do not coadminister**	•	Levels: MVC AUC ↓ 45%. Dose: 600mg BID.
EFV + LPV/r or SQV/r	•	•	•	•	Levels: MVC AUC ↑ 2.5–5x. Dose: 150mg BID.
Etravirine (ETR)	•	•	•	•	Levels: MVC AUC ↓ 53%, Cmax ↓ 60% Dose: 600mg BID
ETR + DRV/r	•	•	•	•	Levels: MVC AUC ↑210%, Cmax ↑77% Dose: 150mg BID
Fosamprenavir (FPV)	Levels: Presumably, similar PK effects as APV: APV AUC ↑ 130%, and DLV AUC ↓ 61%. Dose: Coadministration not recommended.	Levels: APV Cmin ↓ 36% (when dosed at 1,400mg QD with 200mg RTV). Dose: FPV 1,400mg + RTV 300mg QD; or FPV 700mg + RTV 100mg BID.	Levels: APV AUC ↑ 69%, Cmin ↑ 77% **Dose: Do not coadminister with boosted or unboosted FPV**	No data.	Levels: Unknown, possibly ↑ MVC conc. Dose: 150mg BID
Indinavir (IDV)	Levels: IDV ↑ >40%; DLV-No effect. Dose: IDV 600mg q8h. DLV standard.	Levels: IDV ↓ 31%. Dose: IDV 1,000mg q8h; consider IDV/RTV. EFV standard.	Dose: No data. Do not coadminister	Levels: IDV ↓ 28%; NVP no effect. Dose: IDV 1,000mg q8h, or consider IDV/RTV. NVP standard.	Levels: Unknown, possibly ↑ MVC conc. Dose: 150mg BID.
Lopinavir/ Ritonavir (LPV/r)	Levels: LPV levels expected to increase. Dose: Insufficient data.	Levels: With LPV/r tablets 600/150mg BID + EFV 600mg QD, LPV Cmin and AUC ↑ 35% and 36%, respectively. No formal study of LPV/r tablets 400/100mg BID + EFV. EFV no change. Dose: LPV/r tablets 600/150mg BID, when used in with EFV in tx-experienced patients. EFV dose - standard.	Levels: ETR AUC ↑ 17% Cmin ↑ 23%: LPV AUC ↓ 20%, Cmin ↓ 8% Dose: standard for ETR and LPV/RTV The amount of safety data at ↑ ETR exposures is limited, therefore, use with caution	Levels: With LPV/r capsules, LPV Cmin dec. 55%. Dose: LPV/r tablets 600/150mg BID, when used in combination with NVP in tx-experienced patients. NVP standard.	Levels: MVC AUC ↑ 4x. Dose: 150mg BID.

Nelfinavir (NFV)	Levels: NFV ↑ 2 times. DLV ↓50%. Dose: No data.	Levels: NFV ↑ 20%. Dose: Standard.	Dose: no data. Do not coadminister	Levels: NFV ↑ 10%. NVP no effect. Dose: Standard.	Levels: Unknown, possibly ↑ MVC conc. Dose: 150mg BID.
Nevirapine (NVP)	No data.	Levels: NVP-no effect. EFV AUC ↓ 22%.	Potential for ↓ ETR concentration, Do not coadminister	•	Levels: No significant change. Dose: 300mg BID if use without PI 150mg BID – if used with PI (except TPV/r).
Ritonavir (RTV)	Levels: RTV ↑ 70%. DLV no effect. Dose: Appropriate doses not established.	Levels: RTV ↑ 18%. EFV ↑ 21%. Dose: Standard.	Dose: No data. Do not coadminister ETR and RTV 600mg	Levels: RTV ↓ 11%. NVP no effect. Dose: Standard.	Levels: With RTV 100 mg BID, MVC AUC ↑ 2.6x. Dose: 150mg BID.
Saquinavir (SQV)	Levels: SQV‡ ↑ 5 times; DLV no effect. Dose: SQV/RTV 1,000mg/100mg BID.	Levels: SQV‡ ↓ 62%. EFV ↓ 12%. Dose: SQV/RTV 1000mg/100mg BID.	Level: ETR AUC ↓ 33% Cmin ↓ 29% SQV unchanged Dose: SQV/RTV 1000/100mg BID. ETR reduced exposures similar to ETR reduced exposures with DRV/RTV; therefore no dose adjustment	Levels: SQV ↓ 25%. NVP no effect. Dose: SQV/RTV 1,000mg/100mg BID.	Levels: With SQV/r, MVC AUC ↑ 9.8x. Dose: 150mg BID.
Tipranavir (TPV)	No data.	Levels: With TPV/r 500/100mg BID, TPV AUC and Cmin ↓ 31% and 42%, respectively. EFV unchanged. With TPV/r 750/200mg BID, TPV PK unchanged. Dose: No dose adjustments necessary.	Level: ETR AUC ↓ 76%, Cmin ↓ 82%; TPV AUC ↑ 18%, Cmin ↑ 24% Dose: Do not coadminister	Levels: No data on the effect of NVP on TPV/r PK. NVP PK unchanged.[a]	Levels: With TPV/r, no significant change. Dose: 300mg BID.

‡ Study conducted with Invirase.

† Based on between-study comparison.

[a] Study conducted with TPV/r dose(s) other than FDA-approved dose of 500/200mg BID.

Prevention Counseling for the HIV-Infected Patient (Updated October 29, 2004)

Prevention counseling is an essential component of management for HIV-infected persons. Each patient encounter provides an opportunity to reinforce HIV prevention messages. Therefore, each encounter should include assessment and documentation of the following:

- patient's knowledge and understanding of HIV transmission; and
- patient's HIV transmission behaviors since the last encounter with a member of the health care team.

This should be followed by a discussion of strategies to prevent transmission that might be useful to the patient. Each member of the health care team can routinely provide this counseling. Partner notification is a key component of HIV detection and prevention and should be pursued with the patient by the provider or by referral services. Behavior changes among HIV-infected persons have been observed during the era of combination antiretroviral therapy that impacts prevention, however, evidence exists that awareness of the potential benefits of antiretroviral therapy has contributed to relapse into high-risk activities. There is good evidence that the probability of HIV transmission correlates with inoculum size based on precedent in other viral infections and on the basis of the discordant couples study and studies of perinatal transmission. There is an assumption that risk of transmission is reduced with exposure by sex or needle-sharing with therapy to reduce viral load, although there are no clinical studies to support that claim and there are no viral load thresholds that could be considered safe. Further, there is the concern that this impression might lead or has led to high-risk behavior that might more than nullify any potential benefit. Lastly, HIV-infected women may engage in unprotected sex while attempting to become pregnant. Providers should discuss patient plans and desires concerning childbearing at intervals throughout care and should refer women who are interested in getting pregnant to preconception counseling and care.

The following link provides more information that providers can access to provide them with better understanding of the need for prevention and prevention counseling. (**http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5212a1.htm**) *[1]*.

References

1. Centers for Disease Control and Prevention. Incorporating HIV Prevention into the Medical Care of Persons Living with HIV. *MMWR*, 2003. 52(RR-12):1-24.

Conclusion

The Panel has carefully reviewed recent results from clinical trials in HIV therapy and considered how they inform appropriate care guidelines. The Panel appreciates that HIV care is highly complex and rapidly evolving. Guidelines are never fixed and must always be individualized. Where possible, the Panel has based recommendations on the best evidence from prospective trials with defined endpoints. When such evidence does not yet exist, the panel attempted to reflect reasonable options in its conclusions.

HIV care requires, as always, partnerships and open communication. The provider can make recommendations most likely to lead to positive outcomes only if the patient's own point of view and social context are well known. Guidelines are only a starting point for medical decision making. They can identify some of the boundaries of high-quality care, but cannot substitute for sound judgment.

As further research is conducted and reported, guidelines will be modified. The Panel anticipates continued progress in the simplicity of regimens, improved potency and barrier to resistance, and reduced toxicity. The Panel hopes the guidelines are useful and is committed to their continued adjustment and improvement.

- Information included in these guidelines may not represent FDA approval or approved labeling for the particular products or indications in question. Specifically, the terms "safe" and "effective" may not be synonymous with the FDA-defined legal standards for product approval.

Appendix A: Financial Disclosure for Members of the DHHS Panel on Antiretroviral Guidelines for Adult and Adolescents (A Working Group of OARAC) – February 2008

Name	Panel Status*	Company	Relationship
Jean R. Anderson	M	Abbott Laboratories Boehringer-Ingelheim Glaxo Smith Kline Pfizer/Agouron	• Speakers' Bureau; Honoraria • Advisory Board • Speakers' Bureau; Honoraria • Advisory Board; Research support; Speakers' Bureau; Honoraria; Stock holder
A. Cornelius Baker	M	Boehringer-Ingelheim Gilead Sciences Tibotec	• Honoraria • Grant/Program support • Grant/Program support
John G. Bartlett	C	Abbott Laboratories Bristol Myers Squibb Gilead Sciences Glaxo Smith Kline Pfizer Tibotec	• HIV Advisory Board • HIV Advisory Board • Research support • HIV Advisory Board • HIV Advisory Board • HIV Advisory Board
Victoria Ann Cargill	M	None	N/A
Charles Carpenter	M	Bristol Myers Squibb	• Consultant
Laura W. Cheever	M	None	N/A
Judith Currier	M	Achillon Pharmaceuticals Bristol Myers Squibb Gilead Sciences Glaxo Smith Kline Koronis Merck Pfizer Schering Plough Theratechnologies Tibotec Vertex	• DSMB Member • Advisory Board; Honoraria • Advisory Board • Research support; Honoraria • DSMB Member • Advisory Board; Research support • Advisory Board • Research support • Research support • Advisory Board; Research support • Research support
Paul Dalton	M	Glaxo Smith Kline Merck Napo Pfizer Tibotec Tobira	• Advisory Board; Honoraria; Consultant • Advisory Board • Advisory Board • Advisory Board • Advisory Board; Consultant • Advisory Board
Eric Daar	M	Abbott Laboratories Boehringer-Ingelheim Bristol Myers Squibb Gilead Sciences Glaxo Smith Kline Merck Monogram Pfizer Tibotec	• Advisory Board, Research Support, Speakers' Bureau, Honoraria, Consultant • Advisory Board, Research Support, Speakers' Bureau, Honoraria, Consultant • Advisory Board, Speakers' Bureau, Honoraria, Consultant • Advisory Board, Research Support, Speakers' Bureau, Honoraria, Consultant • Advisory Board, Research Support, Speakers' Bureau, Honoraria, Consultant • Advisory Board, Research Support, Speakers' Bureau, Honoraria, Consultant • Advisory Board, Speakers' Bureau, Honoraria, Consultant • Advisory Board, Speakers' Bureau, Honoraria, Consultant • Advisory Board, Speakers' Bureau, Honoraria, Consultant

Name	Panel Status*	Company	Relationship
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Carlos del Rio	M	Abbot Laboratories Bristol Myers Squibb Merck Roche	• Advisory Board • Advisory Board • Advisory Board; Research support; Honoraria • Advisory Board
Courtney V. Fletcher	M	Abbott Laboratories Bristol Myers Squibb	• Advisory Board • Advisory Board
Gerald H. Friedland	M	Boehringer-Ingelheim Abbott Laboratories Merck	• Research Support • Research Support • Research Support
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Roy M. Gulick	M	Abbott Laboratories Boehringer-Ingelheim Bristol Myers Squibb Gilead Sciences Glaxo Smith Kline Koronis Merck Monogram Panacos Pfizer Schering Plough Trimeris Virco	• Consultant • Consultant • Consultant • Research support; Consultant • Consultant • DSMB Chair • Research support; Consultant • Consultant • Research support • Research support; Consultant • Research support • Consultant • Consultant
W. Keith Henry	M	Bristol Myers Squibb Gilead Sciences Glaxo Smith Kline Pfizer Roche Serono Thera	• Research support; Speakers' Bureau • Speakers' Bureau; Honoraria; Consultant • Advisory Board; Research support; Speakers' Bureau; Honoraria; Consultant • Research support; Speakers' Bureau • Speakers' Bureau; Honoraria • Research support • Research support

Name	Panel Status*	Company	Relationship
		Tibotec	• Speakers' Bureau
Martin S. Hirsch	M	Merck TaiMed	• DSMB Member • DSMB Member
Morris Jackson	M	Gilead Sciences Glaxo Smith Kline Merck	• Consultant • Summer Summit 2006 • Advisory Board
Wilbert Jordan	M	Abbott Laboratories Boehringer-Ingelheim Bristol Myers Squibb Glaxo Smith Kline Roche Serono Tibotec	• Advisory Board, Speakers' Bureau • Advisory Board, Speakers' Bureau • Advisory Board, Speakers' Bureau • Advisory Board, Speakers' Bureau • Advisory Board, Speakers' Bureau • Advisory Board • Advisory Board, Speakers' Bureau
Jonathan E. Kaplan	M	None	N/A
H. Clifford Lane	C	Novartis	• Research support, NIH patent on IL-2 licensed to Novartis
Henry Masur	M	None	N/A
Lynne Mofenson	M	None	N/A
Jeff Murray	M	None	N/A
Heidi M. Nass	M	Tibotec	• Advisory Board
James Neaton	M	Abbott Laboratories Bristol Myers Squibb Chiron/Novartis Gilead Sciences Glaxo Smith Kline Merck	• Research support • Research support • Research support • Research support • Research support • Advisory Board, DSMB member, Consultant, Research support
Alice Pau	E.S.	None	N/A
Michael Saag	M	Anchillion Pharmaccutica Avexa Boehringer Ingelheim Bristol Myers Squibb Gilead Sciences Glaxo Smith Kline Merck Monogram Biosciences Panacos Pfizer Progenics Roche Laboratories Serono Tibotec Virco	• Grant/Research support • Consultant • Grant/Research support; Consultant • Consultant • Grant/Research support; Consultant • Grant/Research support; Consultant • Grant/Research support; Consultant • Consultant • Grant/Research support; Consultant • Grant/Research support; Consultant • Grant/Research support; Consultant • Grant/Research support; Consultant • Grant/Research support • Grant/Research support; Consultant • Consultant
Paul E. Sax	M	Abbott Laboratories Bristol Myers Squibb Gilead Sciences Glaxo Smith Kline Merck Pfizer Tibotec	• Consultant, Honoraria for teaching • Consultant, Honoraria for teaching • Consultant, Honoraria for teaching • Consultant, Honoraria for teaching, Grant support • Honoraria for teaching • Grant support • Honoraria for teaching
Renslow Sherer	M	Abbott Laboratories Glaxo Smith Kline Johnson & Johnson	• Advisory Board; Speakers' Bureau; Honoraria; Consultant; Grant for CME training • Advisory Board; Honoraria • Grant for health worker training

Name	Panel Status*	Company	Relationship
		Pfizer Tibotec	• Grant for health worker training • Advisory Board; Honoraria
Kimberly Struble	M	None	N/A
Paul Volberding	M	Bristol Myers Squibb Gilead Sciences Glaxo Smith Kline Pain Therapeutics, Inc. Pfizer PPD Schering Plough TaiMed	• Advisory Board • Advisory Board • Advisory Board; Honoraria • Scientific Advisory Board • Advisory Board • DSMB • Advisory Board, Endpoints Adjudication Committee • Advisory Board
Suzanne Willard	M	Boehringer-Ingelheim	• Research support
David A. Wohl	M	Abbott Laboratories Boehringer-Ingelheim Bristol Myers Squibb Gilead Sciences Merck Roche Tibotec	• Speakers' Bureau • Speakers' Bureau • Speakers' Bureau • Speakers' Bureau • Research support, Speakers' Bureau • Research support, Speakers' Bureau • Speakers' Bureau

- C = Co-Chair; E.S. = Executive Secretary; M = Member; N/A = not applicable
- Note: The financial disclosure for Panel Members is updated annually. An updated list will be available at **http://aidsinfo.nih.gov** after February 2009.

Appendix B: Tables and Figure

Appendix Table 1a. Probability of Progressing to AIDS or Death According to CD4 Cell Count, Viral Load, and Sociodemographic Factors (Updated October 29, 2004)

	CD4 cell count (cells/µL)									
	< 50		50–99		100–199		200–349		≥ 350	
	Viral load ≥5*	Viral load <5*	Viral load ≥5*	Viral load <5*	Viral load ≥5*	Viral load <5*	Viral load ≥5*	Viral load <5*	Viral load ≥5*	Viral load <5*
CDC stage A/B and no history of IDU										
Age < 50 years										
Year 1	12 (11–14)	9.5 (8.0–11)	9.2 (7.7–11)	7.0 (5.8–8.5)	6.2 (5.2–7.3)	4.7 (4.0–5.6)	2.6 (2.1–3.2)	2.0 (1.6–2.5)	2.0 (1.6–2.5)	1.5 (1.2–1.9)
Year 2	17 (15–20)	13 (11–15)	13 (11–15)	10 (8.4–12)	9.5 (8.1–11)	7.3 (6.2–8.5)	4.5 (3.7–5.4)	3.3 (2.8–4.1)	3.3 (2.7–4.0)	2.5 (2.1–3.0)
Year 3	20 (18–23)	16 (13–19)	16 (14–19)	12 (10–15)	12 (10–14)	9.3 (7.9–11)	6.1 (5.0–7.4)	4.7 (3.9–5.6)	4.4 (3.6–5.4)	3.4 (2.8–4.1)
Age ≥ 50 years										
Year 1	17 (14–20)	13 (11–16)	12 (10–15)	9.6 (7.7–12)	8.5 (7.0–10)	6.5 (5.3–7.9)	3.6 (2.8–4.5)	2.7 (2.2–3.4)	2.8 (2.2–3.5)	2.1 (1.6–2.7)
Year 2	23 (19–27)	18 (15–21)	18 (15–21)	14 (11–17)	13 (10–15)	9.9 (8.2–12)	6.1 (5.0–7.6)	4.7 (3.8–5.8)	4.5 (3.6–5.7)	3.4 (2.8–4.3)
Year 3	27 (23–32)	21 (18–25)	22 (18–26)	17 (14–20)	16 (14–19)	13 (10–15)	8.3 (6.7–10)	6.4 (5.1–7.9)	6.0 (4.8–7.6)	4.6 (3.7–5.8)
CDC stage A/B and history of IDU										
Age < 50 years										
Year 1	17 (14–20)	13 (11–16)	12 (10–15)	9.5 (7.7–12)	8.4 (7.0–10)	6.5 (5.3–7.9)	3.6 (2.8–4.5)	2.7 (2.2–3.4)	2.7 (2.1–3.5)	2.1 (1.6–2.6)
Year 2	24 (21–28)	19 (16–23)	19 (16–22)	15 (12–18)	14 (12–16)	11 (8.8–13)	6.6 (5.4–8.1)	5.0 (4.1–6.1)	4.9 (3.9–6.1)	3.7 (3.0–4.6)
Year 3	30 (26–35)	24 (20–28)	24 (20–28)	19 (15–23)	18 (15–22)	14 (12–17)	9.4 (7.6–11)	7.2 (5.8–8.8)	6.8 (5.4–8.6)	5.2 (4.2–6.5)
Age ≥ 50 years										
Year 1	22 (18–27)	17 (14–22)	17 (13–21)	13 (10–16)	11 (9.1–14)	8.8 (6.9–11)	4.9 (3.7–6.4)	3.7 (2.8–4.9)	3.8 (2.8–5.0)	2.9 (2.2–3.8)
Year 2	32 (26–38)	25 (20–31)	25 (20–31)	20 (15–25)	18 (15–23)	14 (11–18)	9.0 (7.0–11)	6.9 (5.4–8.8)	6.7 (5.1–8.7)	5.1 (3.9–6.6)
Year 3	39 (32–46)	31 (25–38)	33 (26–38)	25 (20–31)	24 (20–30)	19 (15–24)	13 (9.9–16)	9.8 (7.6–12)	9.3 (7.1–12)	7.1 (5.4–9.2)
CDC stage C and no history of IDU										
Age < 50 years										
Year 1	17 (15–19)	13 (11–15)	13 (11–15)	9.8 (8.1–12)	8.7 (7.2–10)	6.6 (5.5–8.1)	3.7 (2.9–4.7)	2.8 (2.2–3.5)	2.8 (2.2–3.6)	2.1 (1.7–2.7)
Year 2	23 (21–26)	18 (16–21)	18 (15–21)	14 (12–17)	13 (11–16)	10 (8.4–12)	6.3 (5.1–7.8)	4.8 (3.9–5.9)	4.6 (3.7–5.9)	3.5 (2.8–4.4)
Year 3	28 (25–31)	22 (19–25)	22 (19–26)	17 (14–21)	17 (14–20)	13 (11–15)	8.5 (6.9–11)	6.5 (5.2–8.1)	6.2 (4.9–7.9)	4.7 (3.7–6.0)
Age ≥ 50 years										
Year 1	23 (20–26)	18 (15–21)	17 (14–20)	13 (11–16)	12 (9.7–14)	9.1 (7.3–11)	5.1 (3.9–6.5)	3.8 (3.0–5.0)	3.9 (3.0–5.1)	3.0 (2.3–3.9)
Year 2	31 (27–35)	24 (20–28)	24 (20–28)	19 (15–23)	18 (15–21)	14 (11–17)	8.6 (6.8–11)	6.6 (5.2–8.3)	6.4 (4.9–8.2)	4.9 (3.8–6.2)
Year 3	36 (32–41)	29 (24–34)	29 (25–34)	23 (19–28)	22 (18–27)	17 (14–21)	12 (9.2–15)	8.9 (7.0–11)	8.5 (6.5–11)	6.5 (5.0–8.3)
CDC stage C and history of IDU										
Age < 50 years										
Year 1	23 (20–26)	18 (15–21)	17 (14–21)	13 (11–16)	12 (9.5–14)	9.0 (7.2–11)	5.0 (3.9–6.5)	3.8 (2.9–5.0)	3.9 (2.9–5.1)	2.9 (2.2–3.9)
Year 2	33 (29–37)	26 (22–30)	26 (22–30)	20 (16–24)	19 (15–23)	15 (12–18)	9.2 (7.3–12)	7.0 (5.6–8.9)	6.8 (5.3–8.8)	5.2 (4.1–6.7)
Year 3	40 (35–45)	32 (27–37)	32 (27–38)	25 (21–31)	25 (22–30)	19 (16–24)	13 (10–16)	10 (7.9–13)	9.5 (7.3–12)	7.3 (5.6–9.4)
Age ≥ 50 years										
Year 1	30 (25–36)	24 (19–29)	23 (18–28)	18 (14–23)	16 (12–20)	12 (9.5–16)	6.9 (5.1–9.2)	5.3 (3.9–7.1)	5.3 (3.9–7.2)	4.0 (3.0–5.5)
Year 2	42 (36–49)	34 (28–41)	34 (27–41)	27 (21–33)	25 (20–31)	20 (15–25)	12 (9.6–16)	9.6 (7.3–13)	9.3 (7.0–12)	7.1 (5.3–9.5)
Year 3	50 (43–58)	41 (34–49)	42 (34–50)	33 (27–41)	33 (26–40)	26 (20–32)	17 (13–23)	14 (10–18)	13 (9.6–17)	9.9 (7.4–13)

IDU=injection-drug use. *Log copies/mL

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Appendix Table 1b. Predicted 6-month Risk of AIDS According to Age and Current CD4 Cell Count and Viral Load, Based on a Poisson Regression Model (Updated October 29, 2004)

Viral load (copies/mL)	Predicted risk (%) at current CD4 cell count (x 10^6 cells/l)[a]									
	50	100	150	200	250	300	350	400	450	500
Age 25 years										
3,000	6.8	3.7	2.3	1.6	1.1	0.8	0.6	0.5	0.4	0.3
10,000	9.6	5.3	3.4	2.3	1.6	1.2	0.9	0.7	0.5	0.4
30,000	13.3	7.4	4.7	3.2	2.2	1.6	1.2	0.9	0.7	0.6
100,000	18.6	10.6	6.7	4.6	3.2	2.4	1.8	1.4	1.1	0.8
300,000	25.1	14.5	9.3	6.3	4.5	3.3	2.5	1.9	1.5	1.2
Age 35 years										
3,000	8.5	4.7	3.0	2.0	1.4	1.0	0.8	0.6	0.5	0.4
10,000	12.1	6.7	4.3	2.9	2.0	1.5	1.1	0.9	0.7	0.5
30,000	16.6	9.3	5.9	4.0	2.8	2.1	1.6	1.2	0.9	0.7
100,000	23.1	13.2	8.5	5.8	4.1	3.0	2.3	1.7	1.3	1.1
300,000	30.8	18.0	11.7	8.0	5.7	4.2	3.1	2.4	1.9	1.5
Age 45 years										
3,000	10.7	5.9	3.7	2.5	1.8	1.3	1.0	0.7	0.6	0.5
10,000	15.1	8.5	5.4	3.6	2.6	1.9	1.4	1.1	0.8	0.7
30,000	20.6	11.7	7.5	5.1	3.6	2.6	2.0	1.5	1.2	0.9
100,000	28.4	16.5	10.6	7.3	5.2	3.8	2.9	2.2	1.7	1.3
300,000	37.4	22.4	14.6	10.1	7.2	5.3	4.0	3.1	2.4	1.9
Age 55 years										
3,000	13.4	7.5	4.7	3.2	2.3	1.7	1.2	0.9	0.7	0.6
10,000	18.8	10.7	6.8	4.6	3.3	2.4	1.8	1.4	1.1	0.8
30,000	25.4	14.6	9.4	6.4	4.6	3.3	2.5	1.9	1.5	1.2
100,000	34.6	20.5	13.3	9.2	6.5	4.8	3.6	2.8	2.2	1.7
300,000	44.8	27.5	18.2	12.6	9.1	6.7	5.0	3.9	3.0	2.4

[a] Shading distinguishes risk: <2%, no shading; 2%–9.9%, light gray; 10%–19.9%, mid-gray; ≥ 20%, darkest gray.

Reprint with permission from Lippincott, Williams & Wilkins [Phillips A; CASCADE Collaboration. Short-term risk of AIDS according to current CD4 cell count and viral load in antiretroviral drug-naïve individuals and those treated in the monotherapy era. *AIDS* 2004; 18 (1):51-8].

Appendix Table 2. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

 (Updated November 3, 2008)

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations	Food Effect	Oral Bio-availability	Serum half-life	Intracellular half-life	Elimination	Adverse Events
Abacavir (ABC) ZIAGEN **TRIZIVIR** - w/ ZDV+3TC **EPZICOM** - w/ 3TC	ZIAGEN 300mg tablets or 20mg/mL oral solution TRIZIVIR ABC 300mg + ZDV 300mg + 3TC 150mg EPZICOM ABC 600mg + 3TC 300mg	ZIAGEN 300mg BID or 600mg once daily TRIZIVIR 1 tablet BID EPZICOM 1 tablet once daily	Take without regard to meals; Alcohol increases abacavir levels 41%; abacavir has no effect on alcohol	83%	1.5 hours	12–26 hours	Metabolized by alcohol dehydrogenase and glucuronyl transferase. Renal excretion of metabolites 82% TRIZIVIR & EPZICOM not for patients with CrCl < 50 mL/min	• Hypersensitivity reaction that can be fatal, symptoms may include fever, rash, nausea, vomiting, malaise or fatigue, loss of appetite, respiratory symptoms such as sore throat, cough, shortness of breath • Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with use of NNRTIs)
Didanosine (ddI) VIDEX EC, Generic didanosine enteric coated (dose same as VIDEX EC)	VIDEX EC 125, 200, 250, 400mg capsules Buffered tablets (non-EC) are no longer available.	Body weight **≥ 60kg**: 400mg once daily with TDF: 250mg once daily **< 60 kg**: 250mg once daily with TDF: 200mg once daily	Levels decrease 55%; Take 1/2 hour before or 2 hours after meal	30–40%	1.5 hours	>20 hours	Renal excretion 50% Dosage adjustment in renal insufficiency (See **Appendix Table 8**)	• Pancreatitis • Peripheral neuropathy • Nausea • Lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity associated with use of NRTIs.
Emtricitabine (FTC) EMTRIVA **ATRIPLA** - w/ EFV+TDF **TRUVADA** - w/ TDF	EMTRIVA 200mg hard gelatin capsule and 10mg/mL oral solution ATRIPLA EFV 600mg + FTC 200mg + TDF 300mg TRUVADA FTC 200mg + TDF 300mg	EMTRIVA 200mg capsule once daily or 240mg (24 mL) oral solution once daily ATRIPLA 1 tablet once daily TRUVADA 1 tablet once daily	Take without regard to meals	93%	10 hours	>20 hours	Renal excretion Dosage adjustment in renal insufficiency (See **Appendix Table 8**) ATRIPLA - not for patients with CrCl <50 mL/min TRUVADA - not for patients with CrCl < 30 mL/min	• Minimal toxicity • Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with use of NRTIs.) • Hyper-pigmentation/ skin discoloration
Lamivudine (3TC) EPIVIR **COMBIVIR**- w/ ZDV **EPZICOM** - w/ ABC **TRIZIVIR**- w/ ZDV+ABC	EPIVIR 150 or 300mg tablets or 10mg/mL oral solution COMBIVIR 3TC 150mg + ZDV 300mg EPZICOM 3TC 300mg + ABC 600mg TRIZIVIR 3TC 150mg + ZDV 300mg + ABC 300mg	EPIVIR 150mg BID or 300mg once daily COMBIVIR 1 tablet BID EPZICOM 1 tablet once daily TRIZIVIR 1 tablet BID	Take without regard to meals	86%	5–7 hours	18–22 hours	Renal excretion Dosage adjustment in renal insufficiency (See **Appendix Table 8**) COMBIVIR, TRIZIVIR & EPZICOM not for patients with CrCl < 50 mL/min	• Minimal toxicity • Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with use of NRTIs)

Appendix Table 2. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

 (Updated November 3, 2008)

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations	Food Effect	Oral Bio-availability	Serum half-life	Intracellular half-life	Elimination	Adverse Events
Stavudine (d4T) ZERIT	ZERIT 15, 20, 30, 40mg capsules or 1mg/mL oral solution	Body weight >60 kg: 40mg BID Body weight <60 kg: 30mg BID Note: WHO recommends 30mg BID dosing regardless of body weight	Take without regard to meals	86%	1.0 hour	7.5 hours	Renal excretion 50% Dosage adjustment in renal insufficiency (See **Appendix Table 8**)	• Peripheral neuropathy • Lipodystrophy • Pancreatitis • Lactic acidosis with hepatic steatosis-higher incidence than w/ other NRTIs • Hyperlipidemia • Rapidly progressive ascending neuromuscular weakness (rare)
Tenofovir Disoproxil Fumarate (TDF) VIREAD **ATRIPLA** - w/ EFV+FTC **TRUVADA -** w/ FTC	VIREAD 300mg tablet ATRIPLA EFV 600mg + FTC 200mg + TDF 300mg TRUVADA TDF 300mg + FTC 200mg	VIREAD 1 tablet once daily ATRIPLA 1 tablet once daily TRUVADA 1 tablet once daily	Take without regard to meals	25% in fasting state; 39% with high-fat meal	17 hours	>60 hours	Renal excretion Dosage adjustment in renal insufficiency (See **Appendix Table 8**) ATRIPLA- not for patients with CrCl <50 mL/min TRUVADA - not for patients with CrCl < 30 mL/min	• Asthenia, headache, diarrhea, nausea, vomiting, and flatulence • Renal insufficiency,, Fanconi syndrome • Potential for osteopenia • Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with use of NRTIs)
Zidovudine (AZT, ZDV) RETROVIR **COMBIVIR -** w/ 3TC **TRIZIVIR- w/** 3TC+ABC	RETROVIR 100mg capsules, 300mg tablets, 10mg/mL intravenous solution, 10mg/mL oral solution COMBIVIR 3TC 150mg + ZDV 300mg TRIZIVIR 3TC 150mg + ZDV 300mg + ABC 300mg	RETROVIR 300mg BID or 200mg TID COMBIVIR 1 tablet BID TRIZIVIR 1 tablet BID	Take without regard to meals	60%	1.1 hours	7 hours	Metabolized to AZT glucuronide (GAZT). Renal excretion of GAZT Dosage adjustment in renal insufficiency (See **Appendix Table 8**) COMBIVIR & TRIZIVIR - not for patients with CrCl < 50 mL/min	• Bone marrow suppression: macrocytic anemia or neutropenia; • Gastrointestinal intolerance, headache, insomnia, asthenia; • Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity associated with use of NRTIs)

Appendix Table 3. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

(Updated November 3, 2008)

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations	Food Effect	Oral Bio-availability	Serum half-life	Elimination	Adverse Events
Delavirdine (DLV)/ RESCRIPTOR	100mg tablets or 200mg tablets	400mg 3 times/day; four 100mg tablets can be dispersed in ≥3 oz. of water to produce slurry; 200mg tablets should be taken as intact tablets; separate dose from antacids by 1 hour	Take without regard to meals	85%	5.8 hours	Metabolized by cytochrome P450 (3A inhibitor); 51% excreted in urine (<5% unchanged); 44% in feces	• Rash* • Increased transaminase levels • Headaches
Efavirenz (EFV)/ SUSTIVA Also available as **ATRIPLA** - with FTC + TDF	50, 100, 200mg capsules or 600mg tablets ATRIPLA - EFV 600mg + FTC 200mg + TDF 300mg	600mg daily on an empty stomach, at or before bedtime	High-fat/high-caloric meals increase peak plasma concentrations of capsules by 39% and tablets by 79%; take on an empty stomach	Data not available	40–55 hours	Metabolized by cytochrome P450 (3A mixed inducer/ inhibitor); No dosage adjustment in renal insufficiency if EFV is used alone; ATRIPLA - not for patients with CrCl <50 mL/min	• Rash* • Central nervous system symptoms† • Increased transaminase levels • False-positive cannabinoid test • Teratogenic in monkeys‡
Etravirine (ETR)/ INTELENCE	100mg tablets	200mg twice daily following a meal	Take following a meal. Fasting conditions reduce drug exposure by approximately 50%	Unknown	41 ± 20 hours	Metabolized by cytochrome P450 (3A4, 2C9, and 2C19 substrate, 3A4 inducer, 2C9 and 2C19 inhibitor)	• Rash* • Nausea
Nevirapine (NVP)/ VIRAMUNE	200mg tablets or 50mg/5 mL oral suspension	200mg daily for 14 days; thereafter, 200mg by mouth twice daily	Take without regard to meals	>90%	25–30 hours	Metabolized by cytochrome P450 (3A inducer); 80% excreted in urine (glucuronidated metabolites; <5% unchanged); 10% in feces Not recommended in patients with moderate-to-severe hepatic impairment (Child Pugh B or C) Dosage adjustment in hepatic insufficiency recommended (See **Appendix Table 8**)	• Rash including Stevens-Johnson syndrome* • Symptomatic hepatitis, including fatal hepatic necrosis, have been reported‡

* During clinical trials, NNRTI was discontinued because of rash among 7% of patients taking nevirapine, 4.3% of patients taking delavirdine, 1.7% of patients taking efavirenz, and 2% of patients taking etravirine. Rare cases of Stevens-Johnson syndrome have been reported with the use of all four NNRTIs, the highest incidence seen with nevirapine use.

† Adverse events can include dizziness, somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, and euphoria. Overall frequency of any of these symptoms associated with use of efavirenz was 52%, as compared with 26% among controls subjects; 2.6% of those persons on efavirenz discontinued the drug because of these symptoms; symptoms usually subside spontaneously after 2–4 weeks.

‡ Symptomatic, sometimes serious, and even fatal hepatic events (accompanied by rash in approximately 50% of cases) occur with significantly higher frequency in treatment-naive female patients with prenevirapine CD4 counts >250 cells/mm3 or in treatment-naive male patients with prenevirapine CD4 counts >400 cells/mm3. Nevirapine should not be initiated in these patients unless the benefit clearly outweighs the risk. This toxicity has not been observed when nevirapine is given as single doses to mothers or infants for prevention of mother-to-child HIV transmission.

Appendix Table 4. Characteristics of Protease Inhibitors (PIs) (Updated November 3, 2008)

Generic Name/ Trade Name	Formulation	Dosing Recommendations	Food Effect	Oral Bio-availability	Serum half-life	Route of Metabolism	Storage	Adverse Events
Atazanavir (ATV)/ REYATAZ	100mg, 150mg, 200mg, 300mg capsules	400mg once daily (unboosted ARV only recommended for PI-naïve pts) With efavirenz or tenofovir TDF, or for ARV-experienced pts: (ATV 300mg + RTV 100mg) once daily With EFV in treatment-naïve pts: (ATV 400mg + RTV 100mg) once daily (for dosing recommendations with H2 antagonists and PPIs, please refer to **Table 15a**)	Administration with food increases bioavailability. Take with food; avoid taking simultaneously with antacids	Not determined	7 hours	Cytochrome P450 3A4 inhibitor and substrate Dosage adjustment in hepatic insufficiency recommended (See **Appendix Table 8**)	Room temperature (up to 25ºC or 77ºF)	• Indirect hyperbilirubinemia • Prolonged PR interval— 1st degree symptomatic AV block in some pts • Use with caution in pts with underlying conduction defects or on concomitant medications that can cause PR prolongation • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in pts with hemophilia • Nephrolithiasis
Darunavir (DRV)/ PREZISTA	300mg, 400mg, 600mg tablets	ARV-naïve pts: (DRV 800mg + RTV 100mg) once daily ARV- experienced pts: (DRV 600mg + RTV 100mg) BID Unboosted DRV is **not** recommended	Food ↑ Cmax & AUC by 30% - should be administered with food	Absolute bioavailability: DRV alone – 37%; w/ RTV – 82%;	15 hours (when combined with RTV)	Cytochrome P450 3A4 inhibitor and substrate	Room temperature (up to 25ºC or 77ºF)	• Skin rash (7%) – DRV has a sulfonamide moiety; Stevens-Johnson syndrome & erythrema multiforme have been reported. • Hepatotoxicity • Diarrhea, nausea • Headache • Hyperlipidemia • Transaminase elevation • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in pts with hemophilia
Fosamprenavir (FPV)/ LEXIVA	700mg tablet or 50mg/mL oral suspension	ARV-naïve pts: • FPV 1,400mg BID or • (FPV 1,400mg + RTV 100-200mg) once daily or • (FPV 700mg + RTV 100mg) BID PI-experienced pts (once daily dosing not recommended): • (FPV 700mg + RTV 100mg) BID With EFV (FPV boosted only): • (FPV 700mg + RTV 100mg) BID or • (FPV 1,400mg + RTV 300mg) once daily	No significant change in amprenavir pharmacokinetics in fed or fasting state	Not established	7.7 hours (amprenavir)	Amprenavir is a cytochrome P450 3A4 inhibitor, inducer, and substrate Dosage adjustment in hepatic insufficiency recommended (See **Appendix Table 8**)	Room temperature (up to 25ºC or 77ºF)	• Skin rash (19%) • Diarrhea, nausea, vomiting • Headache • Hyperlipidemia • Transaminase elevation • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia
Indinavir/ CRIXIVAN	200mg , 333mg, 400mg capsules	800mg every 8 hours; With RTV: (IDV 800mg + RTV 100-200mg) BID	Unboosted IDV Levels decrease by 77% Take 1 hour before or 2 hours after meals; may take with skim milk or low-fat meal RTV-boosted IDV: Take with or without food	65%	1.5–2 hours	Cytochrome P450 3A4 inhibitor (less than ritonavir) Dosage adjustment in hepatic insufficiency recommended (See **Appendix Table 8**)	Room temperature 15º–30ºC (59º–86ºF), protect from moisture	• Nephrolithiasis • GI intolerance, nausea • Indirect hyperbilirubinemia • Hyperlipidemia • Headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, alopecia, and hemolytic anemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in pts with hemophilia

Appendix Table 4. Characteristics of Protease Inhibitors (PIs) (Updated November 3, 2008)

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations	Food Effect	Oral Bio-availability	Serum half-life	Route of Metabolism	Storage	Adverse Events
Lopinavir + Ritonavir (LPV/r)/ **KALETRA**	Each tablet contains LPV 200mg + RTV 50mg Oral solution: Each 5 mL contains LPV 400mg + RTV 100mg Note: Oral solution contains 42% alcohol	LPV 400mg + RTV 100mg (2 tablets or 5 mL) BID or LPV 800mg + RTV 200mg (4 tablets or 10mL) once daily (**Note:** once-daily dosing only recommended for treatment-naïve pts; not for pregnant women or patients receiving EFV, NVP, FPV, or NFV) With EFV or NVP: For ARV-experienced pts: LPV 600mg + RTV 150mg (3 tablets) BID or LPV 533 mg + RTV 133 mg (6.7 mL oral solution) BID with food	Oral tablet -No food effect; take with or without food Oral solution - Moderately fatty meal ↑ LPV AUC & Cmin by 80% & 54%, respectively; take with food	Not determined in humans	5–6 hours	Cytochrome P450 (3A4 inhibitor and substrate)	Oral tablet is stable at room temperature Oral solution is stable at 2°–8°C until date on label; is stable when stored at room temperature (up to 25ºC or 77ºF) for 2 months	• GI intolerance, nausea, vomiting, diarrhea (higher incidence with once-daily than twice-daily dosing) • Asthenia • Hyperlipidemia (esp. hypertriglyceridemia) • Elevated serum transaminases • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia
Nelfinavir (NFV)/ **VIRACEPT**	250mg, 625mg tablets 50mg/g oral powder	1,250mg BID or 750mg TID	Levels increase 2–3 fold Take with meal or snack	20%–80%	3.5–5 hours	Cytochrome P450 3A4 inhibitor and substrate	Room temperature 15º–30ºC (59º–86ºF)	• Diarrhea • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes among patients with hemophilia • Serum transaminase elevation •
Ritonavir (RTV)/ **NORVIR**	100mg capsules or 80 mg/mL oral solution	As pharmacokinetic booster for other PIs: 100mg – 400mg per day in 1–2 divided doses (please refer to other PIs for specific dosing recommendations) 600mg every 12 hours* (when ritonavir is used as sole PI)	Levels increase 15% Take with food if possible; this may improve tolerability	Not determined	3–5 hours	Cytochrome P450 (3A4 > 2D6) substrate; Potent 3A4, 2D6 inhibitor	Refrigerate capsules Capsules can be left at room temperature (up to 25ºC or 77ºF) for ≤30 days; Oral solution should NOT be refrigerated	• GI intolerance, nausea, vomiting, diarrhea • Paresthesias – circumoral and extremities • Hyperlipidemia, esp. hypertriglyceridemia • Hepatitis • Asthenia • Taste perversion • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia
Saquinavir tablets and hard gel capsules (SQV)/ **INVIRASE**	200mg hard gel capsules, 500mg tablets	(SQV 1,000mg + RTV 100mg) PO BID Unboosted SQV is **not** recommended	Take within 2 hours of a meal	4% erratic (when taken as sole PI)	1–2 hours	Cytochrome P450 (3A4 inhibitor and substrate)	Room temperature 15º–30ºC (59º–86ºF)	• GI intolerance, nausea and diarrhea • Headache • Elevated transaminase enzymes • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia

* Dose escalation for Ritonavir when used as sole PI: Days 1 and 2: 300mg two times; Days 3–5: 400mg two times; Days 6–13: 500mg two times; Day 14: 600mg two times/day.

Appendix Table 4. Characteristics of Protease Inhibitors (PIs) (Updated November 3, 2008)

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations	Food Effect	Oral Bio-availability	Serum half-life	Route of Metabolism	Storage	Adverse Events
Tipranavir (TPV)/ APTIVUS	250mg capsules	(TPV 500mg + RTV 200mg) PO BID Unboosted TPV is **not** recommended	No clinically significant change in TPV pharmacokinetics in fed or fasting state	Not determined	6 hours after single dose of TPV/ RTV	TPV – Cytochrome P450 (3A4 inducer and substrate) Net effect when combined with RTV – CYP 3A4 inhibitor and CYP 2D6 inhibitor	Refrigerated capsules are stable until date on label; if stored at room temperature (up to 25ºC or 77ºF) – must be used within 60 days	• Hepatotoxicity – clinical hepatitis including hepatic decompensation has been reported, monitor closely, esp. in patients with underlying liver diseases • Skin rash – TPV has a sulfonamide moiety, use with caution in patients with known sulfonamide allergy • Rare cases of fatal and nonfatal intracranial hemorrhages have been reported. Most patients had underlying comorbidity such as brain lesion, head trauma, recent neurosurgery, coagulopathy, hypertension, alcoholism, or on medication with increase risk for bleeding • Hyperlipidemia (esp. hypertriglyceridemia) • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia

Appendix Table 5. Characteristics of Fusion Inhibitors (Updated January 29, 2008)

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations	Food Effect	Oral Bio-availability	Serum half-life	Route of Metabolism	Storage	Adverse Events
Enfuvirtide (T20)/ FUZEON	• Injectable – in lyophilized powder • Each vial contains 108 mg of enfuvirtide, reconstitute with 1.1 mL of Sterile Water for injection for delivery of approximately 90mg/1 mL	90mg (1 mL) subcutaneously BID	Not applicable	Not applicable	3.8 hours	Expected to undergo catabolism to its constituent amino acids, with subsequent recycling of the amino acids in the body pool	Store at room temperature (up to 25ºC or 77ºF) Reconstituted solution should be stored under refrigeration at 2ºC–8ºC (36ºF–46Fº) and used within 24 hours	• Local injection site reactions – almost 100% of patients (pain, erythema, induration, nodules and cysts, pruritus, ecchymosis) • Increased bacterial pneumonia • Hypersensitivity reaction (<1%) - symptoms may include rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases; rechallenge is not recommended

Appendix Table 6. Characteristics of CCR5 Antagonists (Updated January 29, 2008)

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations	Food Effect	Oral Bio-availability	Serum half-life	Route of Metabolism	Storage	Adverse Events
Maraviroc (MVC)/ SELZENTRY	150mg, 300mg tablets	• **150mg BID** when given with strong CYP3A inhibitors (with or without CYP3A inducers) including PIs (except tipranavir/ritonavir) • **300mg BID** when given with NRTIs, enfuvirtide, tipranavir/ritonavir, nevirapine, and other drugs that are not strong CYP3A inhibitors • **600mg BID** when given with CYP3A inducers, including efavirenz, rifampin, etc. (without a CYP3A inhibitor)	No food effect; take with or without food	23% for 100mg dose and 33% (predicted) for 300mg	14–18 hrs	Cytochrome P450 (CYP3A substrate)	Room temperature	Abdominal pain, cough, dizziness, musculoskeletal symptoms, pyrexia, rash, upper respiratory tract infections, hepatotoxicity, orthostatic hypotension.

Appendix Table 7. Characteristics of Integrase Inhibitors (Updated January 29, 2008)

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations	Food Effect	Oral Bio-availability	Serum half-life	Route of Metabolism	Storage	Adverse Events
Raltegravir (RAL)/ ISENTRESS	400mg tablets	400mg BID	Take with or without food	Not established	≈ 9 hrs	UGT1A1-mediated glucuronidation	Room temperature	Nausea, headache, diarrhea, pyrexia, CPK elevation

Appendix Table 8. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Updated November 3, 2008)

Antiretrovirals	Daily Dose	Dosing in Renal Insufficiency	Dosing in Hepatic Impairment
Nucleoside Reverse Transcriptase Inhibitors – Note: Use of fixed-dose combination NRTI (+/- NNRTI) of: ATRIPLA, COMBIVIR, TRIZIVIR, EPZICOM – not recommended in patients with CrCl <50 mL/min; use of TRUVADA – not recommended in patients with CrCl <30 mL/min			
Abacavir* (ZIAGEN)	300mg PO BID	No need for dosage adjustment	No dosage recommendation
Didanosine (VIDEX EC)	>60 kg 400mg PO once daily <60 kg 250mg once daily	**Dose** **CrCl (mL/min) >60 kg <60 kg** 30-59 200mg 125 mg 10-29 125 mg 100mg < 10 125 mg 75 mg CAPD or HD patients: use same dose as CrCl < 10 ml/min	No dosage recommendation
Emtricitabine (EMTRIVA)	200mg oral capsule PO once daily or 240mg (24mL) oral solution PO once daily	**CrCl capsule solution** 30-49 200mg q48h 120mg q24h 15-29 200mg q72h 80mg q24h <15 200mg q96h 60mg q24h or HD*	No dosage recommendation
Lamivudine* (EPIVIR)	300mg PO once daily or 150mg PO BID	**CrCl (mL/min) Dose** 30-49 150mg q24h 15-29 150mg x 1, then 100mg q24h 5-14 150mg x 1, then 50mg q24h <5 50mg x 1, then 25 mg q24h or HD*	No dosage recommendation
Stavudine (ZERIT)	>60 kg 40mg PO BID <60 kg 30mg PO BID	**Dose** **CrCl (mL/min) >60 kg <60 kg** 26-50 20mg q12h 15 mg q12h 10-25 20mg q24h 15 mg q24h or HD*	No dosage recommendation
Tenofovir (VIREAD)	300mg PO once daily	**CrCl (mL/min) Dose** 30-49 300mg q48h 10-29 300mg twice weekly ESRD 300mg q7d or HD*	No dosage recommendation
Tenofovir + Emtricitabine (TRUVADA)	1 tablet PO once daily	**CrCl (mL/min) Dose** 30-49 tablet q48h <30 not recommended	No dosage recommendation
Zidovudine* (RETROVIR)	300mg PO BID	"Severe" renal impairment (CrCl < 15 mL/min) or HD*: 100mg TID or 300mg once daily	No dosage recommendation
Non-Nucleoside Reverse Transcriptase Inhibitors			
Delavirdine (RESCRIPTOR)	400mg PO TID	No dosage adjustment necessary	No recommendation; use with caution in patients with hepatic impairment
Efavirenz (SUSTIVA) Efavirenz/tenofovir/ emtricitabine (ATRIPLA)	600mg PO once daily One tablet PO once daily	No dosage adjustment necessary ATRIPLA™ - not recommended if CrCl <50 ml/min	No recommendation; use with caution in patients with hepatic impairment
Etravirine (INTELENCE)	200mg PO BID following a meal	No dosage adjustment necessary	No dosage adjustment for Child-Pugh Class A or B. Has not been evaluated in patients with Child-Pugh Class C
Nevirapine (VIRAMUNE)	200mg PO BID	No dosage adjustment necessary	Contraindicated in patients with Child-Pugh Class B or C

HD* = dose after dialysis on dialysis days, HD = hemodialysis, CAPD = chronic ambulatory peritoneal dialysis, ESRD = End Stage Renal Disease

Appendix Table 8. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Updated November 3, 2008)

Antiretrovirals	Daily Dose	Dosing in Renal Insufficiency	Dosing in Hepatic Impairment
Protease Inhibitors			
Atazanavir (REYATAZ, ATV)	400mg PO once daily or (ATV 300mg + RTV 100mg) once daily	No dosage adjustment for patients with renal dysfunction not requiring hemodialysis Treatment-naïve patients on hemodialysis: ATV 300mg + RTV 100mg once daily Treatment-experienced patients on hemodialysis: ATV or RTV-boosted ATV not recommended	**Child-Pugh Score** **Dose** 7-9 300mg once daily >9 not recommended RTV boosting is not recommended in patients with hepatic impairment
Darunavir (PREZISTA, DRV)	(DRV 800mg + RTV 100mg) PO once daily (ARV-naïve pts) (DRV 600mg + RTV 100mg) PO BID	No dosage adjustment necessary	No dosage adjustment in patients with mild to moderate hepatic impairment. DRV is not recommended in patients with severe hepatic impairment.
Fosamprenavir (LEXIVA, FPV)	1,400mg PO BID; or (FPV 1,400mg + 100-200mg RTV) PO once daily; or (FPV 700mg + RTV 100mg) PO BID	No dosage adjustment necessary	**Child-Pugh Score** **Dose** 5-8 700mg BID 9-12 not recommended Ritonavir boosting should not be used in patients with hepatic impairment
Indinavir (CRIXIVAN)	800mg PO q8h	No dosage adjustment necessary	Mild to moderate hepatic insufficiency because of cirrhosis: 600mg q8h
Lopinavir/ritonavir (KALETRA)	400/100mg PO BID or 800/200mg PO once daily (only for treatment-naïve patients)	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment
Nelfinavir (VIRACEPT)	1,250mg PO BID	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment
Ritonavir (NORVIR)	600mg PO BID	No dosage adjustment necessary	No dosage adjustment in mild hepatic impairment; no data for moderate to severe impairment, use with caution
Saquinavir (INVIRASE, SQV)	(SQV 1,000mg + RTV 100mg) PO BID	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment
Tipranavir (APTIVUS)	(TPV 500mg + RTV 200mg) PO BID	No dosage adjustment necessary	No dosage recommendation; use with caution in Child-Pugh Class A; TPV/RTV is contraindicated in pts with moderate to severe (Child-Pugh Class B & C) hepatic insufficiency
Fusion Inhibitors			
Enfuvirtide (FUZEON)	90mg SUB-Q q12h	No dosage adjustment necessary	No dosage recommendation
CCR5 Antagonists			
Maraviroc (SELZENTRY)	The recommended dose differs based on concomitant medications because of drug interactions. See **Appendix Table 6** for detailed dosing information.	No dosage recommendation; use with caution. Patients with CrCL <50 mL/min should receive MVC and CYP3A inhibitor only if potential benefits outweigh the risk.	No dosage recommendations. Concentrations will likely be increased in patients with hepatic impairment.
Integrase Inhibitors			
Raltegravir (ISENTRESS)	400mg twice daily	No dosage adjustment.	No dosage adjustment.

Creatinine Clearance calculation:

Male: $\frac{(140\text{-age in yr}) \times \text{weight (kg)}}{72 \times \text{S.Cr.}}$ Female: $\frac{(140\text{-age in yr}) \times \text{weight (kg)} \times 0.85}{72 \times \text{S.Cr.}}$

Child-Pugh Score

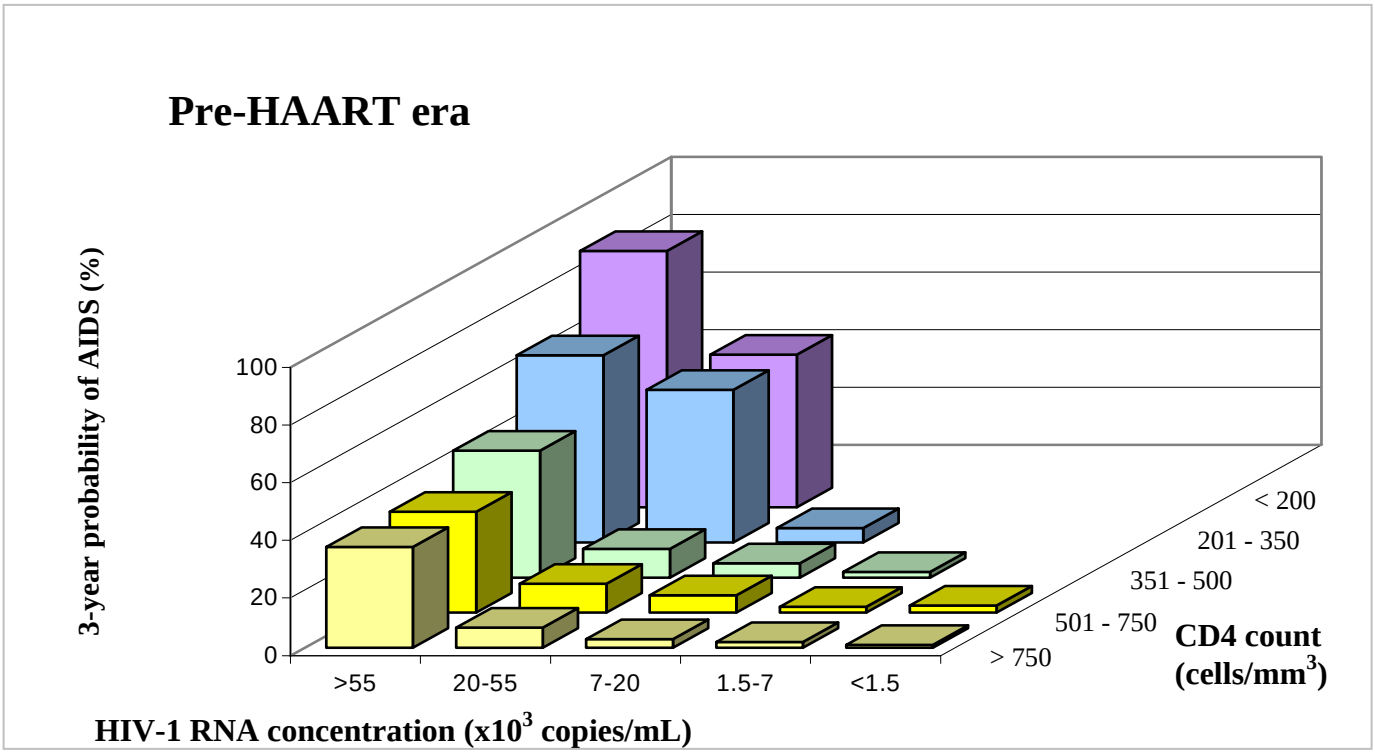
Component	Score Given		
	1	2	3
Encephalopathy*	None	Grade 1-2	Grade 3-4
Ascites	None	Mild or controlled by diuretics	Moderate or refractory despite diuretics
Albumin	>3.5 g/dl	2.8 to 3.5 g/dl	<2.8 g/dl
Total Bilirubin OR Modified Total Bilirubin**	<2 mg/dL (<34 μ mol/L) <4 mg/dL	2 to 3 mg/dL(34 μ mol/L to 50 μ mol/L) 4-7 mg/dL	>3 mg/dL(>50 μ mol/L) >7 mg/dL
Prothrombin time (sec prolonged) OR INR	<4 <1.7	4-6 1.7-2.3	>6 >2.3

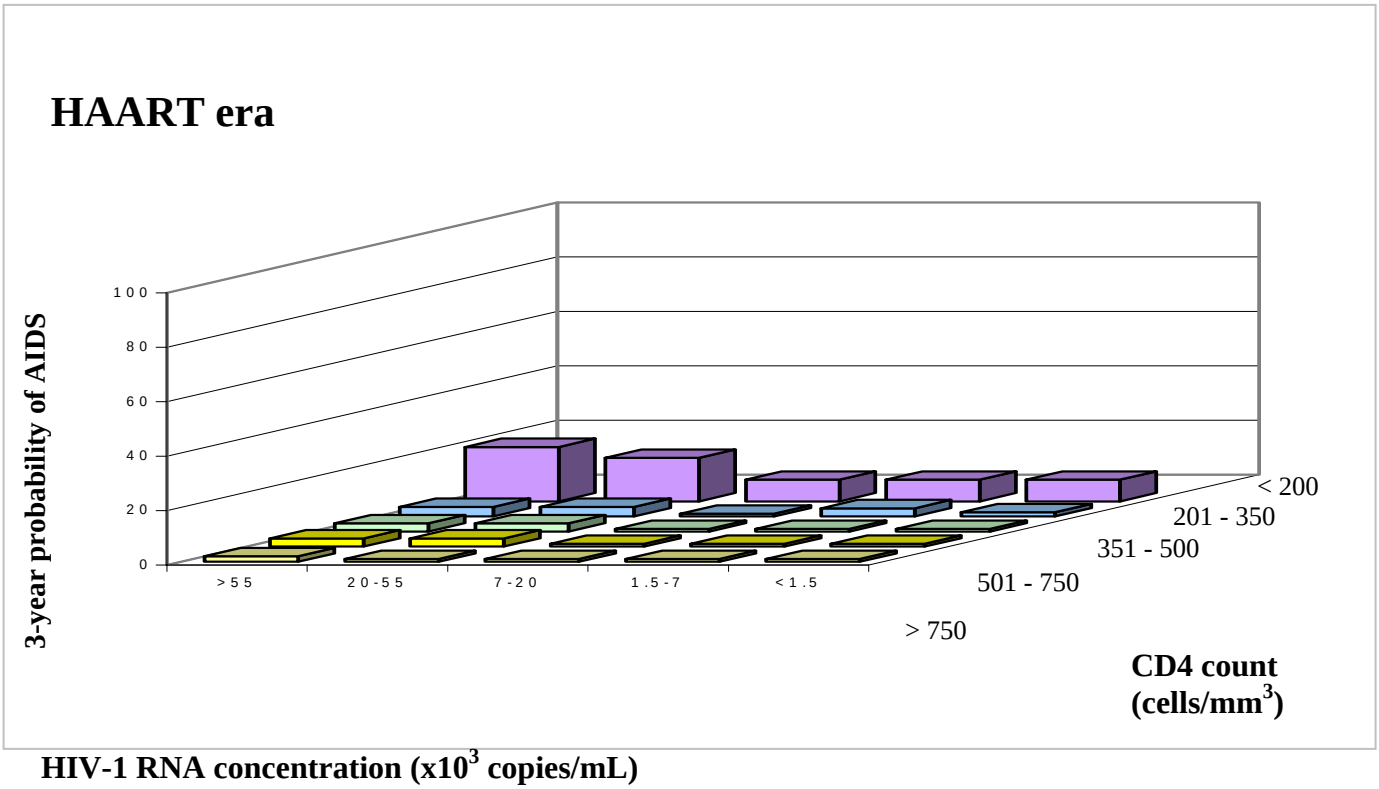
* NB: Encephalopathy Grades - Grade 1: Mild confusion, anxiety, restlessness, fine tremor, slowed coordination; Grade 2: Drowsiness, disorientation, asterixis; Grade 3: Somnolent but rousable, marked confusion, incomprehensible speech, incontinence, hyperventilation; Grade 4: Coma, decerebrate posturing, flaccidity

** Modified Total Bilirubin used to score patients who have Gilbert's syndrome or who are taking indinavir

Child-Pugh Classification - Child-Pugh Class A = score 5–6; Class B = score 7–9; Class C = score >9

Figure A: Prognosis According to CD4 Cell Count and Viral Load in the Pre-HAART and HAART Eras (Updated October 29, 2004)





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