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

December 1, 2009

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

How to Cite the Adult and Adolescent Guidelines:
Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. December 1, 2009; 1-161. Available at **http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf**. Accessed (insert date) [insert page number, table number, etc. if applicable]

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 key changes were made to update the November 3, 2008, version of the guidelines. Significant updates are highlighted throughout the document.

New Section

Based on interests and requests from HIV practitioners, a new section entitled "**Considerations in Managing Patients with HIV-2 Infection**" has been added to the guidelines. This new section briefly reviews the current knowledge on the epidemiology and diagnosis of HIV-2 infection and the role of antiretroviral therapy in the management of patients with HIV-2 mono-infection and HIV-1/HIV-2 coinfection.

Key Updates

Drug Resistance Testing

In this revision, the Panel provides more specific recommendations on when to use genotypic versus phenotypic testing to guide therapy in treatment-experienced patients with viremia while on treatment.

- Genotypic testing is recommended as the preferred resistance testing to guide therapy in patients with suboptimal virologic responses or virologic failure while on first or second regimens **(AIII)**.
- Addition of phenotypic testing to genotypic testing is generally preferred for persons with known or suspected complex drug resistance mutation patterns, particularly to protease inhibitors **(BIII)**.

Initiation of Antiretroviral Therapy

In this updated version of the guidelines, the Panel recommends earlier initiation of antiretroviral therapy with the following specific recommendations:

- Antiretroviral therapy should be initiated in all patients with a history of an AIDS-defining illness or with CD4 count < 350 cells/mm^3 **(AI)**.
- Antiretroviral therapy should also be initiated, regardless of CD4 count, in patients with the following conditions: pregnancy **(AI)**, HIV-associated nephropathy **(AII)**, and hepatitis B virus (HBV) coinfection when treatment of HBV is indicated **(AIII)**.
- Antiretroviral therapy is recommended for patients with CD4 counts between 350 and 500 cells/mm^3. The Panel was divided on the strength of this recommendation: 55% of Panel members for strong recommendation (A) and 45% for moderate recommendation (B) **(A/B-II)**.
- For patients with CD4 counts >500 cells/mm^3, 50% of Panel members favor starting antiretroviral therapy (B); the other 50% of members view treatment as optional (C) in this setting **(B/C-III)**.

Patients initiating antiretroviral therapy should be willing and able to commit to lifelong treatment and should understand the benefits and risks of therapy and the importance of adherence **(AIII)**. Patients may choose to postpone therapy, and providers may elect to defer therapy, based on clinical and/or psychosocial factors on a case-by-case basis.

What to Start in Antiretroviral-Naïve Patients

- Increasing clinical trial data in the past few years have allowed for better distinction between the virologic efficacy and safety of different combination regimens. Instead of providing recommendations for individual antiretroviral components to use to make up a combination, the Panel now defines what regimens are recommended in treatment-naïve patients.
- Regimens are classified as "Preferred," "Alternative," "Acceptable," "Regimens that may be acceptable but more definitive data are needed," and "Regimens to be used with caution."
- The following changes were made in the recommendations:
    - "Raltegravir + tenofovir/emtricitabine" has been added as a "Preferred" regimen based on the results of a Phase III randomized controlled trial **(AI)**.
    - Four regimens are now listed as "Preferred" regimens for treatment-naïve patients. They are:

        - efavirenz/tenofovir/emtricitabine;
        - ritonavir-boosted atazanavir + tenofovir/emtricitabine;
        - ritonavir-boosted darunavir + tenofovir/emtricitabine; and
        - raltegravir + tenofovir/emtricitabine.
    - Lopinavir/ritonavir-based regimens are now listed as "Alternative" **(BI)** instead of "Preferred" regimens, except in pregnant women, where twice-daily lopinavir/ritonavir + zidovudine/lamivudine remains a "Preferred" regimen **(AI)**.

Additional Updates

The following sections and their relevant tables have been substantially updated:

- What Not to Use
- Management of Treatment-Experienced Patients
- Treatment Simplification
- Hepatitis C Coinfection
- Antiretroviral-Associated Adverse Effects
- Antiretroviral Drug Interactions
- Preventing Secondary Transmission of HIV

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DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents Panel Roster

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Guidelines Acknowledgement List
The Panel would also like to acknowledge the following individuals for their assistance in the preparation of this revision: *Geoff Gottlieb (University of Washington, Seattle, WA), Scott Letendre (University of California–San Diego), Christine Malati (National Institutes of Health), Stacy Newula (Food and Drug Administration), and Kevin Robertson (University of North Carolina, Chapel Hill, NC)*

Updated December 1, 2009

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 multi-drug–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 care 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. (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.) The guidelines, therefore, are updated frequently by the Panel and are available as a “living document” on the AIDS*info* Web site (**http://www.aidsinfo.nih.gov**). 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 (Updated November 3, 2008)

Page 1 of 2

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 more than 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 two thirds of the Panel members 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 reporting any association with manufacturers of antiretroviral drugs or diagnostics used for management of HIV infections. A list of the latest disclosures can be found in **Appendix A** of this document.
Users of the guidelines	HIV treatment providers

Topic	Comment
Developer	Panel on Antiretroviral Guidelines for Adults and Adolescents—a working group of the 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 non-occupational exposure to HIV. These guidelines are also available on the AIDS*info* Web site (**http://www.aidsinfo.nih.gov**). There is a brief discussion of the management of women of reproductive age and pregnant women in this document. For a 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.
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 AIDS*Info* Web site until appropriate changes can be made in the guidelines document. Updated guidelines are available on the AIDS*info* Web site (**http://www.aidsinfo.nih.gov**).
Public comments	After release of an update on 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 revisions are indicated. The public is also able to submit comments to the Panel at any time at **contactus@aidsinfo.nih.gov**.

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** that represents the quality of the evidence (see Table 2 below).

Table 2. Rating Scheme for Recommendations (Updated November 3, 2008)

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement **B:** Moderate recommendation for the statement **C:** Optional recommendation for the statement	**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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2. Kitahata MM, Van Rompaey SE, Shields AW. Physician experience in the care of HIV-infected persons is associated with earlier adoption of new antiretroviral therapy. *J Acquir Immune Defic Syndr.* 2000;24(2):106-114.
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Baseline Evaluation (November 3, 2008)

Each HIV-infected patient entering into care should have a complete medical history, physical examination, laboratory evaluation, and counseling regarding the implications of HIV infection. 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 is 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 of 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. (See **Preventing Secondary Transmission of HIV** section.)

References

1. Aberg JA, Kaplan JE, Libman H, et al. Primary care guidelines for the management of persons infected with human immunodeficiency virus: 2009 update by the HIV medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis.* 2009;49(5):651-681.
2. Kaplan JE, Benson C, Holmes KH, et al. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep.* 2009;58(RR-4):1-207.

Laboratory Testing for Initial Assessment and Monitoring While on Antiretroviral Therapy

(Updated December 1, 2009)

A number of laboratory tests are important for initial evaluation of an HIV-1-infected patient upon entry into care, during follow-up if therapy is not yet initiated, and prior to and after initiation or switch of therapy to assess virologic and immunologic efficacy of antiretroviral therapy as well as 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 treatment-experienced patients; a 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 Schedule for Patients Prior to and After Initiation of Antiretroviral Therapy (Updated December 1, 2009)

Abbreviations: ABC = abacavir; ART = antiretroviral therapy; EFV = efavirenz; HIVAN = HIV-associated nephropathy; TDF = tenofovir; ZDV = zidovudine

	Entry into care	**Follow-up before ART**	**ART initiation or switch[1]**	**2–8 weeks post-ART initiation or switch**	**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	√	√[3]	√[2]			√	√
Resistance testing	√		√[4]					√	√
HLA-B*5701 testing			√ (if considering ABC)						
Tropism testing			√ (if considering a CCR5 antagonist)					√ (if considering a CCR5 antagonist)	√
Hepatitis B serology[5]	√		√ (may repeat if not immune **and** if HBsAg was (-) at baseline)					√	√
Basic chemistry[6]	√	every 6–12 months	√	√	√				√
ALT, AST, T. bilirubin, D. bilirubin	√	every 6–12 months	√	√	√				√
CBC with differential	√	every 3–6 months	√	√ (if on ZDV)	√				√
Fasting lipid profile	√	if normal, annually	√	√ (consider after starting new ART)		√ (if borderline or abnormal at last measurement)	√ (if normal at last measurement)		√
Fasting glucose	√	if normal, annually	√		√ (if borderline or abnormal at last measurement)	√ (if normal at last measurement)			√
Urinalysis[7]	√		√			√ (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]If HIV RNA is detectable at 2–8 weeks, repeat every 4–8 weeks until suppression to less than level of detection, then every 3–6 months.
[4]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.
[5] If HBsAg is positive at baseline or prior to initiation of antiretroviral therapy, tenofovir + (emricitabine or lamivudine) should be used as part of antiretroviral regimen to treat both HBV and HIV infections. If HBsAb is negative at baseline, Hepatitis B vaccine series should be administered.
[6] 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 and Gault equation or estimation of glomerular filtration rate based on MDRD equation.
[7]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" *[1]*.

CD4+ T-CELL COUNT

The CD4+ T-cell count (or CD4 count) serves as the major clinical indicator of immune function in patients who have HIV infection. It is one of the key factors in deciding whether to initiate antiretroviral therapy and chemoprophylaxis for opportunistic infections, and is the strongest predictor of subsequent disease progression and survival according to clinical trials and cohort studies *[2-3]*. 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 one of the most important factors 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 **Initiating 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, generally 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 *[4]*. 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 monitored 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 (WBC) count 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 *[5-6]* or coinfection with HTLV-1 *[7]* may cause misleadingly elevated absolute CD4 counts. Alpha-interferon, on the other hand, may reduce the absolute CD4 number without changing the CD4 percentage *[8]*. 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, because 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 *[9]*. Thus, viral load testing serves as a surrogate marker for treatment response *[10]* and can be useful in predicting clinical progression *[11-12]*. 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 12–24 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, such as adherence to prescribed medications, altered pharmacology, or drug interactions, should be assessed. 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** and **Management of the Treatment-Experienced Patient** sections **(AI)**.

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DRUG RESISTANCE TESTING (Updated December 1, 2009)

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 or deferred (AIII). If therapy is deferred, repeat testing at the time of antiretroviral therapy initiation should be considered (CIII). HIV drug resistance testing should be performed to assist in the selection of active drugs when changing antiretroviral regimens in patients with virologic failure and HIV RNA levels >1,000 copies/mL (AI). 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 prescribed antiretroviral drugs, or, if not possible, 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 (AI).***
- ***Genotypic testing is recommended as the preferred resistance testing to guide therapy in antiretroviral naïve patients and in patients with suboptimal virologic responses or virologic failure while on first or second regimens (AIII).***
- ***Addition of phenotypic testing to genotypic testing is generally preferred for persons with known or suspected complex drug resistance mutation patterns, particularly to protease inhibitors (BIII).***

Genotypic and Phenotypic Resistance Assays

Genotypic and phenotypic resistance assays are used to assess viral strains and inform selection of treatment strategies. Standard assays provide information on resistance to nucleoside and non-nucleoside reverse transcriptase and protease inhibitors. Testing to evaluate integrase and fusion inhibitor resistance can also be performed through some commercial laboratories. No commercial assays are currently available for assessing resistance to CCR5 antagonists.

Genotypic Assays

Genotypic assays detect drug resistance mutations present in relevant viral genes. Most genotypic assays involve sequencing of the reverse transcriptase and protease genes to detect mutations that are known to confer drug resistance. A genotypic assay that assesses mutations in the integrase gene is also commercially available. Genotypic assays can be performed rapidly with results available 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, integrase, and envelope genes (see **http://www.iasusa.org/resistance_mutations**) *[1]*. The Stanford University HIV Drug Resistance Database (**http://hivdb.stanford.edu**) also provides helpful guidance for interpreting genotypic resistance test results. 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 test results and the 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 and, more recently, integrase and envelope sequences derived from patient plasma HIV RNA are inserted into the backbone of a laboratory clone of HIV or used to generate pseudotyped viruses that express the patient-derived HIV genes of interest. Replication of these viruses 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 phenotypic assays are commercially available with results reported 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. Despite being present, drug-resistant viruses constituting less than 10%–20% of the circulating virus population will probably not be detected by available assays. This limitation is important because after drugs exerting selective pressure on drug-resistant populations are discontinued, a wild-type virus often re-emerges as the predominant population in the plasma. This results in a decrease of the proportion of virus with resistance mutations to below the 10%–20% threshold *[12-14]*. For some drugs, this reversion to predominantly wild-type virus can occur 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. However, 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 vs. phenotypic) in different clinical situations. In most situations genotypic testing is preferred because of the faster turnaround time, lower cost, and enhanced sensitivity for detecting mixtures of wild-type and resistant virus. 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 is well documented and 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 resistance to drugs from more than one class *[24, 26]*. If the decision is made to initiate therapy in a person with acute HIV infection, resistance testing at baseline will provide guidance in selecting a regimen to optimize virologic response. Therefore, resistance testing in this situation is recommended **(AIII)** using a genotypic assay. 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 it is possible for a patient to acquire drug-resistant virus (i.e., superinfection) between entry into care and initiation of antiretroviral therapy, repeat resistance testing at the time treatment is started 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 *[27-29]*. No prospective trial has addressed whether drug resistance testing prior to initiation of therapy confers benefit in this population. However, data from several, but not all, studies suggest suboptimal virologic responses in persons with baseline mutations *[16-19, 30-32]*. In addition, a cost-effectiveness analysis of early genotypic resistance testing suggests that baseline testing in this population should be performed *[33]*. 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 because of lower cost, more rapid turnaround time, ability to detect mixtures of wild-type and resistant virus, and the relative ease of interpretation **(AIII)**. If therapy is deferred, repeat testing just prior to initiation of antiretroviral therapy should be considered because the patient may have possibly acquired drug-resistant virus (i.e., superinfection) **(CIII)**.

Presently, drug resistance testing in antiretroviral-naïve persons involves genotypic testing for mutations in the reverse transcriptase and protease genes. As the use of integrase inhibitors increases, it is possible that genotypic testing for resistance to this class of drugs will become clinically useful when an integrase inhibitor is being considered as part of an initial regimen.

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. Several prospective studies assessed the utility of resistance testing in guiding antiretroviral drug selection in patients with virologic failure. These studies involved genotypic assays, phenotypic assays, or both *[6, 34-40]*. In general, these studies found 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. Additionally, one observational study demonstrated improved survival in patients with detectable HIV plasma RNA when drug resistance testing was performed *[41]*. Thus, resistance testing appears to be a useful tool in selecting active drugs when changing antiretroviral regimens for virologic failure in persons with HIV RNA >1,000 copies/mL (**AI**). (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 *[42-44]*. 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**.)

Genotypic testing is generally preferred for virologic failure or suboptimal viral load reduction in persons failing their first or second antiretroviral drug regimen because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant virus **(AIII)**. Addition of phenotypic testing to genotypic testing, is generally preferred for persons with known or suspected complex drug resistance mutation patterns, particularly to protease inhibitors **(BIII)**.

The clinical utility of resistance testing for integrase and fusion inhibitor resistance is limited at present because of lack of availability of second-line drugs within these classes; that is, there is no need to test for cross resistance to other drugs. However, in patients failing integrase- or fusion inhibitor-based regimens, testing for integrase or fusion inhibitor resistance may be helpful to determine whether to include drugs from these classes in subsequent regimens **(CIII)**. A coreceptor tropism assay should be performed whenever the use of a CCR5 antagonist is being considered **(AII)**. (See section on **Coreceptor Tropism Assays**.)

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 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)**. Phenotypic testing may provide additional information in those found to have complex drug resistance mutation patterns, particularly to protease inhibitors **(BIII)**. Optimal prevention of perinatal transmission may require initiation of antiretroviral therapy while results of resistance testing are pending. Once the results are available, the antiretroviral regimen can be changed as needed.

Table 4. Recommendations for Using Drug Resistance Assays (Updated December 1, 2009)

Clinical Setting/Recommendation	Rationale
Drug resistance assay recommended	
In acute HIV infection: Drug resistance testing is recommended regardless of whether treatment is initiated immediately or deferred **(AIII)**. A genotypic assay is generally preferred **(AIII)**.	If treatment is to be initiated immediately, drug resistance testing will determine whether drug-resistant virus was transmitted. Test results will help in the design of initial regimens or, if therapy was initiated prior to results, change regimens. Genotypic testing is preferable to phenotypic testing because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant virus.
If treatment is deferred, repeat resistance testing should be considered at the time antiretroviral therapy is initiated **(CIII)**. A genotypic assay is generally preferred **(AIII)**.	If treatment is deferred, testing should still be performed because of the greater likelihood that transmitted resistance-associated mutations will be detected earlier in the course of HIV infection. Results of resistance testing may be important when treatment is initiated. Repeat testing at the time antiretroviral therapy is initiated should be considered because the patient may have acquired a drug-resistant virus (i.e., superinfection).
In treatment-naïve patients with chronic HIV infection: Drug resistance testing is recommended at the time of entry into HIV care, regardless of whether therapy is initiated immediately or deferred **(AIII)**. A genotypic assay is generally preferred **(AIII)**.	Transmitted HIV with baseline resistance to at least one drug is seen in 6%–16% of patients, and suboptimal virologic responses may be seen in patients with baseline resistant mutations. Some drug resistance mutations can remain detectable for years in untreated chronically infected patients.
If therapy is deferred, repeat resistance testing should be considered at the time antiretroviral therapy is initiated **(CIII)**. A genotypic assay is generally preferred **(AIII)**.	Repeat testing prior to initiation of antiretroviral therapy should be considered because the patient may have acquired a drug-resistant virus (i.e., a superinfection). Genotypic testing is preferred for the reasons noted previously.
In patients with virologic failure: Drug resistance testing is recommended in persons on combination antiretroviral therapy with HIV RNA levels >1,000 copies/mL **(AI)**. In persons with HIV RNA levels >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 maximize the clinician's ability to select active drugs for the new regimen. Drug resistance testing should be performed while the patient is taking prescribed antiretroviral drugs or, if not possible, within 4 weeks after discontinuing therapy.
A genotypic assay is generally preferred in those experiencing virologic failure on their first or second regimens **(AIII)**.	Genotypic testing is generally preferred for the reasons noted previously.
Addition of phenotypic assay to genotypic assay is generally preferred for those with known or suspected complex drug resistance patterns, particularly to protease inhibitors **(BIII)**.	Phenotypic testing can provide useful additional information for those with complex drug resistance mutation patterns, particularly to protease inhibitors.

Clinical Setting/Recommendation	Rationale
Drug resistance assay recommended (continued)	
In patients with suboptimal suppression of viral load: Drug resistance testing is recommended in persons with suboptimal suppression of viral load after initiation of antiretroviral therapy **(AII)**.	Testing can help determine the role of resistance and thus assist in identifying the number of active drugs available for a new regimen.
In HIV-infected pregnant women: Genotypic resistance testing is recommended for all pregnant women prior to initiation of antiretroviral therapy **(AIII)** and for those entering pregnancy with detectable HIV RNA levels while on therapy **(AI)**.	The goal of antiretroviral therapy in HIV-infected pregnant women is to achieve maximal viral suppression for treatment of maternal HIV infection and 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 therapy discontinued: Drug resistance testing is not usually recommended after discontinuation (>4 weeks) of antiretroviral 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; however, the absence of resistance does not rule out the presence of minor drug-resistant species.
In patients with low HIV RNA levels: Drug resistance testing is not usually recommended in persons with a plasma viral load <500 copies/mL **(AIII)**.	Resistance assays cannot be consistently performed given 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 12**.) 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, 2009)

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:

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

Adoption of treatment strategies recommended in these guidelines has reduced HIV-related morbidity and mortality *[6-8]* and has reduced vertical transmission *[9-10]*. HIV suppression with antiretroviral therapy may also decrease inflammation and immune activation thought to contribute to higher rates of cardiovascular and other comorbidities reported in HIV-infected cohorts (see **Initiating Antiretroviral Therapy** section). Maximal and durable suppression of plasma viremia delays or prevents the selection of drug resistance mutations, preserves CD4 T-cell numbers, and confers substantial clinical benefits, all of which are important treatment goals *[11]*.

Achieving maximal viral suppression in initial therapy requires the use of antiretroviral regimens with at least two, and preferably three, active drugs from multiple drug classes. Baseline resistance testing should guide the specific regimen design. When maximal initial suppression is not achieved or is lost, changing to a new regimen with at least two active drugs is required (see **Management of Patients with Antiretroviral Treatment Failure** section). The increasing number of drugs and drug classes makes viral suppression below detection limits the goal in all patients, even those with primary or acquired drug resistance.

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 *[12]*,
- low baseline viremia *[13]*,
- higher baseline CD4 T-cell count (>200 cells/mm3), *[14]* and
- rapid reduction of viremia in response to treatment *[13, 15]*.

Successful outcomes are usually observed although adherence difficulties may lower the success rate in clinical practice to below the 90% rate commonly seen in clinical trials *[16]*.

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 individualized strategies to achieve treatment goals.

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**.) Many of these regimens have comparable efficacy but vary to some degree in dosing frequency, pill burden, drug interactions, and potential side effects. A regimen should be tailored to each patient to enhance adherence and thus improve outcome of care. Individual tailoring is based on such considerations as expected side effects, convenience, comorbidities, interactions with concomitant 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 *[17-20]*, and some studies suggest that the presence of transmitted drug-resistant viruses may lead to suboptimal virologic responses *[21]*. 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 and after initiation of antiretroviral therapy. (See **Adherence to Antiretroviral Therapy** section.)

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Initiating Antiretroviral Therapy in Treatment-Naïve Patients (Updated December 1, 2009)

Panel's Recommendations:

- ***Antiretroviral therapy should be initiated in all patients with a history of an AIDS-defining illness or with a CD4 count <350 cells/mm^3 (AI).***
- ***Antiretroviral therapy should also be initiated, regardless of CD4 count, in patients with the following conditions: pregnancy (AI), HIV- associated nephropathy (AII), and hepatitis B virus (HBV) coinfection when treatment of HBV is indicated (AIII).***
- ***Antiretroviral therapy is recommended for patients with CD4 counts between 350 and 500 cells/mm^3. The Panel was divided on the strength of this recommendation: 55% voted for strong recommendation (A) and 45% voted for moderate recommendation (B) (A/B-II).***
- ***For patients with CD4 counts >500 cells/mm^3, the Panel was evenly divided: 50% favor starting antiretroviral therapy at this stage of HIV disease (B); 50% view initiating therapy at this stage as optional (C) (B/C-III).***
- ***Patients initiating antiretroviral therapy should be willing and able to commit to lifelong treatment and should understand the benefits and risks of therapy and the importance of adherence (AIII). Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy based on clinical and/or psychosocial factors.***

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

The primary goal of antiretroviral therapy is to reduce HIV-associated morbidity and mortality. This is best accomplished by using antiretroviral therapy to maximally inhibit HIV replication, as measured by consistent plasma HIV RNA (viral load) values below the level of detection using commercially available assays. Additional benefits of antiretroviral therapy, supported by accumulating evidence, are reduction in HIV-associated inflammation and its associated complications and reduction in HIV transmission.

Over the past 20 years, the Panel has made several changes to the recommendations on when to start therapy based on prevailing clinical trial and cohort data and therapeutic options available at the time of each revision. The standard procedure for the Panel is to only make recommendations in agreement with two-thirds of the Panel members. This has not been possible for the ***When to Start*** recommendations in this updated version of the guidelines. Accordingly, the breakdown of votes is presented for recommendations supported by less than two-thirds of Panel members.

Randomized controlled trials provide evidence supporting the benefit of antiretroviral therapy in patients with CD4 counts of 350 cells/mm^3 or less. However, such evidence showing benefit for patients with higher CD4 cell counts is not yet available. Based on cumulative observational cohort data demonstrating benefits of antiretroviral therapy in reducing AIDS- and non-AIDS-associated morbidity and mortality, the Panel now recommends antiretroviral therapy for patients with CD4 count between 350 and 500 cells/mm^3 **(A-B/II)**. For patients with CD4 count >500 cells/mm^3, Panel members are evenly divided: 50% favor starting antiretroviral therapy at earlier stages of HIV disease **(BIII)**; 50% view initiating therapy at this stage as optional **(CIII)**.

Panel members favoring earlier initiation of therapy base their recommendation on several recent developments: (1) report from at least one recent cohort study demonstrating survival benefit with initiation of antiretroviral therapy at CD4 count >500 cells/mm^3; (2) growing awareness that untreated HIV infection may be associated with development of many non-AIDS-defining diseases, including cardiovascular disease, kidney disease, liver disease, and malignancy; (3) availability of antiretroviral regimens that are more effective, more convenient, and better tolerated than antiretroviral combinations no longer in use; and (4) increasing evidence that effective antiretroviral therapy reduces HIV transmission **(BIII)**.

The other 50% of the Panel members feel that current evidence does not definitively demonstrate clear benefit of antiretroviral therapy in all patients with CD4 count >500 cells/mm^3. They also feel that risks of short- or long-term drug-related complications, nonadherence to lifelong therapy in asymptomatic patients, and potential for development of drug resistance may offset possible benefits of earlier initiation of therapy. Thus, pending more definitive supporting evidence, these panel members recommend that therapy in this setting should be optional and considered on a case-by-case basis **(CIII)**.

The known benefits, risks, and limitations of antiretroviral therapy, as well as the strength of the recommendations according to CD4 count levels, are discussed below.

BENEFITS OF ANTIRETROVIRAL THERAPY

Earlier studies definitively showed that potent combination antiretroviral therapy improves survival and reduces AIDS-related complications in patients with advanced HIV disease. There is now increasing evidence demonstrating the benefits of viral suppression and immunologic responses on reducing mortality and non-AIDS-related complications in patients with higher pretreatment CD4 counts. The following is a focused discussion of the rationale that forms the basis for the Panel's recommendation favoring earlier treatment.

Reduction in Mortality and/or AIDS-Related Morbidity

Patients with a history of an AIDS-defining illness or CD4 count <350 cells/mm^3

HIV-infected patients with CD4 counts <200 cells/mm^3 are at higher risk of opportunistic diseases, non-AIDS morbidity, and death. Randomized controlled trials in patients with CD4 counts <200 cells/mm^3 and/or a history of an AIDS-defining condition provide strong evidence that antiretroviral therapy improves survival and delays disease progression in these patients *[1-3]*. Long-term data from multiple observational cohort studies evaluating earlier antiretroviral therapy (>200 cells/mm^3) compared with later treatment (<200 cells/mm^3) have also provided strong support for these findings *[4-8]*.

Few large, randomized controlled trials address when to start therapy in patients with CD4 counts >200 cells/mm^3. CIPRA HT-001 is a randomized clinical trial conducted in Haiti. Study participants were randomized to start antiretroviral therapy at CD4 count of 200–350 cells/mm^3 or to defer treatment until their CD4 count dropped below 200 cells/mm^3 or they developed an AIDS-defining condition. In an interim analysis of the study, a higher mortality rate (hazard ratio [HR] = 4.0, p = 0.0011) and greater incident tuberculosis (HR = 2.0, p = 0.0125) were observed among patients who deferred therapy compared with participants who began antiretroviral therapy with CD4 counts of 200 to 350 cells/mm^3 *[9]*. This evidence led to the study Data Safety Monitoring Board's recommendation to terminate the trial before completion.

The SMART study was a multi-national trial enrolling more than 5,400 participants with CD4 counts >350 cells/mm^3. Participants were randomized to continuous antiretroviral therapy or to treatment interruption until CD4 count dropped below 250 cell/mm^3. In a subgroup analysis involving the 249 study participants who were treatment naïve at enrollment, a trend of lower risk of serious AIDS- and non-AIDS-related events was seen in those who initiated therapy immediately compared with those who deferred therapy until CD4 count dropped to <250 cells/mm^3 (p = 0.06) *[10]*.

Collectively, these studies support the Panel's recommendation that antiretroviral therapy should be initiated in patients with a history of an AIDS-defining illness or with a CD4 count <350 cells/mm^3 **(AI)**.

Patients with a CD4 count between 350 and 500 cells/mm^3

There are no randomized trials using current combination regimens in patients with CD4 counts >350/mm^3 to provide data that directly address the question of when to start therapy in these patients. Data from the ART Cohort Collaboration (ART-CC), which included 61,798 patient-years of follow-up, showed a declining risk of AIDS or death for up to 5 years in subjects starting therapy with a CD4 count ≥350 cells/mm^3 compared with subjects starting

between 200 and 349 cells/mm^3 *[11]*. A more recent rigorous analysis of this cohort found that deferring therapy until the 251 to 350 cells/mm^3 range was associated with a higher rate of progression to AIDS and death compared with initiating therapy in the 351 to 450 cells/mm^3 range (risk ratio: 1.28, 95% CI: 1.04 to 1.57) *[6]*.

In a collaboration of North American cohort studies (NA-ACCORD) that evaluated patients regardless of whether they had started therapy, the 6,278 patients who deferred therapy until CD4 count <350 cells/mm^3 had an increased risk of death compared with 2,084 patients who initiated therapy with CD4 count between 351 and 500 cells/mm^3 (risk ratio: 1.69, 95% CI: 1.26 to 2.26) after adjustment for other factors that differed between these two groups *[12]*.

When interpreting both of these cohort studies it is important to note that although the relative risk of a mortality event is evident, the overall number of events was small. In these cohort studies, the relative risks determined could have been influenced by unmeasured confounders that cannot be adjusted for in the analysis. The findings from these observational cohort studies point to potential harm if therapy is deferred until CD4 count falls below 350 cells/mm^3. Based on these findings, combined with emerging biologic evidence regarding potential damage to end organs from inflammation associated with untreated HIV replication and the potential reduction in HIV transmission with treatment (see below), the Panel recommends antiretroviral therapy in patients with CD4 counts between 350 and 500 cells/mm^3. The Panel was divided on the strength of this recommendation: 55% voted for strong recommendation (A) and 45% voted for moderate recommendation (B) **(A/B-II)**.

Patients with a CD4 count >500 cells/mm^3

The NA-ACCORD study also observed patients who started treatment at CD4 count >500 cells/mm^3 or after the CD4 count dropped below this threshold. The adjusted mortality rates were significantly higher among the 6,935 patients who deferred therapy until CD4 count fell below 500 cells/mm^3 compared with rates in the 2,200 patients who started therapy while CD4 count was above 500 cells/mm^3 (risk ratio: 1.94, 95% CI: 1.37 to 2.79) *[12]*. Although large and generally representative of care in the United States, the study has several limitations, including the small number of deaths and the potential for unmeasured confounders that might have influenced outcomes independent of antiretroviral therapy.

In contrast, analysis of the ART-CC cohort failed to identify a benefit for patients initiating antiretroviral therapy with CD4 counts above 450 cells/mm^3. This analysis also did not identify a harmful effect of this strategy *[6]*. Deferral of therapy to the 351–450 cells/mm^3 range was associated with a similar rate of progression to AIDS/death compared with initiation of therapy in the 451–550 cells/mm^3 range (risk ratio: 0.99, 95% CI: 0.76 to 1.29). This study also found that the proportion of patients with CD4 counts between 451 and 550 cells/mm^3 who would progress to AIDS or death before having a CD4 count below 450 cells/mm^3 was low (1.6%; 95% CI: 1.1 to 2.1%).

Based on these data, along with a better understanding of the pathogenesis of HIV infection and the growing awareness that untreated HIV infection increases the risk of many non-AIDS-defining diseases (see below), 50% of Panel members favor initiation of antiretroviral therapy in HIV-infected persons with a CD4 count above 500 cells/mm^3 **(BIII)**.

The other 50% of the Panel members are reluctant to broadly recommend starting antiretroviral therapy at higher CD4 cell counts and consider that therapy should be optional at this stage of HIV disease **(CIII)**. In making this recommendation, the Panel members note that the amount of data supporting initiation of therapy decreases as the CD4 count increases above 350–500 cells/mm^3, and concerns remain over the unknown overall benefit and long-term risks with earlier treatment.

When discussing starting antiretrovirals at higher CD4 cell counts (>500 cells/mm^3), clinicians should inform patients that data on the clinical benefit of starting treatment at such levels is not conclusive. There is a need for further ongoing research (both with randomized clinical trials and cohort studies) to assess the short- and long-term clinical and public health benefits, and cost-effectiveness of starting therapy at higher CD4 counts. Such research findings will provide guidance for future recommendations by the Panel.

Effects of Antiretroviral Therapy on HIV-Related Morbidity

HIV-related morbidity and mortality derive not only from immune deficiency but also from direct effects of HIV on specific end organs and the indirect effects of HIV-associated inflammation on these organs. In general, the available data demonstrate that:

- Untreated HIV infection may have detrimental effects at all stages of infection.
- Treatment is beneficial even when initiated later in infection. However, later therapy may not repair damage associated with viral replication during early stages of infection.
- Earlier treatment may prevent the damage associated with HIV replication during early stages of infection.

Clinical studies have demonstrated that sustaining viral suppression and maintaining higher CD4 count, mostly as a result of effective combination antiretroviral therapy, delay or prevent some non-AIDS-defining complications, such as HIV-associated kidney disease. Sustained viral suppression and immune recovery may also delay or prevent other disorders, such as liver disease, cardiovascular disease, and malignancies, as discussed below.

HIV-associated Nephropathy (HIVAN)

HIVAN is the most common cause of chronic kidney disease in HIV-infected individuals that may lead to end-stage kidney disease *[13]*. HIVAN is seen almost exclusively in black patients and can occur at any CD4 count. Ongoing viral replication appears to be directly involved in renal injury *[14]*. HIVAN is extremely uncommon in virologically suppressed patients *[15]*. Antiretroviral therapy in patients with HIVAN has been associated with both preserved renal function and prolonged survival *[16-18]*, and therefore should be started in these patients **(AII)**.

Co-infection with hepatitis B virus (HBV) and/or hepatitis C virus (HCV)

HIV infection is associated with more rapid progression of viral hepatitis-related liver disease, including cirrhosis, end-stage liver disease, hepatocellular carcinoma, and fatal hepatic failure *[19-20]*. Although the mechanisms of accelerated liver disease in HIV-infected patients have not been fully elucidated, HIV-related immunodeficiency and a direct interaction of HIV with hepatic stellate and Kupffer cells have been implicated *[21-24]*. Antiretroviral therapy may attenuate liver disease progression in persons coinfected with HBV and/or HCV by preserving or restoring immune function and reducing HIV-related immune activation and inflammation *[25-27]*. Antiretroviral drugs active against both HIV and HBV (e.g., tenofovir, lamivudine, emtricitabine) may also prevent the development of significant liver disease by directly suppressing HBV replication *[28-29]*. Although antiretroviral drugs do not directly inhibit HCV replication, HCV treatment outcomes may be improved if HIV replication is controlled or if CD4 counts are increased *[30]*. The presence of chronic viral hepatitis increases the risk of antiretroviral therapy-induced liver injury; however, the majority of coinfected persons do not develop clinically significant liver injury, particularly those receiving recommended antiretroviral regimens *[31-33]*. Some studies suggest that the rate of hepatotoxicity is greater in persons with more advanced HIV disease. Nevirapine toxicity is a notable exception: the hypersensitivity reaction and associated hepatotoxicity to this drug are more frequent in patients with higher CD4 cell counts *[34]*. Collectively, these data suggest earlier treatment of HIV infection in persons coinfected with HBV, and possibly HCV **(CIII)**, may reduce the risk of liver disease progression. Furthermore, antiretroviral therapy including drugs active against both HIV and HBV should be started in all patients coinfected with HBV who are also going to receive HBV treatment **(AIII)**.

Cardiovascular disease

Cardiovascular disease is a major cause of mortality among HIV-infected patients, accounting for a third of serious non-AIDS conditions and at least 10% of deaths among HIV-infected patients *[35-36]*. There are studies that link exposure to specific antiretroviral drugs to a higher risk of cardiovascular disease *[37-38]*. Certain HIV treatment regimens are associated with a more atherogenic lipid profile as assessed by lipoprotein particle size analysis among HIV-infected men compared with uninfected controls *[39]*. Untreated HIV infection may also be associated with an increased risk of cardiovascular disease. In some cross-sectional studies, patients with HIV have higher levels of markers of inflammation and endothelial dysfunction than HIV-uninfected controls *[40-42]*. In two randomized trials,

markers of inflammation and coagulation increased following treatment interruption *[43-44]*. One study suggests that antiretroviral treatment may improve endothelial function *[45]*.

In the SMART study, the risk of cardiovascular events was greater in participants randomized to CD4-guided treatment interruption compared with participants who received continuous antiretroviral therapy *[46]*. In other studies, antiretroviral therapy resulted in marked improvement in parameters associated with cardiovascular diseases, including markers of inflammation (e.g., interleukin 6 [IL-6] and high sensitivity C-reactive protein [hsCRP]) and endothelial dysfunction *[41, 45]*. There is also a modest association between lower CD4 count while on therapy and short-term risk of cardiovascular disease *[7, 47-48]*. However, in at least one of these cohorts (the CASCADE study), the link between CD4 count and fatal cardiovascular events was no longer statistically significant when adjusting for plasma HIV RNA level. Collectively, the data linking viremia and endothelial dysfunction and inflammation, the increased risk of cardiovascular events with treatment interruption, and the association between cardiovascular disease and CD4 cell depletion suggest that early control of HIV replication with antiretroviral therapy can be used as a strategy to reduce cardiovascular disease risk **(BIII)**.

Malignancies

Several population-based analyses suggest increased incidence of non-AIDS-associated malignancies during chronic HIV infection. The incidence of non-AIDS malignancy in HIV-infected subjects is higher than in matched HIV-uninfected controls *[49]*. Large cohort studies of mostly patients receiving antiretroviral treatment have reported a consistent link between low CD4 counts (<350–500 cells/mm^3) and the risk of AIDS- and/or non-AIDS-defining malignancy *[7, 47, 50-53]*. The ANRS C04 demonstrated a statistically significant relative risk of all cancers evaluated (except for anal carcinoma) in patients with CD4 counts <500 cells/mm^3 compared with patients with current CD4 counts >500 cells/mm^3 and a protective effect of antiretroviral therapy for HIV-associated malignancies *[50]*. This potential effect of HIV-associated immunodeficiency is particularly striking with regard to cancers associated with chronic viral infections (e.g., HBV, HCV, HPV, EBV, HHV-8) *[54-55]*. Cumulative HIV viremia itself may also be associated with the risk of non-Hodgkin lymphoma and other AIDS-defining malignancies, independent of other factors *[53, 56]*. Together this evidence suggests that initiating antiretroviral therapy to suppress HIV replication and maintain CD4 counts at above 350–500 cells/mm^3 may reduce the risk of both AIDS-defining and non-AIDS-defining malignancy **(CIII)**.

Neurocognitive decline

Early in the HIV epidemic, HIV was identified in brain tissue *[57]* and assumed to be the cause of AIDS dementia complex *[58]*. The improvement of AIDS dementia complex symptoms with the use of antiretroviral therapy supported this assumption *[59-60]*. The CASCADE observational cohort reported a dramatic decline in the incidence of HIV-associated dementia from 6.49 per 1,000 person-years (before 1997) to 0.66 per 1,000 person-years (2003–2006), after the widespread use of potent antiretroviral therapy *[61]*. In this cohort, having a current CD4 count >350 cells/mm^3 was associated with the lowest risk of developing HIV-associated dementia. HIV infection has also been associated with a number of less severe neurologic complications, including changes in neuropsychological ability, speed of processing, and everyday functioning *[62]*. Such syndromes also were predicted by a lower pretherapy CD4 nadir and/or by CD4 count while on therapy *[63-64]*. Additional clinical data are needed to determine the relative roles of ongoing HIV replication and potential neurotoxicity of antiretroviral agents in the development of neurocognitive dysfunction. Whether early initiation of therapy will prevent HIV-associated neurocognitive dysfunction remains unclear. However, the neurological complications that may accompany uncontrolled HIV replication and CD4 depletion suggest a potential benefit of earlier initiation of antiretroviral therapy **(CIII)**.

Age and treatment-related immune reconstitution

The CD4 cell response to therapy is an important predictor of short-term and long-term morbidity and mortality. Treatment initiation at an older age is consistently associated with a less robust CD4 count response; starting therapy at a younger age may result in better immunologic and perhaps clinical outcomes *[65-67]* **(CIII)**.

T-cell activation and inflammation

Early untreated HIV infection is associated with sustained high-level inflammation and T-cell activation *[68-70]*. The degree of T-cell activation during untreated disease is associated with risk of subsequent disease progression, independent of other factors such as plasma HIV RNA levels and the peripheral CD4 T-cell count *[71-72]*. Antiretroviral therapy results in a rapid, but often incomplete, decrease in most markers of HIV-associated immune activation *[73-77]*. Persistent T-cell activation and/or T-cell dysfunction is particularly evident among patients who delay therapy until later stage disease (CD4 count <350 cells/mm^3) *[74, 77-78]*. The degree of persistent inflammation during treatment, as represented by the levels of IL-6, may be independently associated with risk of death *[44]*. Collectively, these observations support earlier use of antiretroviral therapy for at least two reasons. First, treatment decreases the level of inflammation and T-cell activation, which may be associated with reduced short-term risk of AIDS- and non-AIDS-related morbidity and mortality *[44, 79-80]*. Second, because it appears that the degree of residual inflammation and/or T-cell dysfunction during antiretroviral therapy is higher in patients with lower CD4 cell nadirs *[74, 77-78]*, earlier treatment may result in less residual immunological perturbations on therapy, and hence less risk for AIDS- and non-AIDS-related complications **(CIII)**.

Prevention of HIV Transmission

Prevention of Mother-to-Child Transmission

Effective antiretroviral therapy reduces transmission of HIV. The most dramatic and well-established example of this effect is the use of antiretroviral therapy in pregnant women to prevent mother-to-child transmission of HIV. Effective suppression of HIV replication, as reflected in plasma HIV RNA, is a key determinant in reducing perinatal transmission. In the United States, the use of combination antiretroviral therapy during pregnancy has reduced the HIV transmission rate from approximately 20–30% to <2% *[81]*. Thus, antiretroviral therapy is recommended for all HIV-infected pregnant women, both for maternal health and to prevent HIV transmission from mother to child **(AI)**. For detailed recommendations, see **Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission** *[82]*.

Prevention of Sexual Transmission

Emerging evidence supports the concept of "treatment as prevention" of sexual transmission of HIV. Lower plasma HIV RNA levels are associated with decreases in the concentration of the virus in genital secretions *[83-84]*. Studies of HIV serodiscordant heterosexual couples have demonstrated a relationship between the level of plasma viremia and HIV transmission risk: when plasma HIV RNA levels are lower, transmission events are less common *[85-89]*. These investigations, as well as other observational studies and modeling analyses demonstrating a decreased rate of HIV transmission among serodiscordant heterosexual couples following the introduction of antiretroviral therapy, suggest that suppression of viremia in treatment-adherent patients with no concomitant sexually transmitted infections substantially reduces the risk of HIV transmission *[88-93]*. Based on these studies, the use of effective antiretroviral therapy regardless of CD4 count is likely to reduce transmission to the uninfected sexual partner **(BII)**.

POTENTIAL LIMITATIONS OF EARLIER INITIATION OF THERAPY

Although there are benefits associated with earlier initiation of antiretroviral therapy, there are also potential limitations to this approach. Concerns about long-term toxicity and the development of antiretroviral resistance have served as a rationale for the deferral of HIV therapy. Earlier initiation of antiretroviral therapy at higher CD4 counts (e.g., >500 cells/mm^3) results in greater cumulative time on therapy. Assuming treatment for many decades after initiation, the additional therapy represents a small percentage of the total time on treatment for most patients.

Although newer antiretroviral regimens are generally better tolerated, more convenient, and more potent than older regimens, there are fewer longer term safety data for the newer agents. Analyses supporting antiretroviral initiation at CD4 counts above 350/mm^3 (e.g., NA-ACCORD and ART-CC) were conducted with cohorts largely treated with regimens less commonly used in clinical practice. These studies reported on clinical endpoints of death and/or AIDS

disease progression but lacked information on drug toxicities, resistance, or adherence. Therefore, in considering earlier initiation of therapy, concerns for some adverse consequences of antiretroviral therapy remain.

Antiretroviral Drug Toxicities and Quality of Life

Earlier initiation of antiretroviral therapy extends exposure to antiretroviral agents by several years. The D:A:D study found an increased incidence of cardiovascular disease associated with cumulative exposure to some drugs within the NRTI and PI classes *[38, 94]*. In the SMART study, continuous exposure to antiretroviral treatment has been associated with significantly greater loss of bone density compared with interruption or deferral of antiretroviral therapy *[46]*. There may be unknown complications related to cumulative use of antiretroviral drugs for many decades. A list of known antiretroviral-associated toxicities along with prevention and management strategies can be found in the **Adverse Effects of Antiretroviral Agents** section.

Although antiretroviral therapy frequently improves quality of life among symptomatic patients, it may also be associated with reduced quality of life in some patients, especially those who are asymptomatic at initiation of therapy. Although better tolerated and easier to administer than older drugs, most antiretroviral drugs now used in first line regimens can cause side effects that reduce quality of life. Efavirenz, for example, can cause neurocognitive or psychiatric side effects, and all the protease inhibitors have been associated with gastrointestinal side effects. Furthermore, some patients may find that the inconvenience of taking medication every day outweighs the overall benefit and might choose to delay therapy whenever possible.

Drug Resistance

Very early treatment initiation may lead to an earlier onset of drug resistance selection in nonadherent patients. The consequent harm is loss of important drugs or drug classes and risk of transmission of drug-resistant HIV. Some asymptomatic patients may be less motivated to remain adherent to their HIV treatment regimen if treatment is initiated far in advance of an immediate risk of HIV-associated morbidity and mortality. The greater convenience and potency of current antiretroviral regimens facilitate adherence and reduce the risk of antiretroviral resistance. One study suggests that the risk of drug resistance at the time of virologic failure is lower among patients who initiated treatment at higher CD4 counts *[95]*. Treatment adherence is key to viral suppression and should be stressed prior to initiation of therapy and during follow-up visits.

Nonadherence to Antiretroviral Therapy

At any CD4 count, adherence to therapy is essential to achieve viral suppression and prevent emergence of resistance mutations. Several behavioral and social factors associated with lower adherence have been identified, such as untreated major psychiatric disorders, active substance abuse, social circumstances, patients' concerns about side effects, and poor adherence to clinic visits. Clinicians should identify areas where additional intervention is needed to improve adherence both before and after initiation of therapy. Some strategies to improve adherence are discussed in the **Adherence** section.

Cost

Although antiretroviral therapy adds to the annual cost of treatment, several modeling studies support the cost-effectiveness of HIV therapy initiated soon after diagnosis *[96-98]*. Studies have reported that the annual cost of care is 2½ times higher for patients with CD4 counts <50 cells/mm^3 compared with patients with CD4 counts >350 cells/mm^3 *[99]*. A large proportion of the health care expenditure in patients with advanced infection is from nonantiretroviral drugs and hospitalization. However, no cost comparisons have been reported between those starting antiretroviral therapy with a CD4 count between 350 and 500 cells/ mm^3 versus >500 cells/ mm^3.

SUMMARY

In earlier versions of these treatment guidelines, concerns about long-term toxicity, reduced quality of life, and the potential for drug resistance served as key reasons to defer HIV therapy for as long as possible. Inherent in this

argument was the assumption that the harm associated with viral replication was less than the harm associated with the toxicities of antiretroviral drugs in patients with higher CD4 count. There is now more evidence that untreated HIV infection has negative consequences on health at all stages of disease. Also, the drug combinations now available are better tolerated than previous regimens, leading to greater efficacy and improved adherence *[100]*. The current guidelines therefore emphasize avoiding adverse consequences of untreated HIV infection while managing potential drug toxicity.

RECOMMENDATIONS

Based on the cumulative weight of evidence described above, the Panel recommends that:

- Antiretroviral therapy should be initiated in all patients with a history of an AIDS-defining illness, or with CD4 count of < 350 cells/mm^3 **(AI).**
- Antiretroviral therapy should also be initiated, regardless of CD4 count, in patients with the following conditions: pregnancy **(AI)**, HIV associated nephropathy **(AII)**, hepatitis B virus (HBV) co-infection when treatment of HBV is indicated **(AIII)**.
- Antiretroviral therapy is recommended for patients with CD4 counts between 350 and 500 cells/mm^3. The Panel was divided on the strength of this recommendation: 55% of Panel members voted for strong recommendation (A) and 45% voted for moderate recommendation (B) **(A/B-II)**.
- For patients with CD4 counts > 500 cells/mm^3, 50% of the Panel members favor starting antiretroviral therapy (B); the other 50% of members view treatment is optional (C) in this setting **(B/C-III)**.
- Patients initiating antiretroviral therapy should be willing and able to commit to lifelong treatment, and should understand the benefits and risks of therapy and the importance of adherence (**AIII**).
- Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy based on clinical and/or psychosocial factors.

Conditions Favoring More Rapid Initiation of Therapy

Deferring antiretroviral therapy may be appropriate in some cases. However, several conditions increase the urgency for therapy, including:

- Pregnancy **(AI)**
- AIDS-defining conditions **(AI)**
- Acute opportunistic infections (see discussion below)
- Lower CD4 counts (e.g., <200 cells/mm^3) **(AI)**
- Rapidly declining CD4 counts (e.g., >100 cells/ mm^3 decrease per year) **(AIII)**
- Higher viral loads (e.g., >100,000 copies/ml) **(BII)**
- HIV-associated nephropathy **(AII)**
- HBV coinfection when treatment for HBV is indicated **(AIII)**

Acute opportunistic infections

In patients with opportunistic conditions for which there is no effective therapy (e.g., cryptosporidiosis, microsporidiosis, progressive multifocal leukoencephalopathy) but for which antiretroviral therapy may improve outcomes by improving immune responses, the benefits of antiretroviral therapy outweigh any increased risk, and therefore treatment should be started as soon as possible **(AIII)**.

In the setting of opportunistic infections, such as cryptococcal meningitis or non-tuberculous mycobacterial infections, for which immediate therapy may increase the risk of immune reconstitution inflammatory syndrome (IRIS), a short delay may be warranted before initiating antiretroviral treatment *[101-102]***(CIII)**.

In the setting of other opportunistic infections, such as *Pneumocystis jiroveci* pneumonia (PCP), early initiation of antiretroviral therapy is associated with increased survival, and therapy should not be delayed *[3]* **(AI)**.

In patients with tuberculosis with low CD4+ T-cell counts, initiating antiretroviral therapy within the first 2 months of treatment for tuberculosis appears to confer a significant survival advantage *[103-104]*. Clinicians should refer to **Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents** *[105]* for more detailed discussion on when to initiate antiretroviral therapy in the setting of a specific opportunistic infection.

Conditions Where Deferral of Therapy Might be Considered

Some patients and their clinicians may decide to defer therapy for a period of time based on clinical or personal circumstances. The degree to which these factors might argue for deferral of therapy depends on the CD4 count and viral load. Although deferring therapy for the reasons discussed below may be reasonable for patients with high CD4 counts (e.g., >500 cells/mm^3), deferral for patients with much lower CD4 counts (e.g., <200 cells/mm^3) should be considered only in rare situations and should be undertaken with close clinical follow-up. A brief delay in initiating therapy may be considered to allow a patient more time to prepare for lifelong treatment.

When there are significant barriers to adherence

Deferring treatment for patients with higher CD4 counts who are at risk of poor adherence may be prudent while the barriers are being addressed. However, potential predictors of poor adherence may be overridden when more urgent antiretroviral therapy is indicated (see above).

Several methodologies exist to help providers assess adherence. When the most feasible measure of adherence is self-report, this assessment should be completed at each clinic visit, using one of the available reliable and valid instruments *[106-107]*. If other objective measures are available (e.g., pharmacy refill data, pill count), these methods should also be implemented as therapy begins *[108-110]*. Continuous assessment and counseling make it possible for the clinician to intervene early to address barriers to adherence occurring at any point during treatment.

Presence of comorbidities that complicate or prohibit antiretroviral therapy

Deferral of antiretroviral therapy may be considered when either the treatment or manifestations of other medical conditions could complicate the treatment of HIV infection or vice versa. Examples include patients:

- requiring surgery that might result in an extended interruption of antiretroviral therapy
- taking medications that have clinically significant drug interactions with antiretroviral agents and for whom alternative therapy is not available.

In each of these cases, it is assumed that the situation is temporary and that antiretroviral therapy will be initiated after the conflicting condition has resolved.

There are some less common situations in which antiretroviral therapy may not be indicated at any time while CD4 counts remain high. In particular, such situations include patients with a poor prognosis due to a concomitant medical condition who would not be expected to derive survival or quality-of-life benefits from antiretroviral therapy. Examples include patients with incurable non-HIV-related malignancies or end-stage liver disease who are not being considered for liver transplantation. The decision to forego antiretroviral therapy in such patients may be easier in those with higher CD4 counts; they are likely asymptomatic for HIV, and their survival is unlikely to be prolonged by antiretroviral therapy. However, it should be noted that antiretroviral therapy may improve outcomes, including survival, in patients with some HIV-associated malignancies (e.g., lymphoma or Kaposi's sarcoma) and in patients with liver disease due to chronic HBV or HCV.

Elite HIV controllers or long-term nonprogressors

A small subset of antiretroviral-untreated HIV-infected persons (~3%–5%) are able to maintain normal CD4 cell counts for many years (long-term nonprogressors), while an even smaller subset (~1%) are able to maintain suppressed viral loads for years (elite controllers). It is possible that such patients would not benefit from antiretroviral therapy. However, some nonprogressors have high viral loads, while some elite controllers progress clinically or

immunologically *[111-112]*. Although therapy may be theoretically beneficial for patients in either group, clinical data supporting therapy for nonprogressors and elite controllers are lacking.

THE NEED FOR EARLY DIAGNOSIS OF HIV

Fundamental to the earlier initiation of therapy recommended in these guidelines is the assumption that patients will be identified early in the course of HIV infection, making earlier initiation of therapy an option. Unfortunately, most HIV-infected patients are not diagnosed until they are at much later stages of disease *[113-116]*. Despite the 2006 CDC recommendations for routine, opt-out HIV screening in the health care setting *[117]* regardless of perceived risk of infection, the median CD4 count for newly diagnosed patients remains in the ~200 cells/mm^3 range. (The exception is pregnant women diagnosed during prenatal care, who have a much higher median initial CD4 count.) Delay in HIV diagnosis is more often seen in nonwhites, injection drug users, and older patients; a substantial proportion of these individuals develop AIDS-defining illnesses within 1 year of diagnosis *[114-116]*. Therefore, for the current treatment guidelines to have maximum impact, routine HIV screening per current CDC recommendations is essential. It is critical that all newly diagnosed patients be educated about HIV disease and linked to care for full evaluation, follow-up, and management. Once in care, focused effort is required to retain patients in the health care system.

CONCLUSION

These revised recommendations are based on increasing evidence that supports earlier initiation of antiretroviral therapy than was advocated in previous guidelines. The strength of the recommendations varies with the quality and availability of existing evidence. The Panel members are divided regarding the strength of recommendations for starting therapy in patients with higher CD4 cell counts as discussed above. The Panel will continue to monitor and assess the results of ongoing and planned randomized clinical trials and observational studies, which will provide the Panel with additional guidance to form future recommendations.

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What to Start: Initial Combination Regimens for the Antiretroviral-Naïve Patient (Updated December 1, 2009)

Panel's Recommendations:

- ***The Panel recommends initiating antiretroviral therapy in treatment naïve patients with 1 of the following 3 types of regimen:***
  - ***NNRTI + 2 NRTI***
  - ***PI (preferably boosted with ritonavir) + 2 NRTI***
  - ***INSTI + 2 NRTI***
- ***The Panel recommends the following as preferred regimens for treatment naïve patients:***
  - ***Efavirenz + tenofovir + emtricitabine (AI)***
  - ***Ritonavir-boosted atazanavir + tenofovir + emtricitabine (AI)***
  - ***Ritonavir-boosted darunavir + tenofovir + emtricitabine (AI)***
  - ***Raltegravir + tenofovir + emtricitabine (AI)***
- ***A list of Panel recommended alternative and acceptable regimens can be found in Table 5a.***
- ***Selection of a regimen should be individualized based on virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance testing results, and comorbid conditions.***
- ***Based on individual patient characteristics and needs, in some instances, an alternative regimen may actually be a preferred regimen for a patient.***

INSTI = integrase strand transfer inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleos(t)ide reverse transcriptase inhibitor, PI = protease inhibitor

There are more than 20 approved antiretroviral drugs in 6 mechanistic classes with which to design combination regimens. These 6 classes include the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (FIs), CCR5 antagonists, and integrase strand transfer inhibitors (INSTI). The most extensively studied combination regimens for treatment-naïve patients that provide durable viral suppression generally consist of two NRTIs plus either one NNRTI or a PI (with or without ritonavir boosting). In July 2009, a regimen consisting of raltegravir was approved for treatment-naïve patients, making the combination of an INSTI + 2 NRTIs an additional option.

In the current guidelines, the Panel refines its recommendations for the selection of regimens for use in antiretroviral-naïve persons. This reflects a change from previous versions of the guidelines where a list of preferred or alternative choices within each drug class was provided to allow clinicians to construct the regimen by combining drugs from each list. We now provide recommendations for preferred, alternative, and acceptable regimens as well as regimens that may be acceptable but more definitive data are needed and regimens to be used with caution (**Tables 5a, 5b**). Potential advantages and disadvantages of the components recommended as initial therapy for treatment-naïve patients are listed in **Table 6** 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 7**. Some agents or components that are not recommended for use because of lack of potency or potential serious safety concerns are listed in **Table 8**.

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 published data from a randomized, prospective clinical trial with an adequate sample size that demonstrate durable viral suppression and immunologic enhancement (as evidenced by increase in CD4 T-cell count). Few of these trials include clinical endpoints, such as development of AIDS-defining illness or death. Thus, assessment of regimen efficacy and potency is primarily based on surrogate marker endpoints (HIV RNA and CD4 responses). The Panel reviewed data from randomized clinical trials to arrive at preferred versus alternative ratings in **Table 5a**. "Preferred regimens" are those studied in randomized controlled trials and shown to have optimal and durable virologic efficacy, have favorable tolerability and toxicity profiles, and are easy to use. "Alternative regimens" are those regimens that are effective but have potential disadvantages when compared to preferred regimens. On the basis of individual patient characteristics and needs, a regimen listed as an alternative regimen may actually be the preferred regimen in certain situations. Some regimens are now classified as "Acceptable Regimens" because of less virologic activity, lack of efficacy data from large clinical trials, or greater toxicities when compared to the preferred or alternative regimens.

Table 5b includes other regimens that maybe acceptable but definitive data from randomized trials are not yet published. Lastly, Table 5b includes several regimens shown to be efficacious in some studies; however, the Panel recommends using them with caution because of some safety or efficacy concerns.

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;
- coreceptor tropism assay if considering maraviroc;
- 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 B, Tables 1–6**. Additionally, **Appendix B, Table 7** provides clinicians with antiretroviral dosing recommendations for patients who have renal or hepatic insufficiency.

Recommended regimens use combinations of two NRTIs with an NNRTI, PI (preferably boosted with ritonavir), or an INSTI, namely raltegravir. In many clinical trials, NNRTI-, PI-, and INSTI-based regimens result in suppression of HIV RNA levels and CD4 T-cell increases in a large majority of patients *[1-6]*. Some comparative data are available (see below).

Tables 5a and 5b include the Panel's recommendations for initial therapy.

Table 5a. Antiretroviral Regimens Recommended for Treatment-Naïve Patients (Updated December 1, 2009)

Patients naïve to antiretroviral therapy should be started on one of the following three types of combination regimens:

- **NNRTI + 2 NRTIs; or**
- **PI (preferably boosted with ritonavir) + 2 NRTIs; or**
- **INSTI + 2 NRTIs.**

Selection of a regimen should be individualized based on virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance testing results, and comorbid conditions. Refer to **Table 6** for a list of advantages and disadvantages, and **Appendix B, Tables 1–6** for dosing information for individual antiretroviral agents listed below. The regimens in each category are listed in alphabetical order.

Preferred Regimens (Regimens with optimal and durable efficacy, favorable tolerability and toxicity profile, and ease of use) **The preferred regimens for non-pregnant patients are arranged by order of FDA approval of components other than nucleosides, thus, by duration of clinical experience.**	
NNRTI-based Regimen • EFV/TDF/FTC[1] **(AI)** **PI-based Regimens** *(in alphabetical order)* • ATV/r + TDF/FTC[1] **(AI)** • DRV/r (once daily) + TDF/FTC[1] **(AI)** **INSTI-based Regimen** • RAL + TDF/FTC[1] **(AI)** **Preferred Regimen[2] for Pregnant Women** • LPV/r (twice daily) + ZDV/3TC[1] **(AI)**	**Comments** **EFV** should not be used during the first trimester of pregnancy or in women trying to conceive or not using effective and consistent contraception. **ATV/r** should not be used in patients who require >20mg omeprazole equivalent per day. Refer to **Table 14a** for dosing recommendations regarding interactions between ATV/r and acid-lowering agents.
Alternative Regimens (Regimens that are effective and tolerable but have potential disadvantages compared with preferred regimens. An alternative regimen may be the preferred regimen for some patients.)	
NNRTI-based Regimens *(in alphabetical order)* • EFV + (ABC or ZDV)/3TC[1] **(BI)** • NVP + ZDV/3TC[1] **(BI)** **PI-based Regimens** *(in alphabetical order)* • ATV/r + (ABC or ZDV)/3TC[1] **(BI)** • FPV/r (once or twice daily) + either [(ABC or ZDV)/3TC[1]] or TDF/FTC[1] **(BI)** • LPV/r (once or twice daily) + either [(ABC or ZDV)/3TC[1]] or TDF/FTC[1] **(BI)** • SQV/r + TDF/FTC[1] **(BI)**	**Comments** **NVP:** • Should not be used in patients with moderate to severe hepatic impairment (Child-Pugh B or C)[3] • Should not be used in women with pre-ARV CD4 >250 cells/mm^3 or men with pre-ARV CD4 >400 cells/mm^3 **ABC:** • Should not be used in patients who test positive for HLA-B*5701 • Use with caution in patients with high risk of cardiovascular disease or with pretreatment HIV-RNA >100,000 copies/mL (see text) **Once-daily LPV/r** is not recommended in pregnant women.
Acceptable Regimens (Regimens that may be selected for some patients but are less satisfactory than preferred or alternative regimens.)	
NNRTI-based Regimen • EFV + ddI + (3TC or FTC) **(CI)** **PI-based Regimen** • ATV + (ABC or ZDV)/3TC[1] **(CI)**	**Comments** EFV + ddI + FTC or 3TC has only been studied in small clinical trials. ATV/r is generally preferred over ATV. Unboosted ATV may be used when ritonavir boosting is not possible.

[1]3TC may substitute for FTC or vice versa.
[2]For more detailed recommendations on antiretroviral use in an HIV-infected pregnant woman, 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**.
[3]Refer to **Appendix B, Table 7** for the criteria for Child-Pugh classification.

Abbreviations:
INSTI = integrase strand transfer inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleos(t)ide reverse transcriptase inhibitor, PI = protease inhibitor
ABC = abacavir, ATV = atazanavir, 3TC = lamivudine, ddI = didanosine, DRV = darunavir, EFV =efavirenz, FPV = fosamprenavir, FTC = emtricitabine, LPV = lopinavir, NVP = nevirapine, RAL = raltegravir, r = low dose ritonavir, SQV = saquinavir, TDF = tenofovir, ZDV = zidovudine
The following combinations in the recommended list above are available as fixed-dose combination formulations: ABC/3TC, EFV/TDF/FTC, LPV/r, TDF/FTC, and ZDV/3TC.

Table 5b. Antiretroviral Regimens that May be Acceptable and Regimens to be Used with Caution (Updated December 1, 2009)

Regimens that may be acceptable but more definitive data are needed	
CCR5-Antagonist-based Regimen • MVC + ZDV/3TC[1] **(CIII)** **INSTI-based Regimen** • RAL + (ABC or ZDV)/3TC[1] **(CIII)** **PI-based Regimen** • (DRV/r or SQV/r) + (ABC or ZDV)/3TC[1] **(CIII)**	**Comment** With MVC, tropism testing required before treatment. Only patients found to have CCR-5 tropic-only virus (i.e., absence of CXCR4 tropic virus) are candidates for MVC.
Regimens to be Used with Caution (Regimens that have demonstrated virologic efficacy in some studies, but have safety, resistance, or efficacy concerns.)	
NNRTI-based Regimens • NVP + ABC/3TC[1] **(CIII)** • NVP + TDF/FTC[1] **(CIII)** **PI-based Regimen** • FPV + [(ABC or ZDV)/3TC[1] or TDF/FTC[1]] **(CIII)**	**Comments** Use NVP and ABC together with caution because both can cause hypersensitivity reactions within first few weeks after initiation of therapy. Early virologic failure with high rates of resistance has been reported in some patients receiving NVP + TDF + (3TC or FTC). Larger clinical trials are currently in progress. FPV/r is generally preferred over unboosted FPV. Virologic failure with unboosted FPV-based regimen may select mutations that confer cross resistance to DRV.

[1]3TC maybe substituted with FTC or vice versa.

Abbreviations:
INSTI = integrase strand transfer inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor, PI = protease inhibitor
ABC = abacavir, 3TC = lamivudine, DRV = darunavir, FPV = fosamprenavir, FTC = emtricitabine, MVC = maraviroc, NVP = nevirapine, RAL = raltegravir, r = low dose ritonavir, SQV = saquinavir, TDF = tenofovir, ZDV = zidovudine

NNRTI- Versus PI- Versus INSTI-Based Regimens

Efavirenz-based regimens were superior to indinavir- and nelfinavir-based regimens in earlier comparative studies *[3, 7]*. 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 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 *[8]*.

PI-based regimens generally are associated with more gastrointestinal symptoms and lipid abnormalities, whereas efavirenz-based regimens are associated with more rash and central nervous system adverse effects. Both kinds of regimens may be associated with hepatic transaminase elevations *[9]*.

Drug resistance to most PIs requires multiple mutations in the HIV protease gene, and it seldom develops after early virologic failure *[10]*, especially when ritonavir boosting is used. Resistance to efavirenz or nevirapine, however, is conferred by a single mutation in the reverse transcriptase gene, and it develops rapidly after virologic failure *[10]*. An estimated 7% of HIV-infected patients in the United States are infected with NNRTI-resistant viruses *[11]*. 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, the coformulated tablet of tenofovir, emtricitabine, and efavirenz allows for once-daily dosing with a single tablet. Most 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 when compared to earlier years. Drug-drug

interactions are important with both kinds of regimens, but more clinically significant interactions are seen with ritonavir-boosted regimens.

Another option for initial therapy is the combination of tenofovir, emtricitabine, and the INSTI raltegravir *[6]*. This combination has shown similar virologic efficacy as a combination of tenofovir, emtricitabine, and efavirenz up to 96 weeks *[12]* and is generally well tolerated. There are no clinical trial data comparing INSTI-based with PI-based regimens. Raltegravir requires twice-daily dosing, has a low genetic barrier for selection of resistance mutations, and has had relatively limited use with other dual-NRTI combinations.

The discussions below focus on the rationale for the Panel's recommendations, based on the efficacy, safety, and other characteristics of different agents within the individual drug classes.

NNRTI-BASED REGIMENS (1 NNRTI + 2 NRTIs)

Summary: NNRTI-Based Regimens

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

NNRTI-based regimens have demonstrated virologic potency and durability. The major disadvantages of currently available NNRTIs involve prevalence of NNRTI-resistant viral strains in treatment-naïve patients *[11, 13-15]* and the low genetic barrier of NNRTIs for development of resistance. Resistance testing should be performed for treatment-naïve patients to guide therapy selection (see **Drug Resistance Testing** section). The first three approved NNRTIs (i.e., efavirenz, nevirapine, delavirdine) require only 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 *[16]*.

On the basis of clinical trial results and safety data, the Panel recommends either efavirenz or nevirapine as the NNRTI for initial antiretroviral therapy. In most instances, efavirenz should be the preferred choice based on its potency and tolerability (as discussed below). 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 $\leq$250 cells/mm^3 or in men with pretreatment CD4 counts $\leq$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

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, 17]*. Studies that compared efavirenz-based regimens with other regimens have demonstrated the combination of efavirenz with two NRTIs was superior virologically to some PI-based regimens, including indinavir *[3]*, lopinavir/ritonavir *[4]*, and nelfinavir *[7]*, and to triple-NRTI–based regimens *[18-19]*. Efavirenz-based regimens also had comparable activities to nevirapine- *[20-21]*, atazanavir-, *[5]*, and raltegravir-based regimens *[6]*.

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 *[20]*.

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 *[22]*. Several cases of neural tube defects in human newborns, when mothers were exposed to efavirenz during the first trimester of pregnancy, have been reported in the literature and to the Antiretroviral Pregnancy Registry *[23-24]*. 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 dual-NRTI combinations (abacavir, didanosine, stavudine, tenofovir, or zidovudine together with emtricitabine or lamivudine) show durable virologic activity, although there may be differences among the various combinations chosen (see **Dual NRTI Options** section). A single tablet coformulated with tenofovir, emtricitabine, and efavirenz provides one-tablet, once-daily dosing and is currently the preferred NNRTI-based regimen **(AI)**.

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 *[20]*. Two deaths were attributed to nevirapine use. One resulted from fulminant hepatitis and one from staphylococcal sepsis as a complication of Stevens-Johnson syndrome.

In a randomized controlled trial, presented in abstract form, nevirapine was found to be noninferior to boosted atazanavir when combined with tenofovir/emtricitabine *[25]*. This study enrolled only women and men with <250 and <400 CD4 cell counts/mm^3, respectively, the threshold recommended to reduce the incidence of hepatic toxicity (see below). Three smaller 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 *[26-28]*. Pending published results from randomized trials, clinicians should closely monitor virologic responses if using this combination **(CIII)**.

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 *[29-30]*. 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 *[30-31]*. 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 *[32]*.

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 12**.

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

Summary: PI-Based Regimens

PI-based regimens have demonstrated virologic potency, durability, and high barriers to resistance. In patients who experience virologic failure during their first PI-based regimen, few or no PI mutations are detected at failure. 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 6** and **Appendix B, Table 3**. In selecting a boosted PI-based regimen for a treatment-naïve patient, clinicians should consider factors such as dosing frequency, food requirements, pill burden, daily ritonavir dose, 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 and insulin resistance, have been associated with PI use. The currently available PIs differ in their propensity to cause these metabolic complications, which are also dependent on the dose of ritonavir used as a pharmacokinetic boosting agent. These complications may result in adverse long-term consequences, such as increased cardiovascular events. In an analysis from the D:A:D study, cumulative use of lopinavir/ritonavir or indinavir was associated with an increased risk of myocardial infarction, coronary heart disease, and stroke *[33]*. In another observational analysis from a French cohort, use of amprenavir or fosamprenavir (with or without ritonavir), or use of lopinavir/ritonavir, was associated with a higher rate of myocardial infarction *[34]*. It should be noted that in both studies, there were too few patients receiving ritonavir-boosted atazanavir or darunavir to be included in the analysis.

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 (Cmin) 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 *[35-37]*, and also may contribute to the lower risk of resistance upon virologic failure compared to unboosted PIs. 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. In patients without pre-existing PI resistance, there is growing support for the use of once-daily boosted PI regimens that use only 100mg per day of ritonavir, because they tend to cause fewer gastrointestinal side effects and less metabolic toxicity than regimens that use ritonavir at a dose of 200mg per day. In the case of ritonavir-boosted darunavir (800/100mg once daily) and atazanavir (300/100mg once daily), there are large head-to-head trials demonstrating noninferiority or superiority compared with lopinavir/ritonavir, with less gastrointestinal and lipid toxicity.

The Panel uses the following criteria to distinguish between preferred versus alternative PIs in treatment-naïve subjects: (1) demonstrated superior or noninferior virologic efficacy when compared with at least one other PI-based regimen, with at least published 48-week data; (2) ritonavir-boosted PI with no more than 100mg of ritonavir per day; (3) once-daily dosing; (4) low pill count; and (5) good tolerability. Using these criteria, the Panel recommends atazanavir + ritonavir (once daily) **(AI)** and darunavir + ritonavir (once daily) **(AI)** as preferred PIs.

Preferred PI Components (in alphabetical order, by active PI component)

Ritonavir-Boosted Atazanavir (AI). Ritonavir boosting of atazanavir, given as two pills once daily, enhances the concentrations of atazanavir and improves virologic activity compared with unboosted atazanavir in a clinical trial *[38]*.

The CASTLE study compared once-daily atazanavir/ritonavir with twice-daily lopinavir/ritonavir, each in combination with tenofovir/emtricitabine, in 883 antiretroviral-naïve participants. In this open-label, noninferiority study, analysis at 48 weeks *[39]* and at 96 weeks *[40]* 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 in combination with tenofovir/emtricitabine 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 *[41]*. Atazanavir/ritonavir requires 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. **Table 14a** 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, three pills per day) 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 ($p<0.001$). The virologic response rates were lower in the lopinavir/ritonavir arm among those participants whose baseline HIV RNA levels were >100,000 copies/mL ($p<0.05$). Grades 2 to 4 adverse events, primarily diarrhea, were seen more frequently in lopinavir/ritonavir recipients ($p<0.01$) *[42]*. At 96 weeks, virologic response to darunavir/ritonavir was superior to response to lopinavir/ritonavir ($p=0.012$) *[43]*.

Alternative PI Components (in alphabetical order, by active PI component)

Ritonavir-Boosted Fosamprenavir (once or twice daily) (BI). Ritonavir-boosted fosamprenavir is recommended as an alternative PI. The KLEAN trial compared twice-daily ritonavir-boosted fosamprenavir with lopinavir/ritonavir, each in combination with abacavir and lamivudine, in treatment-naïve patients. At weeks 48 and 144, similar percentages of subjects achieved viral loads of <400 copies/mL *[44-45]*. 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. Metabolic adverse effects occurred at similar frequencies with boosted fosamprenavir as with lopinavir/ritonavir in the KLEAN study. Based on the above criteria for preferred PIs, which favor once-daily regimens with no more than 100mg/day of ritonavir, twice-daily fosamprenavir is now considered an alternative choice.

In a study comparing once-daily ritonavir-boosted fosamprenavir (1,400 mg with ritonavir 200mg once daily) with nelfinavir *[46]*, similar virologic efficacy was reported in both arms. A comparative trial of once-daily ritonavir-boosted fosamprenavir (1,400/100mg) with once-daily ritonavir-boosted atazanavir, both in combination with tenofovir/emtricitabine, was conducted in 106 antiretroviral-naïve participants *[47]*. Similar virologic and CD4 T-cell benefits were seen with both regimens. The small sample size of this study precludes the assessment of superior or noninferior virologic efficacy required for a preferred PI. Collectively, fosamprenavir/ritonavir regimens, with once- or twice-daily dosing, are recommended as alternatives.

Lopinavir/Ritonavir (coformulated) **(BI).** Lopinavir/ritonavir is the only available coformulated boosted PI. In PI-naïve patients, it can be given once or twice daily. However, the need for 200mg/day of ritonavir, and the higher rate of gastrointestinal side effects and hyperlipidemia when compared with boosted PIs using ritonavir 100mg/day, make it an alternative rather than preferred PI for PI-naïve patients. Several clinical trials show that regimens containing twice-daily lopinavir/ritonavir with two NRTIs have virologic activity in treatment-naïve patients. Early studies showed that lopinavir/ritonavir was superior to nelfinavir in maintaining undetectable viral loads *[48]*. 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 *[49]*. Results of clinical trials that compared 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]*.

Several trials have evaluated different formulations and dosages of lopinavir/ritonavir administered once or twice daily *[42, 50-52]*. In the largest trial that compared once-daily with 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 *[53]*. At week 48, 77% of once-daily and 76% of twice-daily lopinavir/ritonavir recipients achieved viral loads <50 copies/mL. Rates of moderate to severe drug-related diarrhea were similar between the two groups. In addition to diarrhea, major adverse effects of lopinavir/ritonavir include insulin resistance and hyperlipidemia, especially hypertriglyceridemia; these require pharmacologic management in some patients. In the D:A:D and French observational cohorts, cumulative use of lopinavir/ritonavir was associated with a slightly increased risk of myocardial infarction *[33-34]*. Once-daily lopinavir/ritonavir should not be used in patients who have HIV mutations associated with PI 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 *[54]*. 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***" *[54]*.

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 (64.7% vs. 63.5%) and increases in CD4 counts were seen in both arms *[55]*. Triglyceride levels were significantly higher in the lopinavir/ritonavir arm. The higher pill burden (6 pills per day), need for twice-daily dosing, and use of 200mg of ritonavir make ritonavir-boosted saquinavir an alternative PI for treatment-naive patients.

Acceptable PI-Based Component

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, 38, 56-57]*. 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) *[58]*. If unboosted atazanavir is prescribed for a treatment-naïve patient, clinicians should consider using an alternative dual-NRTI backbone other 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. Atazanavir should not be used without ritonavir if tenofovir or efavirenz are used concomitantly because these two agents have been shown to lower the concentrations of atazanavir. 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 13 and 14a**.)

PI Component to be Used with Caution

Fosamprenavir (twice daily) (BI). In a study comparing unboosted fosamprenavir given twice daily with nelfinavir, 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 *[59]*. However, virologic failure on unboosted fosamprenavir may select for resistance mutations that confer cross

resistance to darunavir *[60-61]*, a PI with an important role in management of treatment-experienced patients. As such, ritonavir-boosted fosamprenavir is preferred over unboosted fosamprenavir, and the unboosted strategy should be used with caution.

INSTI-BASED REGIMEN (INSTI + 2 NRTIs)

Raltegravir is an INSTI that was first approved for use in combination antiretroviral regimens for treatment-experienced patients with HIV strains resistant to multiple antiretroviral drugs. It is now approved by the FDA for use in treatment-naïve patients, based on results of STARTMRK, a Phase III study that compared raltegravir (400mg twice daily) to efavirenz (600mg once daily), each in combination with tenofovir/emtricitabine, in treatment-naïve subjects. This multinational double-blind, placebo-controlled study enrolled 563 subjects with plasma HIV-1 RNA levels >5,000 copies/mL. At week 48, similar numbers of subjects achieved HIV-1 RNA levels <50 copies/mL in both groups (86.1% and 81.9% for raltegravir and efavirenz, respectively, $p<0.001$ for noninferiority). CD4 cell counts rose by 189/mm^3 in the raltegravir group versus 163/mm^3 in the efavirenz group. Serious adverse events occurred at a similar frequency in both groups *[6]*. At 96 weeks, virologic and immunologic responses remained similar in both groups with no new safety concerns identified *[12]*. Based on these data, the Panel recommends raltegravir + tenofovir + emtricitabine (or lamivudine) as a preferred regimen for treatment-naïve patients **(AI)**.

Comparisons of raltegravir-based regimens with other regimens in treatment-naïve subjects have not yet been reported, and there is less experience with raltegravir than with efavirenz or boosted PIs for initial therapy. In addition, raltegravir has to be administered twice daily, a potential disadvantage when compared with some other regimens. Raltegravir, like efavirenz, has a lower genetic barrier to resistance than ritonavir-boosted PIs, and resistance mutations were observed at approximately the same frequency in the comparative trial. Its use with other dual NRTIs (such as abacavir/lamivudine or zidovudine/lamivudine) may be acceptable, but more definitive data for these regimens are needed **(CIII)**.

DUAL-NRTI OPTIONS AS PART OF INITIAL COMBINATION THERAPY

Summary: Dual-NRTI Components

Dual NRTIs are commonly used in combination with an NNRTI, a PI (usually boosted with ritonavir), or an INSTI. Most dual-NRTI combinations used in clinical practice consist of a primary NRTI plus lamivudine or emtricitabine. Both lamivudine and emtricitabine have few adverse effects and may select 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 *[62]*.

All NRTIs except didanosine can be taken without food restrictions. Adherence may be additionally improved with once-daily dosing (available for 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

Tenofovir/Emtricitabine (coformulated) (AI). Tenofovir is a nucleotide analog with potent activity against both 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 tablet 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 *[17]* and was superior to zidovudine/lamivudine in virologic efficacy at up to 144 weeks *[63]*. 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 *[63]*. 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 and raltegravir in randomized clinical trials; all such trials demonstrate good virologic benefit *[6, 39, 42, 47, 51]*.

Tenofovir/emtricitabine was compared with abacavir/lamivudine in the ACTG 5202 study *[64]* and the HEAT trial *[65]*. Preliminary data from the ACTG trial suggest potential inferior virologic responses in participants randomized to abacavir/lamivudine who had a pretreatment HIV-RNA >100,000 copies/mL. This was not confirmed by the results from HEAT. (See the abacavir/lamivudine section below for more detailed discussion.)

One randomized controlled trial, presented in abstract form, found nevirapine to be noninferior to boosted atazanavir when combined with tenofovir/emtricitabine *[25]*. 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 *[26-28]*. Pending published results from randomized 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 *[66-67]*. Risk factors may include advanced HIV disease, greater treatment experience, and pre-existing renal impairment *[68]*. 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), tenofovir dosage adjustment is required (see **Appendix B, Table 7** for dosage recommendations). 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 concentrations can be increased by some PIs, and studies have suggested a greater risk of renal dysfunction when tenofovir is used in PI-based regimens *[66, 69-72]*. Tenofovir has been used in combination with PIs without renal toxicity in several clinical trials that involved patients who had CrCl >50–60 mL/min.

Tenofovir plus either emtricitabine or lamivudine is the preferred NRTI combination, especially for patients coinfected with both HIV and HBV because 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 NRTIs (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 of this reaction is highly associated with the presence of the HLA-B*5701 allele (see **HLA-B*5701 Screening** section) *[73-74]*. 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 based on test results, abacavir hypersensitivity should be noted on the patient's allergy list. 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 *[75]*. 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 *[64]*. Participants who had HIV RNA levels <100,000 copies/mL at study screening remain randomized and on study. In another 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. 58% for those who had <100,000 copies/mL and 56% vs. 58% for those who had >100,000 copies/mL, respectively) *[65]*.

There have been concerns regarding the potential cardiovascular risks of abacavir-containing regimens. The D:A:D study, a large, multinational, observational cohort, found that recent (within 6 months) or current use of abacavir predicted an increased risk of MI (relative risk [RR] 1.9; 95% CI, 1.5–2.6) *[76]*. The heightened risk of MI was accentuated in participants who had pre-existing cardiac risk factors. In a subsequent analysis from the same study, such an association was not seen with recent use of tenofovir (RR 1.14; 95% CI, 0.85–1.52) *[33]*. Several additional studies have addressed the possible association between abacavir use and cardiovascular risk *[34, 76-81]*,and some have explored possible biologic mechanisms underlying such an association *[82-83]*. In a pooled analysis of 52 clinical trials involving more than 9,500 participants who received abacavir, no increase risk of MI was found *[84]*. Thus, no consensus has been reached yet, either on the association or a possible mechanism. Channeling bias may sometimes interfere with the causal evaluation of medication effects due to the differential allocation of medications to patient groups with varying risk factors for disease outcomes *[85]*. It is possible that channeling bias may, in part, account for some of the differences observed among the reported studies. However, 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 of cardiovascular disease. However, the combination of abacavir/lamivudine remains a good alternative dual-NRTI option for some treatment-naïve patients.

Zidovudine/Lamivudine (coformulated) (BI). The dual-NRTI combination of zidovudine/lamivudine has extensive durability, safety, and tolerability experience *[3, 5, 7, 18, 86-88]*. 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 *[75]*.

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 *[63]*. 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 *[9]*. 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)**.

Zidovudine/lamivudine remains the preferred option in pregnant women. This dual NRTI has the most pharmacokinetic, 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***" *[54]*, available at **http://aidsinfo.nih.gov**.

Acceptable Dual NRTI

Didanosine + (Emtricitabine or Lamivudine) (CI). The FTC-301A trial tested didanosine + emtricitabine with efavirenz in treatment-naïve patients and demonstrated potent virologic suppression (78% of patients achieved HIV RNA <50 copies/ml at 48 weeks) *[89]*. The GESIDA 3903 study compared didanosine/lamivudine with zidovudine/lamivudine, and both were given with food and were combined with efavirenz *[90]*. At 48 weeks, virologic

response for didanosine/lamivudine was noninferior to zidovudine/lamivudine, with 70% and 63% of the participants, respectively, achieving 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) *[58]*. Alternative PIs should be considered if didanosine + (emtricitabine or lamivudine) are used. Didanosine use also is associated with an increased risk of pancreatitis, peripheral neuropathy, other mitochondria-associated toxicities, and possibly noncirrhotic portal hypertension *[91]*. 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 *[76]*. This increase in cardiovascular risk was not seen in the SMART study *[92]*.

Based on the limited clinical trial experience with the use of didanosine + lamivudine (or emtricitabine) with another antiretroviral drug other than efavirenz, the unfavorable results from ACTG 5175, and the many side effects associated with didanosine, the Panel considers it an acceptable but inferior option, and only to be used with efavirenz **(CI)**.

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 *[93-95]*. 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 **Initiating Antiretroviral Therapy** sections.)

ALL-NRTI REGIMENS

A triple-NRTI combination regimen has some potential advantages: fewer drug-drug interactions, 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 *[18-19, 96-99]*, 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 *[87-88]* and nelfinavir-based regimens *[99]* but was inferior virologically to an efavirenz-based regimen *[18]*. This combination is **generally not recommended (BI)** and should be used only when a preferred, an alternative, or an acceptable NNRTI-, PI-, or INSTI- 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 *[100]*; however, comparative data with standard regimens are not available and therefore this combination **cannot be recommended** in routine clinical practice **(BIII)**.

Zidovudine + Lamivudine + Abacavir + Tenofovir. A quadruple-NRTI regimen of zidovudine + lamivudine + abacavir + tenofovir first showed comparable virologic responses to an efavirenz-based regimen in a small pilot study *[101]*. A larger study randomized 322 subjects to receive tenofovir/emtricitabine combined with efavirenz, atazanavir/ritonavir, or a quadruple-NRTI regimen with zidovudine and abacavir. Although the threshold of noninferiority for the protocol-defined virologic response was satisfied by the quadruple-NRTI regimen, the proportion of patients reaching HIV RNA ≤50 copies/ml was significantly lower with the quadruple-NRTI regimen and the rate of serious toxicity was twice as high as that observed with the efavirenz-based regimen *[102]*. Thus, this regimen **cannot be recommended** at this time **(BI)**.

OTHER TREATMENT OPTION UNDER INVESTIGATION: INSUFFICIENT DATA TO RECOMMEND

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 *[103]*. 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 count 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%). Follow-up results at 96 weeks demonstrated durable responses *[104]*. Based on the results, the U.S. FDA recently approved maraviroc for use in regimens for treatment-naïve patients. Our guidelines will provide further recommendations regarding maraviroc-based regimens in the next revision.

Table 6. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (Updated December 1, 2009)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
NNRTI (in alphabetical order)		**NNRTI Class Advantages:** • Saves PIs and RAL 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 of resistance at the time of failure or treatment interruption • Potential for cross resistance • Skin rash • Potential for CYP450 drug interactions (see Tables 13, 14b, and 15b) • Transmitted resistance to NNRTIs more common than resistance to PIs
	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 • Fewer 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 for females, >400 cells/mm^3 for males) are at higher risk of 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 • Fewer clinical trial data than with EFV
PI (in alphabetical order)		**PI Class Advantages:** • 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 and substrates: potential for drug interactions (more pronounced with RTV-based regimens) (See Tables 13–14a.)
	Atazanavir (unboosted) (ATV)	• Fewer adverse effects on lipids than other PI • Once-daily dosing • Low pill burden (two pills per day) • Good GI tolerability • Signature mutation (I50L) not associated with broad PI cross resistance	• 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 TDF, EFV, or NVP (see ATV/r) • Nephrolithiasis • Skin rash • Food requirement • Absorption depends on food and low gastric pH (See Table 14a for detailed information regarding interactions with H2 antagonists, antacids, and proton pump inhibitors [PPIs].)
	Atazanavir/ ritonavir (ATV/r)	• RTV boosting: higher trough ATV concentration and greater antiviral effect • Once-daily dosing • Lowest 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 14a for interactions with H2 antagonists, antacids, and PPIs.) • RTV boosting required with TDF and EFV. With EFV, use ATV 400mg and RTV 100mg once daily (PI-naïve patients only). • Should not be coadministered with NVP

ARV Class	ARV Agent(s)	Advantages	Disadvantages
	Darunavir/ ritonavir (DRV/r)	• Once-daily dosing	• Skin rash • Food requirement
	Fosamprenavir (unboosted) (FPV)	No food effect	• Skin rash • Potential for PI resistance with failure, including emergence of mutations that can cause DRV cross resistance
	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 • For FPV 1,400mg + RTV 200mg: Requires 200mg of ritonavir and no coformulation • Fewer data on FPV 1,400mg + RTV 100mg dose than with DRV/r and ATV/r
	Lopinavir/ ritonavir (LPV/r)	• Coformulated • Once- or twice-daily dosing in treatment-naïve patients • No food requirement • Recommended PI in pregnant women (twice daily only) • Greater CD4 T-cell count increase than with EFV-based regimens	• Requires 200mg per day of ritonavir • 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 • Possible higher risk of myocardial infarction associated with cumulative use of LPV/r • PR and QT interval prolongation have been reported. Use with caution in patients at risk of cardiac conduction abnormalities or receiving other drugs with similar effect.
	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 pills per day) • Requires 200mg of ritonavir • Food requirement
INSTI	**Raltegravir (RAL)**	• Virologic response noninferior to EFV • Fewer drug-related adverse events and lipid changes than EFV • No food effect • Fewer drug-drug interactions than PI- or NNRTI-based regimens	• Less long-term experience in treatment-naïve patients than with boosted PI- or NNRTI-based regimens • Twice-daily dosing • Lower genetic barrier to resistance than with boosted PI-based regimens • No data with NRTIs other than TDF/FTC in treatment-naïve patients
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)**	• Virologic response noninferior to ZDV/3TC • 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; however, this was not seen in the HEAT study.
	Didanosine + (lamivudine or emtricitabine) (ddI + [3TC or FTC])	• Once-daily dosing • No cumulative TAM-mediated resistance	• Peripheral neuropathy, pancreatitis • Reports of noncirrhotic portal hypertension • 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.

ARV Class	ARV Agent(s)	Advantages	Disadvantages
	Tenofovir/ emtricitabine (or lamivudine) (TDF/FTC or TDF + 3TC)	• Better virologic responses than with ZDV/3TC • Better virologic responses than with ABC/3TC in patients with baseline HIV RNA >100,000 copies/mL in ACTG 5202 study; however, this was not seen in the HEAT 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 (although better tolerated with food) • Preferred 2 NRTI in pregnant women	• Bone marrow suppression, especially anemia and neutropenia • Gastrointestinal intolerance, headache • 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 7. Antiretroviral Components Not Recommended as Initial Therapy
(Updated December 1, 2009)

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 + lamivudine + zidovudine + tenofovir as quadruple NRTI combination **(BI)**	• Inferior virologic efficacy
Abacavir + didanosine **(BIII)**	• Insufficient data in treatment-naïve patients
Abacavir + tenofovir **(BIII)**	• Insufficient data in treatment-naïve patients
Darunavir (unboosted)	• Use 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
Nelfinavir **(BI)**	• Inferior virologic efficacy • High incidence of diarrhea
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 (Updated December 1, 2009)

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, although the use of a potent combination regimen is generally preferred. (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***" *[1]*, available at **http://aidsinfo.nih.gov**.)

Single-drug treatment regimens with a ritonavir-boosted PI, either lopinavir *[2]*, atazanavir *[3]*, or darunavir *[4-5]* are under investigation with mixed results, and **cannot be recommended** outside of a clinical trial at this time.

Dual-NRTI regimens. These regimens **are not recommended** because they have not demonstrated potent and sustained antiviral activity compared with triple-drug combination regimens *[6]* **(AI)**.

Triple-NRTI regimens. In general, triple-NRTI regimens other than abacavir/lamivudine/zidovudine **(BI)** and possibly zidovudine/lamivudine + tenofovir **(BII) should not be used** because of suboptimal virologic activity *[7-9]* 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 adverse effects may be possible when these agents are used concomitantly. Therefore, these two PIs **are not recommended** for combined use **(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 *[10-13]*. 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 *[14]*. Therefore, the combined use of didanosine and stavudine **is not recommended (AII)**.

Two-NNRTI combinations. 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 *[15]*. 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 *[16]*. 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 nonhuman 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 *[17-18]*. 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, the provider should consult 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***" *[1]* , 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 *[19]*. 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 unboosted PIs. Appropriate doses of the PIs have not been established *[16]* **(AII)**.

Etravirine + ritonavir-boosted atazanavir or fosamprenavir. Etravirine may alter the concentrations of these PIs. Appropriate doses of the PIs have not been established *[16]* **(AII)**.

Etravirine + ritonavir-boosted tipranavir. Ritonavir-boosted tipranavir significantly reduces etravirine concentrations. These drugs **should not be coadministered** *[16]* **(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 hepatic events, including serious and life-threatening events, have been observed in these patient groups. Nevirapine **should not be initiated** in these patients **(BI)** unless the benefit clearly outweighs the risk *[20-22]*. Patients who experience CD4 count increases to levels above these thresholds as a result of antiretroviral therapy can be safely switched to nevirapine *[23]*.

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 antagonism demonstrated *in vitro [24]* and *in vivo [25]* **(AII)**.

Table 8. 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[1]
Dual-NRTI regimens (AI)	• Rapid development of resistance • Inferior antiretroviral activity when compared with combination of three or more antiretrovirals	• No exception[2]
Triple-NRTI regimens (AI) 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 **(BI)**, 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 (AII)	• 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 (AI)	• 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 (ETR) exposure; thus, they **should not be used** in combination with ETR.	• 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)**
Emtricitabine + lamivudine (AIII)	• Similar resistance profiles • 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 or fosamprenavir (AII)	• Etravirine may alter the concentrations of these PIs; appropriate doses not yet established	• No exception
Etravirine + ritonavir-boosted tipranavir (AII)	• Etravirine concentration may be significantly reduced by ritonavir-boosted tipranavir	• No exception
Nevirapine in treatment-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

[1] **When constructing an antiretroviral regimen for an HIV-infected pregnant woman, 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***" *[1]* at **http://www.aidsinfo.nih.gov.**

[2] **When considering an antiretroviral regimen to use in post-exposure prophylaxis, 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 when feasible. 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 and response, adherence history, and drug intolerance/toxicity; the use of concomitant medications with consideration of adverse drug interactions with antiretrovirals; HIV RNA and CD4 T-cell count trends over time; and the results of prior drug resistance testing.***
- ***Optimal virologic response to treatment is maximal virologic suppression (e.g., HIV RNA level <400 copies/mL after 24 weeks, <50 copies/mL after 48 weeks). Persistent low-level viremia (e.g., HIV RNA 50–200 copies/mL) does not necessarily indicate virologic failure or a reason to change treatment.***
- ***Drug resistance testing should be obtained (AI) while the patient is taking the failing antiretroviral regimen (or, if not possible, within 4 weeks of treatment discontinuation).***
- ***The goal of treatment for patients with prior drug exposure and drug resistance is to re-establish maximal virologic suppression, with HIV RNA suppressed to below the limit of detection of a sensitive assay (e.g., <50 copies/mL) (AI).***
- ***The patient's treatment history and the past and current resistance test results should be used 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 the patient's treatment history, susceptibility on drug resistance testing, and mechanistic class. 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 and should be sought. Adding at least two (preferably three) fully active agents to an optimized background antiretroviral regimen can provide significant antiretroviral activity (AII).***
- ***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. The immunomodulator interleukin-2 has not demonstrated clinical benefits in randomized trials and is not recommended (AI).***
- ***For some highly treatment experienced patients, maximal virologic suppression is not possible. In this case, antiretroviral therapy should be continued with regimens designed to minimize toxicity, preserve CD4 cell counts, and avoid clinical progression. In this scenario, expert advice is essential and should be sought.***

THE TREATMENT-EXPERIENCED PATIENT (Updated December 1, 2009)

Most HIV-infected patients benefit from antiretroviral treatment. In clinical trials and in clinical practice using effective combination regimens, a majority of study participants maintain virologic suppression for at least 3 to 7 years *[1-5]*. Given our current understanding of viral dynamics during treatment, it is expected that most first-line antiretroviral regimens should be able to suppress virus indefinitely, assuming that the optimal regimen is selected and assuming that the patient can adhere to that regimen indefinitely.

In a patient with virologic suppression on antiretroviral therapy, 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 reduces dosing frequency and pill counts. Changing antiretroviral drugs to reduce or manage toxicity also is reasonable.

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

MANAGEMENT OF PATIENTS WITH ANTIRETROVIRAL TREATMENT FAILURE
(December 1, 2009)

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:
    - starting therapy in earlier years, when 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 abuse),
    - 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 toxicities;
- suboptimal pharmacokinetics (variable absorption, metabolism, or, theoretically, penetration into reservoirs; food/fasting requirements, adverse drug-drug interactions with concomitant medications);
- suboptimal potency of the antiretroviral regimen;
- provider experience, and/or
- other or unknown reasons.

Data from some patient cohorts suggest that suboptimal adherence and toxicity accounted for 28%–40% of treatment failure and regimen discontinuations *[6-7]*. Treatment failure in an individual patient can occur for multiple reasons.

Assessment of Antiretroviral Treatment Failure and Changing Therapy

In general, the cause of treatment failure should be explored by reviewing the medical history and performing a physical examination to assess for signs of clinical progression.

A medical history review should include:

- 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 abuse).

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., difficulties accessing or tolerating medications, depression, active substance abuse) and simplify the regimen if possible (e.g., decrease pill count or dosing frequency) **(AIII)**. (See **Adherence** section.)

- **Medication Intolerance.** Assess the patient's tolerance of the current regimen and the severity and duration of side effects (e.g., the limited duration of gastrointestinal symptoms with some regimens). Management strategies for intolerance in the absence of drug resistance 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 from one drug class to another (e.g., from an NNRTI to a PI, from enfuvirtide to raltegravir) if necessary and no drug resistance is suspected **(AI)**.

- **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 (consult **Drug Interactions** section and tables for common 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 is best defined as a maximal inhibition of viral replication *in vivo*, as evidenced by a sustained reduction in plasma 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 (e.g., <50 copies/mL) and may manifest as any of the following:

- ***Incomplete virologic response***: For example, two consecutive plasma HIV RNA >400 copies/mL after 24 weeks or above the limit of assay detection (e.g., >50 copies/mL) by 48 weeks on an antiretroviral regimen. 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 *[8]*. 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 *[9-11]*.

- ***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 *[12]* 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 *[13]* and usually are not associated with subsequent virologic failure. However, rebound to higher viral load levels or more frequent episodes of viremia increase the risk of virologic failure *[14-15]*.

When assessing virologic failure, the clinician should evaluate the degree of drug resistance and consider the patient's 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. Ideally, a new antiretroviral regimen should contain at least two, and preferably three, fully active drugs on the basis of drug history, resistance testing, or new mechanistic class **(AII)** *[16-24]*. Some antiretroviral drugs (e.g., NRTIs) may contribute partial antiretroviral activity to an antiretroviral regimen, despite drug resistance *[25]*, while others (e.g., enfuvirtide, non-nucleoside reverse transcriptase inhibitors, raltegravir) likely do not provide partial activity *[25-27]*. 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. Archived drug resistance mutations may not be detected by standard drug resistance tests. Drug potency and viral susceptibility are more important than the number of drugs prescribed. Early studies of treatment-experienced patients identified factors associated with better virologic responses to subsequent regimens *[28-29]*. These factors included lower HIV RNA and/or higher CD4 cell count at the time of therapy change, using a new (i.e., not yet taken) class of antiretroviral drugs, and using ritonavir-boosted PIs in PI-experienced patients.

More recent clinical trials illustrate effective therapeutic strategies for treatment-experienced patients *[17-18, 20-21, 30]*. In these studies, patients received an optimized background antiretroviral regimen based on drug treatment history and resistance testing (genotype and phenotype) and then were randomized to add on a new active antiretroviral agent or placebo. Patients who received more active drugs had a better and more prolonged virologic response than those with fewer active drugs in the regimen. Higher genotypic and/or phenotypic susceptibility scores (indicating a greater number of active agents) were associated with better virologic responses *[20-21]*.

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. Active antiretroviral drugs include those with activity against drug-resistant viral strains, including newer members of existing classes (the NNRTI etravirine, the PIs darunavir and tipranavir) and drugs with new mechanisms of action (the fusion inhibitor enfuvirtide, the CCR5 inhibitor maraviroc, and the integrase inhibitor raltegravir).

Clinical Scenarios in Management of Patients with Antiretroviral Treatment Failure.

- ***Prior treatment with low-level viremia (50–1,000 copies/mL).*** Assess adherence. Consider variability in HIV RNA assays. Patients with isolated increases in HIV RNA ("blips") do not require a change in treatment *[13]* **(AII)**. Some HIV RNA assays are associated with more frequent "blips" *[31]* and results should be interpreted with caution. It is not clear how to manage patients with persistent low-level viremia; many experts would not change therapy and would follow the patient closely **(CII).**

- ***Prior treatment with detectable viremia (e.g., HIV RNA >1,000 copies/mL) and no resistance identified.*** Consider the timing of the drug resistance test (e.g., Was the patient off antiretroviral medications for >4 weeks and/or nonadherent?). 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 pharmacokinetic enhancement (ritonavir boosting for an unboosted PI such as atazanavir, fosamprenavir) **(BII)**.

- ***Prior treatment and drug resistance.*** The goals in this situation are to re-suppress 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 (e.g., etravirine). Similarly, consideration should be given to discontinuing enfuvirtide or raltegravir in a failing regimen to decrease selection of additional drug mutations. A new regimen should include at least two, and preferably three, fully active agents **(AII)**.

- ***Extensive prior treatment and drug resistance.*** The goal is to re-suppress 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 *[32]*; however, this must be balanced with the ongoing risk of accumulating additional resistance mutations.

- ***Extensive prior treatment and highly drug resistant HIV.*** There exists a subset of patients who have developed resistance to all or most currently available regimens, and designing a regimen with two or three fully active drugs is not possible. Many of these patients received newer agents in suboptimal regimens (i.e., did not have access to more than one or two of the drugs at the time they became available) or have been unable to adhere to any regimen. There is no consensus on how to optimize the management of these patients. 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 *[33]*. Other cohort studies suggest continued immunologic and clinical benefits if the HIV RNA level is maintained <10,000–20,000 copies/mL *[34-35]*. 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/mm3) 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)**. 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. Patients with ongoing viremia and with an insufficient number of approved treatment options to construct a fully suppressive regimen may be candidates for single-patient access of investigational new drug(s) (IND), as specified in FDA regulations: *http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm163982.htm*). Access requires ineligibility or inability to participate in ongoing study protocols, agreement from the sponsor to supply the investigational drug, and local institutional review board approval.

- ***Discontinuing antiretroviral therapy.*** 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 increases the risk of clinical progression *[36-37]*. Therefore, this strategy is not recommended **(AII)**. See **Discontinuation or Interruption of Antiretroviral Therapy** section.

- ***Prior treatment and suspected drug resistance, now presenting to care in need of therapy and with limited information (i.e., incomplete or absence of medical records or previous resistance data).*** This is a common scenario. Every effort should be made to obtain medical records and prior drug resistance testing results; however, this is not always possible. One strategy is to restart the most recent antiretroviral regimen and assess drug resistance in 2–4 weeks to help guide the choice of the next regimen.

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 data linking these thresholds with the risk of non-AIDS clinical events *[38]*.

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) *[39]*; increases in CD4 T-cell counts in treatment-naïve patients with initial antiretroviral regimens are approximately 150 cells/mm^3 over the first year *[40]*. A CD4 T-cell count plateau may occur after 4–6 years of treatment with suppressed viremia *[39, 41-44]*.

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 *[45-46]*. For example, in the FIRST study *[47]*, a low CD4 T-cell count on therapy was associated with an increased risk of 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 of non-AIDS events, including cardiovascular, hepatic, renal, and cancer events. Other studies support these associations *[48-50]*.

Factors associated with poor CD4 T-cell response:

- CD4 count <200/mm^3 when starting ART;
- Older age;
- Coinfection (e.g., HCV, HIV-2, HTLV-1, HTLV-2);
- Medications, both antiretrovirals (zidovudine *[51]*, tenofovir + didanosine *[52-54]*) and other medications;
- Persistent immune activation;
- Loss of regenerative potential of the immune system; and
- Other medical conditions

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), and consideration should be given to substituting or discontinuing these drugs, if possible. 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 *[55]*. Others suggest changing the regimen 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. These two strategies, however, have not been completely tested.

An immune-based therapy, interleukin-2, demonstrated CD4 T-cell count increases but no clinical benefit in two large randomized studies *[56]* and therefore is not recommended **(AI)**. 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 *[57-58]*. In one earlier study using older combination regimens, 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 *[59]*.

Management of Clinical Progression. Identify and consider treatment for potential HIV-related illnesses. Consider the possibility of immune reconstitution syndrome (IRS) *[57-58]*, which typically occurs within the first 3 months after starting effective antiretroviral therapy. IRS may respond better to anti-inflammatory treatment(s) and treatment of the specific opportunistic infection than to 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 *[60]*. 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 *[61]*.

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REGIMEN SIMPLIFICATION (**Updated December 1, 2009**)

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) 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) they were prescribed a regimen prior to the availability of newer options or formulations 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

Unlike antiretroviral agents developed earlier in the HIV epidemic, many antiretroviral medications that have been approved in recent years have sufficiently long half-lives 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 patients who do not simplify treatment *[5]*. However, some patients may have unrecognized 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 nonsuppressive 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 PIs. Despite success of this treatment in suppressing viral replication, 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 tolerance, and resistance test results. 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; 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)**:*** This may be considered for a patient who has no history of viral resistance on an NRTI-containing regimen. Other NRTIs may be substituted to create a regimen with lower dosing frequency (e.g., once daily) that takes advantage of coformulated agents and potentially avoids some long-term toxicities (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, to the same PI at a lower dosing frequency or, in the case of atazanavir, to administration without ritonavir boosting *[6]*. (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. Unboosted atazanavir 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 *[7]*. Although the baseline regimens in the study are no longer in widespread use, the NEFA findings are still relevant, and 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 *[8]*.

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. Switching patients who are suppressed on a lopinavir/ritonavir-based regimen to a raltegravir-based regimen has been reported to be associated with increased risk of virologic rebound in patients with more extensive prior treatment history, therefore should be done with caution *[9]*.

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, causes 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 an active oral agent. Because the majority of patients on enfuvirtide have highly drug-resistant virus, substitution must be with another fully active agent. Data from one randomized trial and one observational study suggest that raltegravir can safely substitute for enfuvirtide in patients not previously treated with integrase inhibitors *[10-11]*. Although this strategy generally maintains virologic suppression and is well tolerated, clinicians should be aware that any drug substitution may introduce unanticipated adverse effects or drug-drug interactions. Another study reported continued viral suppression with an enfuvirtide to raltegravir switch but raised concern about decreased levels of the concurrent boosted PI after the switch (darunavir or tipranavir) *[12]*. In one report, four patients 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 *[13]*. Use of novel combinations of antiretrovirals for which there are limited drug interaction data is also a concern, as illustrated by a report of liver toxicity after raltegravir was substituted for enfuvirtide in three patients who received ritonavir-boosted tipranavir *[14]*. Although a similar substitution can be considered with etravirine or maraviroc, this strategy can be limited by the inability to perform testing to assess etravirine resistance or viral tropism in virologically suppressed patients. No data are currently available using maraviroc in this setting. In the etravirine early access program, switching from enfuvirtide to etravirine showed promise in maintaining viral suppression at 24 weeks, but only 37 subjects were included in this report *[15]*.

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 *[16]*. More recently, studies have evaluated the use of a ritonavir-boosted PI as monotherapy after virologic suppression with a two-NRTI + boosted-PI regimen *[17-18]*. The major motivations for this approach are a reduction in NRTI-related toxicity and a lower cost. In the largest of these studies *[18]*, 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. Studies of darunavir/ritonavir monotherapy, both as once- or twice-daily dosing, have reported mixed results *[19-20]*. In aggregate,

boosted-PI monotherapy as initial *[21]* or as simplification treatment has 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 and liver function. 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 9**).

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 9** 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 9. 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[1]	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

[1]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 10** 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 10**)

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 **Laboratory Testing for 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 10. 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 of 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 14c**.) 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 14b**.) 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 14a** 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 14a 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***" *[1]* 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/mm^3 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 **Initiating Antiretroviral Therapy** section.)

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CONSIDERATIONS IN MANAGING PATIENTS WITH HIV-2 INFECTION

(New, December 1, 2009)

HIV-2 infection is endemic in West Africa, and although the virus has had only limited spread outside this area, it should be considered in persons of West African origin or those who have had sexual contact or shared needles with persons of West African origin. The prevalence of HIV-2 infection is also disproportionately high in countries with strong socioeconomic ties to West Africa (e.g., France; Spain; Portugal; and former Portuguese colonies such as Brazil, Angola, Mozambique, and parts of India near Goa).

The clinical course of HIV-2 infection is generally characterized by a longer asymptomatic stage, lower plasma HIV-2 viral loads, and lower mortality rates compared with HIV-1 infection *[1-2]*. However, HIV-2 infection can progress to AIDS, and thus antiretroviral therapy may become necessary during the course of infection. Concomitant HIV-1 and HIV-2 infection may occur and should be considered in patients from a high prevalence area. In the appropriate epidemiologic setting, HIV-2 infection should be suspected in patients with clinical conditions suggestive of HIV infection but with atypical serologic results (e.g., a positive screening assay with an indeterminate HIV-1 Western blot *[3]*). The possibility of HIV-2 infection should also be considered in the appropriate epidemiologic setting in patients with serologically confirmed HIV infection but low or undetectable viral loads, or in those with declining CD4 cell counts despite apparent virologic suppression on antiretroviral therapy.

The Multispot HIV-1/HIV-2 Rapid Test (Bio-Rad Laboratories) is FDA approved for differentiating HIV-1 from HIV-2 infection. Commercially available HIV-1 viral load assays do not reliably detect or quantify HIV-2, and there are no HIV-2 commercial viral load assays currently available *[4-5]*. Most studies reporting HIV-2 viral loads use “in-house” assays that are not widely available, making it difficult to monitor virologic response in the clinical setting. In addition, there are no available validated HIV-2 genotypic or phenotypic antiretroviral resistance assays.

To date, there have been no randomized trials addressing the question of when to start antiretroviral therapy or the choice of initial or second-line therapy for HIV-2 infection *[6]*; thus, the optimal treatment strategy has not been

defined. HIV-2 appears intrinsically resistant to NNRTIs *[7]* and to enfuvirtide *[8]*. *In vitro* data suggest HIV-2 is sensitive to the currently available NRTIs, although with a lower barrier to resistance than HIV-1 *[9-10]*. Variable sensitivity among PIs has been reported, with lopinavir, saquinavir, and darunavir having greater activities than other approved PIs *[11-12]*. The integrase inhibitor, raltegravir, *[13]* and the CCR5 antagonist, maraviroc, appear active against some HIV-2 isolates, although there are no approved assays to determine HIV-2 coreceptor tropism and HIV-2 is known to utilize multiple minor coreceptors in addition to CCR5 and CXCR4 *[14]*. Several small studies suggest poor responses among HIV-2 infected individuals treated with some antiretroviral regimens, including dual-NRTI regimens, regimens containing two NRTIs + NNRTI, and some unboosted PI-based regimens including nelfinavir or indinavir plus zidovudine and lamivudine *[6, 15-17]*. There are conflicting clinical data on the utility of triple-NRTI regimens *[18-19]*. In general, boosted PI-containing regimens have resulted in more favorable virologic and immunologic responses *[19]*. One small study suggested satisfactory responses to lopinavir/ritonavir-containing regimens in 17 of 29 (59%) of antiretroviral-naïve subjects *[20]*.

Resistance-associated mutations develop commonly in HIV-2 patients on therapy *[15, 19, 21]* and genotypic algorithms used to predict drug resistance in HIV-1 may not be applicable to HIV-2 *[10, 19]*. CD4 cell recovery on therapy may be poor *[22]*, suggesting that more reliable methods for monitoring disease progression and treatment efficacy in HIV-2 infection are needed.

Until more definitive data are available in a treatment-naïve patient with HIV-2 mono-infection or with HIV-1/HIV-2 dual infection who requires treatment, clinicians should initiate a boosted PI-based regimen. Monitoring of treatment response in such patients is problematic because of the lack of a commercially available HIV-2 viral load assay; however, clinical and CD4 count improvement can be used to assess treatment response.

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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 December 1, 2009)

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 *[1-2]*. This rate of progression increases with older age, alcoholism, male sex, and HIV infection *[3-6]*. A meta-analysis demonstrated that the rate of progression to cirrhosis for persons coinfected with HCV/HIV was about three times higher compared with the rate for HCV mono-infected patients *[5]*. This accelerated rate is magnified in patients with low CD4 counts. Chronic HCV infection also complicates HIV treatment due to the increased frequency of antiretroviral-associated hepatotoxicity *[7]*. Multiple studies have shown poor prognosis for HCV/HIV coinfection in the era of combination antiretroviral therapy. It is unclear if HCV infection accelerates the rate of HIV progression *[8-9]* or if the accelerated rate primarily reflects the impact of injection drug use, which is strongly linked to HCV infection *[10-11]*. Although whether antiretroviral therapy reduces the attributable morbidity/mortality from untreated HCV is unknown, the presence of chronic HCV infection influences the treatment of HIV with antiretroviral therapy as discussed below.

Assessment of HCV/HIV Coinfection Prior to Antiretroviral Therapy

- Prior to initiation of antiretroviral therapy, HIV-infected patients should be screened for HCV infection with sensitive immunoassays licensed for detection of antibody to HCV in blood. To confirm the presence of chronic infection, HCV-seropositive persons should be tested for HCV RNA using a qualitative or quantitative assay *[12]*.

- Patients with HCV/HIV coinfection should be advised to avoid alcohol consumption, use appropriate precautions to prevent transmission of both viruses to others, and should be given hepatitis A and B vaccine if susceptible.

- All patients with HCV/HIV coinfection should be evaluated for HCV therapy. HCV treatment is recommended according to standard guidelines with strong preference for treating patients with higher CD4 counts. For patients with lower CD4 counts (<200 cell/mm^3), it may be preferable to initiate antiretroviral therapy and delay HCV therapy until CD4 counts increase as a result of HIV treatment *[12-15]*.

- Concurrent treatment of both HIV and HCV is feasible but may be complicated by pill burden, drug toxicities, and drug interactions. Some notable considerations include:

    - Didanosine should not be given with ribavirin because of the potential for drug-drug interactions leading to life-threatening didanosine-associated mitochondrial toxicity including hepatomegaly/steatosis, pancreatitis, and lactic acidosis *[16]*.
    - Zidovudine combined with ribavirin should be avoided when possible because the higher rates of anemia associated with the combination make ribavirin dose reduction necessary *[17]*.
    - Abacavir has been associated with decreased response to peginterferon plus ribavirin in some, but not all, retrospective studies; current evidence is insufficient to recommend avoiding this combination *[18-20]*.
    - Growth factors (e.g., filgrastim and erythropoietin) may be required to manage interferon-associated neutropenia and ribavirin-associated anemia; zidovudine may increase the need for adjuvant growth factors due to increased bone marrow suppression *[17]*.

Antiretroviral Therapy in HCV/HIV Coinfection

- Hepatotoxicity: Drug-induced liver injury (DILI) following antiretroviral therapy is more common in HIV/HCV coinfection. The greatest risk for DILI may be observed in coinfected persons with advanced liver disease (e.g., cirrhosis or end-stage liver disease) *[21]*. Eradication of HCV infection may decrease the likelihood of antiretroviral-associated DILI *[22]*.

    - Given the substantial heterogeneity in patient populations and drug regimens, comparison of DILI incidence rates for individual antiretroviral agents across clinical trials is difficult. In such studies, the highest incidence rates of grade 3 or 4 elevations in liver enzyme levels have been observed during therapy with regimens that include stavudine (with or without didanosine), nevirapine, full-dose ritonavir (600mg twice daily), or tipranavir (boosted by low-dose ritonavir) *[23]*. Also, due to the potential for concurrent fatty liver disease (steatosis), the use of stavudine or didanosine should be limited *[24]*.

    - Patients should be monitored by following alanine and aspartate aminotransferase levels at 1 month and then every 3 months following initiation of antiretroviral therapy. Mild to moderate fluctuations in liver enzyme levels are typical in persons with chronic HCV infection. In the absence of signs and/or symptoms of liver disease these fluctuations do not require interruption of antiretroviral therapy. Significant elevation in liver enzyme levels (>5 times the upper limit of the laboratory reference range) should prompt careful evaluation for signs and symptoms of liver insufficiency and for alternative causes of liver injury (e.g., acute viral hepatitis A or B infection, hepatobiliary disease, or alcoholic hepatitis); short-term antiretroviral interruption may be required *[25]*.

- When to start antiretroviral therapy: The rate of liver disease (fibrosis) progression is accelerated by HIV/HCV coinfection, particularly in persons with low CD4 cell counts ($\leq 350/mm^3$). Data derived largely from retrospective cohort studies regarding the effect of antiretroviral therapy on the natural history of HCV disease are inconsistent *[6, 26-27]*. However, antiretroviral therapy may slow the progression of liver disease by preserving or restoring immune function and reducing HIV-related immune activation and inflammation *[28-30]*. Thus, for most coinfected patients including those with cirrhosis, the potential benefits of antiretroviral therapy outweigh concerns regarding DILI.
    - Antiretroviral therapy should be started in HCV/HIV-coinfected persons in accordance with the Panel's recommendation for initiating antiretroviral therapy in treatment-naïve patients.

- What to start and what not to use: Initial combination regimens for the antiretroviral-naïve patient with HCV/HIV are the same as for persons without HCV infection. HCV infection does not significantly alter the virologic or immunologic response to effective antiretroviral therapy *[31]*. Special considerations for antiretroviral therapy in persons with HCV/HIV coinfection include:

    - Patients receiving or considering therapy with ribavirin should avoid didanosine, stavudine, and zidovudine.

- Antiretroviral agents with the greatest risk of DILI should be used with caution.

- Cirrhotic patients should be carefully assessed for signs of liver decompensation according to the Child-Turcotte-Pugh classification system because hepatically metabolized antiretroviral drugs may require dose modification or avoidance in patients with Child-Pugh class B and C disease (see **Appendix B, Table 7**).

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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 $\geq$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 <100 cells/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 >350 cells/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 14b**). 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 14a and 14b**. 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—2009**: 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 11. 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 December 1, 2009)**

Adverse effects have been reported with all antiretroviral drugs and are among the most common reasons for switching or discontinuing therapy as well as 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 and are generally now less than 10%. In the Swiss Cohort study, the presence of laboratory adverse events was associated with higher rates of mortality during 6 years of follow-up, highlighting the importance of adverse events in overall patient management *[2]*. Whereas some common adverse effects were identified during premarketing clinical trials, other 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 in use 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 treatment-naïve women with CD4 counts greater than 250 cells/mm^3) *[3-5]*. Women have also been observed to suffer higher rates of lactic acidosis from NRTIs *[6-8]*. Other factors may also contribute to the development of adverse events: concomitant use of 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 viral hepatitis, 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 factors 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 regimen that is not only effective but is also safe. This requires taking into account an individual patient's underlying conditions, concomitant medications, and history of drug intolerance.

Information on adverse events is outlined in multiple tables in the guidelines:
Appendix B, Tables 1–6 summarize common adverse effects of individual antiretroviral agents. **Table 12** 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 12. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations

(Updated December 1, 2009)

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, and soft tissues) and hematuria	For ICH: 24 reported cases with TPV/r use, including 12 fatalities *[18]* For hemophilia: frequency unknown	For ICH: • CNS lesions • Head trauma • Recent neurosurgery • Coagulopathy • Hypertension • Alcohol abuse • 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 TPV For ICH: Avoid using TPV/r in patients at risk of ICH For hemophiliac patients: • Consider using a non-PI-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) or drugs that cause hemolytic anemia (e.g., ribavirin) or neutropenia (e.g. alpha interferon)	• Avoid use in patients at risk • Avoid other bone marrow suppressants if possible • Monitor CBC with differential after the first few weeks, then at least every 3 months (more frequently in at-risk patients)	• Switch to another NRTI if possible • Discontinue concomitant bone marrow suppressant if possible; 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 cerebro-vascular accidents (CVA)	MI and CVA: associated with PI but not NNRTI use in cohort study MI only: association between recent ABC and ddI use found in observational cohort; association not seen in randomized studies of ABC (see **What to Start** text)	Onset: Months to years after beginning of therapy Presentation: Coronary artery disease or CVA	3–6 per 1,000 patient-years CVA: ~1 per 1,000 patient-years	• Smoking • Age • Hyperlipidemia • Hypertension • Diabetes mellitus • Family history of premature coronary artery disease • Personal history of coronary artery disease	• Assess cardiac disease risk factors • Monitor and identify patients with hyperlipidemia or hyperglycemia • Consider regimen with fewer adverse lipid effects • Recommend life style modifications to reduce risk factors (e.g., smoking cessation, diet, physical activity)	• Prevent or manage other cardiovascular risk factors (e.g., hyperlipidemia, hypertension, insulin resistance/diabetes mellitus) with early diagnosis, lifestyle modifications, and medication • Modify lifestyle risk factors (smoking, diet, physical activity) • Switch to agents with less propensity for increasing cardiovascular risk factors, especially in patients at greatest risk of CVD

Adverse Effects	Associated ARVs	Onset/Clinical Manifestation	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Central nervous system effects	EFV	Onset: Within first doses Symptoms: • May include one or more of the following: drowsiness, somnolence, insomnia, abnormal dreams, dizziness, impaired concentration and attention span, depression, hallucination, exacerbation of psychiatric disorders, psychosis, suicidal ideation • Most symptoms subside or diminish after 2–4 week	>50% of patients may have some symptoms	• History of psychiatric illness • Concomitant use of medication with neuropsychiatric effects • History of injection drug use • Higher plasma EFV concentrations in people with G→T polymorphism at position 516 (516G → T) of CYP2B6 *[19]*	• Take at bedtime or 2–3 hours before bedtime • Take on an empty stomach to reduce drug concentration and CNS effects • Restrict risky activities (e.g., operating heavy machinery) during first 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
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, some RTV-boosted PIs, and buffered formulations of ddI	Varies with different agents	All patients	• Taking with food may reduce symptoms (ddI and unboosted IDV are recommended on empty stomach) • Some patients may require antiemetics or antidiarrheals pre-emptively to reduce symptoms	• Rule out other causes such as pancreatitis or infectious gastroenteritis • Symptoms may spontaneously resolve or become tolerable with time; if not, consider, For nausea and vomiting: • Antiemetic prior to dosing • Switch to less emetogenic ARV For diarrhea: • Bulk-forming agents (e.g., psyllium products) • Antimotility agents (e.g., loperamide, diphenoxylate/atropine) • Calcium tablets • Pancreatic enzymes • L-glutamate may reduce diarrhea, especially when associated with NFV or LPV/r For severe GI symptoms: Rehydration and electrolyte replacement as indicated
Hypersensitivity with 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, malaise, fatigue), abdominal pain, jaundice, or fever with or without skin rash • May progress to fulminant hepatic failure particularly in those with rash • Rhabdomyolysis may accompany hepatic failure • Approximately 1/2 of the cases have accompanying skin rash, some presenting 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% with pre-NVP CD4 >250 cells/mm^3 vs. 0.9% with CD4 <250 cells/mm^3 • In men: 6.3% with pre-NVP CD4 >400 cells/mm^3 vs. 2.3% with CD4 <400 cells/mm^3	• Treatment-naïve patients with higher CD4 count at initiation (>250 cells/mm^3 in women and >400 cells/mm^3 in men) • Women (risk is 3 times higher than in men) • HIV(-) individuals when NVP is used for post-exposure prophylaxis • Possibly, high NVP concentrations	• 2-week dose escalation may reduce incidence; follow instructions for dose escalation • Avoid initiation of NVP in women with CD4 >250 cells/mm^3 or men with CD4 >400 cells/mm^3 • Do not use NVP in HIV(-) individuals for post-exposure prophylaxis • Counsel patients on signs and symptoms of hypersensitivity and hepatitis; instruct them to stop NVP and seek medical attention if signs and symptoms of hepatitis, severe skin rash, or hypersensitivity reactions appear • Monitor ALT and AST (every 2 weeks x first month, then monthly x 3 months, then every 3 months) • Obtain AST and ALT in patients with rash	• Discontinue ARVs, including NVP • Discontinue all other hepatotoxic agents if possible • Rule out other causes of hepatitis • Manage with aggressive supportive care as indicated • Hepatic injury may progress despite treatment discontinuation. Careful monitoring should continue until symptom resolution. Do not .rechallenge patient with NVP. • Use other NNRTIs (e.g., EFV, ETR, DLV) with caution; it is unknown if they can be safely used in patients who experienced significant hepatic event from NVP.

Adverse Effects	Associated ARVs	Onset/Clinical Manifestation	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Hepatotoxicity (clinical hepatitis or asymptomatic serum transaminase elevation)	All NNRTIs; all PIs; most NRTIs; maraviroc	Onset: • NNRTIs: for NVP, 2/3 of patients within first 12 weeks • NRTIs: over months to years • PIs: generally after weeks to months Symptoms/findings: NNRTIs: • Asymptomatic to nonspecific symptoms (e.g., 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 have greater risk of hepatotoxicity associated with lactic acidosis with microvesicular or macrovesicular hepatic steatosis because of mitochondrial toxicity • ddI: prolonged exposure associated with noncirrhotic portal hypertension with esophageal varicees *[20]* • 3TC, FTC, or TDF: HBV-coinfected patients may develop severe hepatic flare when these drugs are initiated, withdrawn, or when resistance develops PIs: • Clinical hepatitis and hepatic decompensation (and rare cases of fatalities) have been reported with TPV/r and also with other PIs to varying degrees. • May be asymptomatic, some with anorexia, weight loss, jaundice, etc.	Varies with different agents	• HBV or HCV coinfection • Alcoholism • Concomitant hepatotoxic drugs, particularly rifampin • Elevated ALT and/or AST at baseline • For NVP-associated hepatic events: female with pre-NVP CD4 >250 cells/mm^3 or male with pre-NVP CD4 >400 cells/mm^3 • Higher drug concentrations for PIs, particularly TPV • Underlying liver disease • Hepatitis B or C infection	NVP • Monitor liver-associated enzymes at baseline, at 2 and 4 weeks, then monthly for first 3 months; then every 3 months TPV/RTV • Contraindicated in patients with moderate to severe hepatic insufficiency; follow other patients frequently during treatment Other agents • Monitor liver-associated enzymes at least every 3–4 months or more frequently in at-risk patients	• Rule out other causes of hepatotoxicity (alcoholism; viral hepatitis; chronic HBV with 3TC, FTC, or TDF initiation or withdrawal; HBV resistance, etc.) For symptomatic patients: • Discontinue all ARVs and other potential hepatotoxic agents • After symptoms subside and 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 is also elevated • After serum transaminases return to normal, construct a new ARV regimen without the potential offending agent(s) • Refer to information regarding NVP-associated symptomatic hepatic events and NRTI-associated lactic acidosis with hepatic steatosis in this table

Adverse Effects	Associated ARVs	Onset/Clinical Manifestation	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Hyperlipidemia	All PIs (except unboosted ATV); d4T; EFV > NVP	Onset: Weeks to months after beginning of therapy Presentation: All PIs (except unboosted ATV): •↑in LDL, total cholesterol (TC), and triglycerides (TG) •↑ HDL seen with ATV, DRV, FPV, LPV, SQV when boosted with RTV LPV/r and FPV/r: Disproportionate ↑ in TG compared with either DRV/r or ATV/r *[21-23]* EFV and to a lesser extent NVP: •↑ LDL and TC •Slight ↑ TG •↑ HDL d4T and ZDV: ↑ LDL, TC, and TG	Varies with different agents Swiss Cohort: ↑ TC and TG; 1.7–2.3x higher in patients receiving (non-ATV) PI	•Underlying hyperlipidemia •Risk based on ARV therapy PI: •All RTV-boosted PIs may ↑ LDL and TG •ATV/r may produce less of an ↑ in LDL and TG NNRTI: EFV >NVP *[24]* NRTI: d4T >ZDV >ABC>TDF *[25-26]*	•Assess cardiac disease risk factors •Use PIs and NNRTIs with less adverse effect on lipids, and non–d4T-based regimen •Monitor 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 modifications (e.g., diet, exercise, smoking cessation) •Switch to agents with less propensity for causing hyperlipidemia Pharmacologic Management: •Per HIVMA/ACTG guidelines *[27]* and National Cholesterol Education Program ATP III guidelines *[28]* •For potential interactions between ARV and lipid-lowering agents, refer to **Tables 14a and 14b**
Hypersensitivity reaction (HSR)	ABC	Onset of first reaction: Median onset is 9 days; approximately 90% of reactions occur within the first 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 first 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 •In one study, higher incidence of grade 3 or 4 HSR with 600mg once-daily dose than with 300mg twice-daily dose (5% vs. 2%)	•HLA-B*5701 screening prior to initiation of ABC •ABC should not be started if HLA B*5701 (+) •Indicate allergy to ABC in medical records of patients tested (+) for HLA-B*5701 •Educate patients about potential signs and symptoms of HSR and to report symptoms promptly •Provide patients with wallet card with warning information •Note multiple names for products containing 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: •Manage with 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.

Adverse Effects	Associated ARVs	Onset/Clinical Manifestation	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Insulin resistance/ diabetes mellitus (DM)	Thymidine analogs (ZDV, d4T); some PIs linked to insulin resistance and diabetes mellitus (but unclear if 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	3%–5% of patients developed diabetes in some series; D:A:D cohort incidence rate of 5.72 per 1,000 person-years of follow-up (95% CI: 5.31–6.13) *[29]* Incidence of DM in HIV (+) women in WHIS (2.5–2.9 per 100 person-years) *[30]* and associated with NRTIs	• 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 using NNRTI if feasible • Pharmacotherapeutic management per American Diabetic Association and American Association of Clinical Endocrinologists guidelines *[31-32]*
Lactic acidosis/ hepatic steatosis +/- pancreatitis (severe mitochondrial toxicities)	NRTIs, especially d4T, ddI, ZDV	Onset: Generally 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) • Mortality up to 50% in some case series, especially in patients with serum lactate >10 mmol/L Laboratory findings: • Increased lactate (often >5 mmol/L) • Low arterial pH (as low as <7.0) • Low serum bicarbonate • Increased anion gap • Elevated serum transaminases, prothrombin time, bilirubin • Low serum albumin • Increased serum amylase and lipase in patients with pancreatitis • Histologic findings of the liver: microvesicular or macrovesicular steatosis	Rare Depends on regimen and patient gender U.S.: <1 case per 1,000 patient-years South Africa: 16.1 cases per 1,000 patient-years in females and 1.2 cases per 1,000 patient-years in males *[33]*	• d4T + ddI • d4T, ZDV, ddI (d4T most frequently implicated) • Long duration of NRTI use • Female sex • Obesity • Pregnancy (especially with d4T + ddI) • ddI + hydroxyurea or ribavirin	• Routine monitoring of lactic acid is not recommended • Consider obtaining lactate levels in patients with low serum bicarbonate or high anion gap and with symptoms consistent with lactic acidosis • Employ appropriate phlebotomy technique for obtaining lactate level	• For mild cases, switch offending drugs to safer 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 rapidly resolved 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

Adverse Effects	Associated ARVs	Onset/Clinical Manifestation	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Lipodystrophy	Lipoatrophy: NRTIs (d4T > ZDV > TDF, ABC, 3TC, FTC), especially when combined with EFV *[34]* Lipo-hypertrophy: PI- or NNRTI-based regimens and with thymidine analogs (e.g., d4T, ZDV)	Onset: Gradual (i.e., 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 and lipohypertrophy: Low baseline body mass index	Lipoatrophy: Avoid thymidine analogs (especially 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, which may slow or halt progression but 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 and GH-releasing hormone analogue under investigation • Improvement in visceral fat seen in patients on LPV/r switched to ATV/r *[35]*
Nephrolithiasis/ urolithiasis/ crystalluria	IDV, ATV, FPV	Onset: Any time after beginning of therapy, especially at times of reduced fluid intake Laboratory abnormalities: Pyuria, hematuria, crystalluria; rarely, rise in serum creatinine and acute renal failure Symptoms: Flank pain and/or abdominal pain (can be severe), dysuria, urinary frequency	IDV: 12.4% of nephrolithiasis reported in clinical trials (4.7%–34.4% in different trials) ATV and FPV: rare; case reports only	• History of nephrolithiasis • Patients unable to maintain adequate fluid intake • High peak IDV concentration (↑ATV levels not found to correlate with risk) • ↑ duration of exposure • Hot climate	• Drink at least 1.5–2 liters of noncaffeinated fluid (preferably water) per day • Increase fluid intake at first sign of darkened urine • Monitor urinalysis and serum creatinine every 3–6 months	• Increase hydration • Control pain • If possible, switch to alternative agent • May require stent placement
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, interstitial nephritis, acute renal failure, or Fanconi syndrome with weakness and myalgias	Severe toxicity 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, prior adefovir renal toxicities	• Avoid use of other nephrotoxic drugs • Hydrate adequately if on IDV therapy • Monitor serum creatinine, urinalysis, serum potassium, and phosphorus in at-risk patients • Do not use in patients with prior history of adefovir-associated nephrotoxicity	• Stop offending agent, generally reversible • Supportive care • Electrolyte replacement as indicated

Adverse Effects	Associated ARVs	Onset/Clinical Manifestation	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Neuromuscular weakness syndrome (ascending)	d4T is ARV most frequently implicated	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 • 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 cases [88%] in one report) *[36]*	• Early recognition and discontinuation of ARVs may avoid further progression	• Discontinue ARVs • Supportive care, including mechanical ventilation if needed (as in cases of lactic acidosis listed previously) • Other measures attempted with variable success include plasmapheresis, high-dose corticosteroids, 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	Linked to older PIs, but unclear whether 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 • Older age • Alcohol use • Hyperlipidemia • Role of ARVs and osteonecrosis is still controversial	• Risk reduction (e.g., limit steroid and alcohol use) • For asymptomatic cases with <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 • Total joint arthroplasty for more severe and debilitating disease
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 bone loss after starting variety of ARVs; association with TDF or d4T; similar rate of bone loss with EFV- (-2.3%) or LPV/r- (-2.5%) based regimens over 96-week period *[37]*	Onset: Months to years after starting ART Symptoms: Generally asymptomatic, bone pain, increased risk of fractures	Wide range depending on methodology and patient population; rate appears much higher than seen in the general population: 20%–54% for osteopenia and 2%–27% for osteoporosis. *[38]*	General: • Low body weight, history of significant weight loss • Female • White, Southeast Asian • Older age • Alcohol use, smoking, caffeine • Hypogonadism • Hyperthyroidism • Corticosteroids • Vit D deficiency HIV: • Low CD4 count • Duration of HIV • Lipoatrophy • Increased lactic acid levels • TDF exposure	• Consider assessment of bone mineral density with DEXA scan (baseline and follow-up if abnormal; proper interval in setting of HIV(+) not determined) *[39]* • Weight-bearing exercise • Calcium and vitamin D supplementation • Hormone replacement	• Switch from potentially contributing ARVs (i.e., d4T or TDF) and stop other contributing drugs • Follow National Osteoporosis Foundation Guidelines *[40]* and/or IDSA Guidelines *[41]* • Increase exercise, improve diet, decrease alcohol and tobacco use, increase calcium and vitamin D supplementation • Bisphosphonate (e.g., once-weekly alendronate) • Judicious hormone replacement • Intranasal calcitonin

Adverse Effects	Associated ARVs	Onset/Clinical Manifestation	Estimated Frequency	Risk Factors	Prevention/ Monitoring	Management
Pancreatitis	ddI alone; ddI + d4T, hydroxyurea (HU), ribavirin (RBV), or TDF. rare reports with LPV/r	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: ↑ 4–5 times ddI with d4T, TDF, or ribavirin: ↑ frequency	• High intraceullar and/or serum ddI concentrations • History of pancreatitis • Alcoholism • Hyper-triglyceridemia • Concomitant use of ddI with d4T, HU, or RBV • Use of ddI + TDF without ddI dose reduction	• Do not use ddI 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) • Manage symptoms 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	Onset: Weeks to months after initiation of therapy (may be sooner in patients with pre-existing neuropathy) Symptoms: • Begins with numbness and paresthesia of toes and feet • May progress to painful neuropathy of feet and calves • 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 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, TDF, or RBV)	• Avoid using these agents in at-risk patients, if possible • Avoid combined use of these agents • Ask patient about possible symptoms 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, carbamazepine (potential for CYP interactions), topiramate • Tramadol • Narcotic analgesics • Topical capsaicin • Topical lidocaine
Stevens-Johnson syndrome (SJS)/toxic epidermal necrosis (TEN)	NVP > DLV, EFV, 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: • Decreased oral intake and fluid depletion • Bacterial or fungal superinfection • Multi-organ failure	NVP: 0.3%–1% DLV, EFV: 0.1% ETR: approximately <0.1% ABC, FPV, ddI, ZDV, IDV, LPV/r, ATV, DRV: 1–2 case reports	NVP: • Female • Black, Asian, Hispanic	• Educate patients to report symptoms as soon as they appear	• 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: • Corticosteroids • Intravenous immunoglobulin **Note:** • 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 13–15b** 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]*. **Tables 14a and 14b** 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 14c** 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 13. Drugs That Should Not Be Used With PI, NNRTI, or CCR5 Antagonist Antiretrovirals
(Updated December 1, 2009)

Drug Categories										
Antiretrovirals [1,2]	**Cardiac Agents**	**Lipid-Lowering Agents**	**Anti-mycobacterials**	**Gastro-intestinal Drugs**	**Neuro-leptics**	**Psycho-tropics**	**Ergot Alkaloids (vasoconstrictors)**	**Herbs**	**Antiretrovirals**	**Others**
Atazanavir (+/– ritonavir) (ATV +/− RTV)	none	simvastatin lovastatin	rifampin rifapentine[3]	cisapride[5]	pimozide	midazolam[6] triazolam	dihydroergotamine (D.H.E. 45) ergotamine[7] (various forms) ergonovine methylergonovine	St. John's wort	ETR IDV NVP	fluticasone irinotecan proton pump inhibitors (with unboosted ATV)
Darunavir/ ritonavir (DRV/r)	none	simvastatin lovastatin	rifampin rifapentine[3]	cisapride[5]	pimozide	midazolam[6] triazolam	as above	St. John's wort	none	carbamazepine phenobarbital phenytoin fluticasone[8]
Fosamprenavir (+/– ritonavir) (FPV +/− RTV)	none	simvastatin lovastatin	rifampin rifapentine[3]	cisapride[5]	pimozide	midazolam[6] triazolam	as above	St. John's wort	ETR	fluticasone oral contraceptives
Indinavir (+/– ritonavir) (IDV +/− RTV)	amiodarone	simvastatin lovastatin	rifampin rifapentine[3]	cisapride[5]	pimozide	midazolam[6] triazolam	as above	St. John's wort	ATV	
Lopinavir/ ritonavir (LPV/r)	flecainide propafenone	simvastatin lovastatin	rifampin[4] rifapentine[3]	cisapride[5]	pimozide	midazolam[6] triazolam	as above	St. John's wort	none	fluticasone[8]
Nelfinavir (NFV)	amiodarone quinidine	simvastatin lovastatin	rifampin rifapentine[3]	cisapride[5]	pimozide	midazolam[6] triazolam	as above	St. John's wort	ETR	none
Ritonavir (RTV)	amiodarone flecainide propafenone quinidine	simvastatin lovastatin	rifapentine[3]	cisapride[5]	pimozide	midazolam[6] triazolam	as above	St. John's wort	none	voriconazole (with RTV ≥400mg BID) fluticasone alfuzosin
Saquinavir/ ritonavir (SQV/r)	none	simvastatin lovastatin	rifampin[4] rifapentine	cisapride[5]	pimozide	midazolam[6] triazolam	as above	St. John's wort garlic supplements	none	fluticasone[8]
Tipranavir/ ritonavir (TPV/r)	amiodarone flecainide propafenone quinidine	simvastatin lovastatin	rifampin rifapentine[3]	cisapride[5]	pimozide	midazolam[6] triazolam	as above	St. John's wort	ETR	fluticasone[8]
Efavirenz (EFV)	none	none	rifapentine[3]	cisapride[5]	pimozide	midazolam[6] triazolam	as above	St. John's wort	other NNRTIs	none
Etravirine (ETV)	none	none	rifabutin (if used with ritonavir-boosted PI) rifampin rifapentine[3]	none	none	none	none	St John's wort	unboosted PIs, ATV/r, FPV/r, or TPV/r; other NNRTIs	carbamazepine phenobarbital phenytoin
Nevirapine (NVP)	none	none	rifapentine[3]	none	none	none	none	St. John's wort	ATV +/− RTV other NNRTIs	none
Maraviroc (MVC)	none	none	rifapentine[3]	none	none	none	none	St. John's wort	none	none

1 Delavirdine is not included in this table. Refer to the FDA package insert for information regarding delavirdine drug interactions.
2 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 in patients.
3 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.
4 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.
5 The manufacturer of cisapride has a limited-access protocol for patients who meet specific clinical eligibility criteria.
6 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.
7 This is likely a class effect.
8 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 14a**); 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 14a and 14b**)
Midazolam, triazolam: temazepam, lorazepam, oxazepam

Table 14a. Drug Interactions Between Protease Inhibitors (PIs) and Other Drugs

Page 1 of 6 **(Updated December 1, 2009)**

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 for dosing recommendations, refer to **Table 15a**.

Concomitant Drug	Protease Inhibitor (PI)	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Antacids	ATV +/− RTV	↓ ATV expected when given simultaneously	Give ATV at least 2 hrs before or 1 hr after antacids or buffered medications.
	FPV	APV AUC ↓ 18%; no significant change in APV Cmin	FPV can be given simultaneously or separated at least 2 hrs before or 1 hr after antacids.
	TPV/r	TPV AUC ↓ 27%	Give TPV at least 2 hrs before or 1 hr after antacids.
H_2 receptor antagonists	**RTV-boosted PIs**		
	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. Administer ATV 300mg + RTV 100mg simultaneously with and/or ≥10 hours after the H_2 receptor antagonist. If using TDF and H_2 receptor antagonist in treatment-experienced patients, use ATV 400mg + RTV 100mg.
	DRV/r, LPV/r	No significant effect	
	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. Give ATV at least 2 hours before and at least 10 hours after the H_2 receptor antagonist.
	FPV	APV AUC ↓ 30%; no significant change in APV Cmin	Give separately if coadministration is necessary. Consider boosting with RTV.
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 PI-naïve patients. PPIs should be administered at least 12 hrs prior to ATV/r. **PPIs are not recommended in PI-experienced patients**.
	DRV/r, TPV/r	↓ omeprazole PI: no significant effect	May need to increase omeprazole dose with TPV/r.
	FPV +/– RTV, IDV, LPV/r	No significant effect	
	NFV	NFV AUC ↓ 36%; M8 AUC ↓ 92%	**Do not coadminister PPIs and NFV.**
	SQV/r	SQV AUC ↑ 82%	Monitor for SQV toxicities.
Antifungals			
Fluconazole	**RTV-boosted PIs**		
	ATV/r	No significant effect	
	SQV/r	No data with RTV boosting SQV (1,200mg TID) AUC ↑ 50%	
	TPV/r	TPV AUC ↑ 50%	Fluconazole >200mg daily is not recommended.
	PIs without RTV		
	IDV	No significant effect	
Itraconazole	**RTV-boosted PIs**		
	ATV/r, DRV/r, FPV/r, IDV/r, TPV/r	↑ itraconazole possible ↑ PI possible	Consider monitoring itraconazole level to guide dosage adjustments. High doses (>200 mg/day) are not recommended unless dosing is guided by drug levels.
	LPV/r	↑ itraconazole	Consider not exceeding 200mg itraconazole daily or monitor itraconazole level.
	SQV/r	Bidirectional interaction has been observed	Dose not established, but decreased itraconazole dosage may be warranted. Consider monitoring itraconazole level.

Concomitant Drug	Protease Inhibitor (PI)	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Itraconazole (continued)	**PIs without RTV**		
	ATV, FPV, NFV	↑ itraconazole possible ↑ PI possible	Consider monitoring itraconazole level to guide dosage adjustments.
	IDV	↑ IDV With IDV 600mg Q8h + itraconazole 200mg BID: IDV AUC similar to IDV 800mg Q8h	Dose: IDV 600mg Q8h (without ritonavir); do not exceed 200mg itraconazole BID. IDV dosage when used with ritonavir and itraconazole has not been established.
Ketoconazole	**RTV-boosted PIs**		
	ATV/r, FPV/r, IDV/r	↑ ketoconazole expected	Use with caution. Do not exceed 200mg ketoconazole daily. Potential for bidirectional interaction between ketoconazole and IDV/r, SQV/r, and TPV/r.
	DRV/r	ketoconazole AUC ↑ 212% DRV AUC ↑ 42%	
	LPV/r	ketoconazole AUC ↑ 204% LPV Cmin ↓ 25%	
	SQV/r	SQV (unboosted) AUC ↑ 190%	
	PIs without RTV		
	ATV, NFV	ATV: no significant change NFV AUC ↑ 35%	No dosage adjustment necessary.
	FPV	No data with FPV APV AUC ↑ 31% ketoconazole AUC ↑ 44%	Consider ketoconazole dose reduction if dose is >400mg/day. Presumably similar interaction as seen with APV.
	IDV	IDV AUC ↑ 68%	Dose: IDV 600mg Q8h IDV/r dosage when used with ketoconazole has not been established.
Posaconazole	ATV/r	ATV AUC ↑ 146%	Monitor for adverse effects of ATV.
	ATV	ATV AUC ↑ 268%	Monitor for adverse effects of ATV.
Voriconazole	**RTV-boosted PIs**		
	ATV/r, DRV/r, FPV/r, IDV/r, LPV/r, SQV/r, TPV/r	voriconazole AUC ↓ 82% with RTV 400mg BID voriconazole AUC ↓ 39% with RTV 100mg BID	Concomitant use 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	↑ voriconazole possible ↑ PI possible	Monitor for toxicities.
	IDV	No significant effect	No dose adjustment
Anticonvulsants			
Carbamazepine	**RTV-boosted PIs**		
	ATV/r, FPV/r, IDV/r, LPV/r, SQV/r, TPV/r	↑ carbamazepine possible TPV/r ↑ carbamazepine AUC 26% May ↓ PI levels substantially	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. Do not coadminister with LPV/r once daily.
	DRV/r	carbamazepine AUC ↑ 45% DRV: no significant change	Monitor anticonvulsant level and adjust dose accordingly.
	PIs without RTV		
	ATV, FPV, NFV, IDV	May ↓ PI levels substantially ↓ IDV	Monitor anticonvulsant level and virologic response. Consider alternative anticonvulsant; RTV boosting for ATV, FPV, and IDV; and/or monitoring PI level.
Lamotrigine	LPV/r	lamotrigine AUC ↓ 50% LPV: no significant change	Titrate lamotrigine dose to effect. A similar interaction is possible with other RTV-boosted PIs.
Phenobarbital	All PIs	May ↓ PI levels substantially	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. Do not coadminister with LPV/r once daily.
Phenytoin	**RTV-boosted PIs**		
	ATV/r, DRV/r, IDV/r, SQV/r, TPV/r	↓ phenytoin possible ↓ PI possible	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response.
	FPV/r	phenytoin AUC ↓ 22% APV AUC ↑ 20%	Monitor phenytoin level and adjust dose accordingly. No change in FPV/r dose recommended.

Concomitant Drug	Protease Inhibitor (PI)	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Phenytoin (continued)	LPV/r	phenytoin AUC ↓ 31% LPV/r AUC ↓ 33%	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. Do not coadminister with LPV/r once daily.
	PIs without RTV		
	ATV, FPV, NFV, IDV	NFV ↓ phenytoin AUC 30% May ↓ PI levels substantially	Consider alternative anticonvulsant; RTV boosting for ATV, FPV, and IDV; and/or monitoring PI level. Monitor anticonvulsant level and virologic response.
Valproic acid (VPA)	LPV/r	↓VPA possible LPV AUC ↑ 75%	Monitor VPA levels and response. Monitor for LPV-related toxicities.
Anti-mycobacterials			
Clarithromycin (Clar)	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 expected; RTV 500mg BID ↑ Clar 77%; SQV unboosted ↑ Clar 45%; Clar ↑ unboosted SQV 177%; TPV/r ↑ Clar 19% and ↓ active metabolite 97%; Clar ↑ TPV 66%	Monitor for clarithromycin-related toxicities. 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 AUC ↑ 18%	No dose adjustment
Rifabutin	**RTV-boosted PIs**		
	ATV +/– RTV	rifabutin (150mg daily) AUC ↑ 110% and metabolite AUC ↑ 2,101% compared with rifabutin 300mg daily alone	Rifabutin 150mg every other day or 3x/week Acquired rifamycin resistance has been reported in patients with inadequate rifabutin levels while on 150mg twice weekly and RTV-boosted PIs. Rifabutin 150mg three times weekly in combination with LPV/r has resulted in inadequate rifabutin levels and has led to acquired rifamycin resistance in patients with HIV-associated tuberculosis. Pharmacokinetic data reported in this table are results from healthy volunteer studies. Therapeutic drug monitoring for rifabutin is recommended.
	DRV/r	rifabutin (150mg every other day) and metabolite AUC ↑ 55% compared with rifabutin 300mg daily alone	
	FPV/r	rifabutin (150mg every other day) and metabolite AUC↑ 64% compared with rifabutin 300mg daily alone	
	IDV/r	↑ rifabutin expected	
	LPV/r	rifabutin (150mg once daily) and metabolite AUC ↑ 473% compared with rifabutin 300mg daily alone	
	SQV/r	↑ rifabutin with unboosted SQV	
	TPV/r	rifabutin (150mg x 1 dose) and metabolite AUC ↑ 333%	
	PIs without RTV		
	FPV	↑ rifabutin AUC expected	Rifabutin 150mg daily or 300mg 3x/week
	IDV	rifabutin AUC ↑ 204% IDV AUC ↓ 32%	Rifabutin 150mg daily or 300mg 3x/week + IDV 1,000mg q8h or consider RTV boosting
	NFV	rifabutin AUC ↑ 207% NFV (750mg Q8H) AUC ↓ 32%	Rifabutin 150mg daily or 300mg 3x/week
Rifampin	All PIs	↓ PI >75% approximately	**Do not coadminister rifampin and PIs.**
Benzodiazepines			
Alprazolam **Diazepam**	All PIs	↑ benzodiazepine possible 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	Protease Inhibitor (PI)	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Midazolam	All PIs	↑ midazolam expected SQV/r ↑ midazolam (oral) AUC 1,144% and 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	↑ triazolam expected RTV 200mg BID ↑ triazolam half-life 1,200% and AUC 2,000%	**Do not coadminister triazolam and PIs.**
Cardiac Medications			
Bosentan	All RTV-boosted PIs	LPV/r ↑ bosentan 48-fold (Day 4) and 5-fold (Day 10)	In patients on RTV >10 days: start bosentan at 62.5mg once daily or every other day. In patients on bosentan who require RTV: discontinue bosentan ≥36 hours prior to initiation of RTV and restart 10 days after initiating RTV at 62.5mg once daily or every other day.
Digoxin	RTV, SQV/r	RTV 200mg BID ↑ digoxin AUC 29% and half-life 43% SQV/r ↑ digoxin AUC 49%	Monitor digoxin levels. Digoxin dose may need to be decreased.
Dihydropyridine calcium channel blockers (CCB)	All PIs	↑ dihydropyridine possible IDV/r ↑ amlodipine AUC 90%	Use with caution. Titrate CCB dose and monitor closely. ECG monitoring is recommended when used with ATV.
Diltiazem	ATV +/– RTV	diltiazem AUC ↑ 125%	Decrease diltiazem dose by 50%. ECG monitoring is recommended.
	DRV/r, FPV +/– RTV, IDV +/– RTV, LPV/r, NFV, SQV/r, TPV/r	↑ diltiazem possible IDV/r ↑ diltiazem AUC 26%	Use with caution. Adjust diltiazem according to clinical response and toxicities.
Herbal Products			
St. John's wort	All PIs	↓ PI expected	**Do not coadminister.**
Hormonal Contraceptives			
Hormonal contraceptives	**RTV-boosted PIs**		
	ATV/r	↓ ethinyl estradiol ↑ norgestimate	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	ethinyl estradiol AUC ↓ 44% norethindrone AUC ↓ 14%	Use alternative or additional method.
	FPV/r	ethinyl estradiol AUC ↓ 37% norethindrone AUC ↓ 34%	Use alternative or additional method.
	LPV/r	ethinyl estradiol AUC↓ 42% norethindrone AUC ↓ 17%	Use alternative or additional method.
	SQV/r	↓ ethinyl estradiol	Use alternative or additional method.
	TPV/r	ethinyl estradiol AUC ↓ 48% norethindrone: no significant change	Use alternative or additional method.
	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 and ↑ norethindrone; ↓ APV 20%	Use alternative method.
	IDV	ethinyl estradiol AUC ↑ 25% norethindrone AUC ↑ 26%	No dose adjustment
	NFV	ethinyl estradiol AUC ↓ 47% norethindrone AUC ↓ 18%	Use alternative or additional method.

Concomitant Drug	Protease Inhibitor (PI)	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
HMG-CoA Reductase Inhibitors			
Atorvastatin	All PIs	↑ atorvastatin; DRV/r + atorvastatin 10mg similar to atorvastatin 40mg alone; FPV +/– RTV ↑ atorvastatin AUC 130%–153%; LPV/r ↑ atorvastatin AUC 488%; NFV ↑ atorvastatin AUC 74%; SQV/r ↑ atorvastatin AUC 79%; TPV/r ↑ atorvastatin AUC 836%	Use lowest possible starting dose with careful monitoring for toxicities or consider other HMG-CoA reductase inhibitors with less potential for interaction.
Lovastatin	All PIs	Significant ↑ lovastatin expected	**Contraindicated – do not coadminister.**
Pravastatin	DRV/r	pravastatin AUC ↑ 81%	Use lowest possible starting dose with careful monitoring.
	LPV/r	pravastatin AUC ↑ 33%	No dose adjustment necessary
	NFV, SQV/r	pravastatin AUC ↓ 47%–50%	No dose adjustment necessary
Rosuvastatin	ATV/r	rosuvastatin AUC ↑ 213% and Cmax ↑ 600%	Use lowest possible starting dose with careful monitoring or consider other HMG-CoA reductase inhibitors with less potential for interaction.
	DRV/r, IDV +/– RTV, NFV, SQV/r	↑ rosuvastatin possible	
	FPV +/- RTV	No significant change	No dosage adjustment necessary
	LPV/r	rosuvastatin AUC ↑ 108% and Cmax ↑ 366%	Use lowest possible starting dose with careful monitoring or consider other HMG-CoA reductase inhibitors with less potential for interaction.
	TPV/r	rosuvastatin AUC ↑ 26% and Cmax ↑ 123%	
Simvastatin	All PIs	Significant ↑ simvastatin level NFV ↑ simvastatin AUC 505% SQV/r 400mg/400mg BID ↑ simvastatin AUC 3,059%	**Contraindicated – do not coadminister**.
Methadone			
Methadone	**RTV-boosted PIs**		
	ATV/r, DRV/r, FPV/r, IDV/r, LPV/r, SQV/r, TPV/r	↓ methadone levels ATV/r, DRV/r, FPV/r ↓ R-methadone AUC 16%–18%; LPV/r ↓ methadone AUC 26%–53%; SQV/r 1,000/100mg BID ↓ R-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 significant effect	
	FPV	No data with FPV With APV: R-methadone Cmin ↓ 21%, AUC no significant change	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	DRV/r + sildenafil 25mg similar to sildenafil 100mg alone; IDV ↑ sildenafil AUC 340%; RTV 500mg BID ↑ sildenafil AUC 1,000%; SQV unboosted ↑ sildenafil AUC 210%	Sildenafil For treatment of erectile dysfunction: start with 25mg every 48 hours and monitor for adverse effects of sildenafil For treatment of pulmonary arterial hypertension: contra-indicated
Tadalafil	All PIs	RTV 200mg BID ↑ tadalafil AUC 124%; TPV/r (1st dose) ↑ tadalafil AUC 133%; TPV/r steady state: no significant effect	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	IDV ↑ vardenafil AUC 16-fold; RTV 600mg BID ↑ vardenafil AUC 49-fold	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
All PIs	**Dexamethasone**	↓ PI levels possible	
DRV/r	**Paroxetine** **Sertraline**	paroxetine AUC ↓ 39% sertraline AUC ↓ 49%	Monitor closely for antidepressant response. Titrate SSRI dose based on clinical assessment.
FPV/r	**Paroxetine**	paroxetine AUC ↓ 55%	Monitor closely for antidepressant response. Titrate paroxetine dose based on clinical assessment.
IDV	**Grapefruit juice** **Vitamin C >1 g/day**	↓ IDV ↓ IDV	Monitor for virologic responses.
LPV/r	**Bupropion**	bupropion AUC ↓ 57%	Titrate bupropion based on clinical response.
RTV	**Salmeterol**	↑ salmeterol	Coadministration is not recommended.
	Trazodone	RTV 200mg BID ↑ trazodone AUC 240%	Use lowest dose of trazodone and monitor for CNS and cardiovascular adverse effects.
TPV/r	**Bupropion**	bupropion AUC ↓ 46%	Titrate bupropion based on clinical response.

Abbreviations: APV = amprenavir (FPV is a prodrug of APV), ATV = atazanavir, ATV/r = atazanavir + ritonavir, DRV/r = darunavir + ritonavir, FPV = fosamprenavir (FPV is a prodrug of APV), 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 14b. Drug Interactions Between NNRTIs* and Other Drugs (Updated December 1, 2009)

*Delavirdine is not included in this table. Please refer to the FDA package insert for information regarding delavirdine drug interactions.

This table provides information relating to pharmacokinetic interactions between NNRTIs and non-antiretroviral drugs. For interactions among antiretroviral agents and for dosing recommendations, refer to **Table 15b**.

Concomitant Drug Class/Name	NNRTI	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comment
Antifungals			
Fluconazole	EFV	No significant effect	
	ETR	↑ ETR possible	No dosage adjustment necessary
	NVP	NVP AUC ↑ 110%	Increased risk of hepatotoxicity possible with this combination Monitor NVP toxicity or use alternative antiretroviral agent.
Itraconazole	EFV	itraconazole and OH-itraconazole AUC, Cmax, and Cmin ↓ 35%–44%	Dose adjustments for itraconazole may be necessary. Monitor itraconazole level.
	ETR	↓ itraconazole possible ↑ ETR possible	Dose adjustments for itraconazole may be necessary. Monitor itraconazole level.
	NVP	↓ itraconazole possible ↑ NVP possible	Consider monitoring NNRTI and itraconazole levels.
Ketoconazole	EFV	↓ ketoconazole possible	
	ETR	↓ ketoconazole possible ↑ ETR possible	Dose adjustment for ketoconazole may be necessary depending on other coadministered drugs.
	NVP	ketoconazole AUC ↓ 72% ↑ NVP 15%–30%	**Coadministration not recommended.**
Posaconazole	EFV	posaconazole AUC ↓ 50%	Consider alternative antifungal if possible or consider monitoring posaconazole level if available.
	ETR	↑ ETR possible	No dosage adjustment necessary
Voriconazole	EFV	voriconazole AUC ↓ 77% EFV AUC ↑ 44%	**Contraindicated at standard doses**. Dose: voriconazole 400mg BID, EFV 300mg daily
	ETR	↑ voriconazole possible ↑ ETR possible	Dose adjustments for voriconazole may be necessary depending on other coadministered drugs. Monitor voriconazole level.
	NVP	↓ voriconazole possible ↑ NVP possible	Monitor for toxicity and antifungal outcome and/or voriconazole level.
Anticonvulsants			
Carbamazepine **Phenobarbital** **Phenytoin**	EFV	carbamazepine + EFV: carbamazepine AUC ↓ 27% and EFV AUC ↓ 36% phenytoin + EFV: ↓ EFV and ↓ phenytoin possible	Monitor anticonvulsant and EFV levels, or if possible, use alternative anticonvulsant.
	ETR	↓ anticonvulsant and ETR possible	**Do not coadminister.** Consider alternative anticonvulsants.
	NVP	↓ anticonvulsant and NVP possible	Monitor anticonvulsant and NVP levels and virologic responses.
Anti-mycobacterials			
Clarithromycin	EFV	clarithromycin AUC ↓ 39%	Monitor for efficacy or consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
	ETR	clarithromycin AUC ↓ 39% OH-clarithromycin AUC ↑ 21% ETR AUC ↑ 42%	Consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
	NVP	Clarithromycin AUC ↓ 31% OH-clarithromycin AUC ↑ 42%	Monitor for efficacy or use alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
Rifabutin	EFV	Rifabutin ↓ 38%	Dose: rifabutin 450–600mg once daily or 600mg 3x/week if EFV is not coadministered with a PI.
	ETR	rifabutin and metabolite AUC ↓ 17% ETR AUC ↓ 37%	Dose: rifabutin 300mg once daily **if** ETR is not coadministered with a RTV-boosted PI. **If ETR is coadministered with a RTV-boosted PI, rifabutin should not be coadministered.**
	NVP	rifabutin AUC ↑ 17% and metabolite AUC ↑ 24% NVP Cmin ↓ 16%	No dosage adjustment necessary. Use with caution.
Rifampin	EFV	EFV AUC ↓ 26%	Maintain EFV dose at 600mg once daily and monitor for virologic response. Some clinicians suggest EFV 800mg dose in patients >60kg.
	ETR	Significant ↓ ETR possible	**Do not coadminister.**
	NVP	NVP ↓ 20%–58%	**Do not coadminister.**

Concomitant Drug Class/Name	NNRTI	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comment
Benzodiazepines			
Alprazolam	EFV, ETR, NVP	No data	Monitor for therapeutic efficacy of alprazolam.
Diazepam	ETR	↑ diazepam possible	Decreased dose of diazepam may be necessary.
Lorazepam	EFV	lorazepam Cmax ↑ 16%, AUC no significant effect	No dosage adjustment necessary
Midazolam	EFV	Significant↑ midazolam expected	**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.
Triazolam	EFV	Significant ↑ triazolam expected	**Do not coadminister.**
Cardiac Medications			
Dihydropyridine Calcium channel blockers (CCBs)	EFV, NVP	↓ CCBs possible	Titrate CCB dose based on clinical response.
Diltiazem	EFV	diltiazem AUC ↓ 69%	Titrate diltiazem dose based on clinical response.
	NVP	↓ diltiazem possible	
Herbal Products			
St. John's wort	EFV, ETR, NVP	↓ NNRTI	**Do not coadminister.**
Hormonal Contraceptives			
Hormonal contraceptives	EFV	ethinyl estradiol AUC ↑ 37%	Clinical significance unknown
	ETR	ethinyl estradiol AUC ↑ 22% norethindrone: no significant effect	No dosage adjustment necessary
	NVP	ethinyl estradiol AUC ↓ 20% norethindrone AUC ↓ 19%	Use alternative or additional methods.
		depomedroxyprogesterone acetate: no significant change	No dosage adjustment necessary
HMG-CoA Reductase Inhibitors			
Atorvastatin	EFV, ETR, NVP	atorvastatin AUC ↓ 32%–43% with EFV, ETR	Adjust atorvastatin according to lipid responses, not to exceed the maximum recommended dose.
Fluvastatin	ETR	↑ fluvastatin possible	Dose adjustments for fluvastatin may be necessary.
Lovastatin Simvastatin	EFV	simvastatin AUC ↓ 68%	Adjust 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.
	ETR	↓ lovastatin possible ↓ simvastatin possible	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.
	NVP	↓ lovastatin possible ↓ simvastatin possible	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	EFV	pravastatin AUC ↓ 44% rosuvatatin: no data	Adjust statin dose according to lipid responses, not to exceed the maximum recommended dose.
	ETR	No significant effect expected	No dosage adjustment necessary
Methadone			
Methadone	EFV	methadone AUC ↓ 52%	Potential for opiate withdrawal; increased methadone dose often necessary.
	ETR	No significant effect	No dosage adjustment necessary
	NVP	↓ methadone NVP: no significant effect	Opiate withdrawal common; increased methadone dose often necessary.
Oral Anticoagulant			
Warfarin	EFV, NVP	↑ or ↓ warfarin possible	Monitor INR and adjust warfarin accordingly.
	ETR	↑ warfarin possible	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
EFV	**Sertraline**	sertraline AUC ↓ 39%	Titrate sertraline dose based on clinical response.
	Bupropion	bupropion AUC ↓ 55%	Titrate bupropion dose based on clinical response.
ETR	**Dexamethasone**	↓ ETR	Use systemic dexamethasone with caution or consider alternative corticosteroid for long-term use.
	Sildenafil	sildenafil AUC ↓ 57%	May need to increase sildenafil dose based on clinical effect.

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

Table 14c. Drug Interactions Between NRTIs and Other Drugs (including antiretroviral agents)
(Updated December 1, 2009)

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	**Contraindicated—do not coadminister.** Fatal hepatic failure and other ddI-related toxicities have been reported with coadministration.
	ZDV	Ribavirin inhibits phosphorylation of ZDV	Avoid coadministration if possible or closely monitor virologic response and hematologic toxicities.
Integrase Inhibitor			
Raltegravir (RAL)	TDF	RAL AUC ↑ 49%, Cmax ↑ 64%	No dosage adjustment necessary.
Methadone			
Methadone	ABC	↓ methadone	Monitor for opiate withdrawal and titrate methadone as clinically indicated. May need to increase methadone dose.
	d4T	↓ d4T	No dosage adjustment necessary
	ZDV	ZDV AUC ↑ 43%	Monitor for ZDV-related adverse effects.
NRTIs			
Didanosine (ddI)	d4T	No significant effect	**Avoid coadministration**. Peripheral neuropathy, lactic acidosis, and pancreatitis seen with this combination.
	TDF	ddI-EC AUC and Cmax ↑ 48%–60%	Avoid coadministration if possible. Dose if CrCl >60mL/min ≥60kg: ddI-EC 250mg/day <60kg: ddI-EC 200mg/day Monitor for ddI-associated toxicity.
Other			
Allopurinol	ddI	ddI AUC ↑ 113% ddI AUC ↑ 312% with renal impairment	**Contraindicated—do not coadminister.** Potential for increased didanosine-associated toxicities.
PIs			
Atazanavir (ATV)	ddI	With ddI-EC + ATV (with food): ddI AUC ↓ 34%; ATV no change	Administer ATV with food 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%–37%	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/ritonavir (DRV/r)	TDF	TDF AUC↑ 22%, Cmax ↑ 24%, and Cmin ↑ 37%	Clinical significance unknown. Monitor for TDF toxicity.
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.
	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 14d. Drug Interactions Between CCR5 Antagonist and Other Drugs

(Updated December 1, 2009)

This table provides information relating to pharmacokinetic interactions between maraviroc and non-antiretroviral drugs. For interactions among antiretroviral agents and for dosing recommendations, please refer to **Table 15b**.

Concomitant Drug Class/Name	CCR5 Antagonist	Effect on CCR5 Antagonist or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comment
Antifungals			
Itraconazole	MVC	↑ MVC possible	Dose: MVC 150mg BID
Ketoconazole	MVC	MVC AUC ↑ 400%	Dose: MVC 150mg BID
Voriconazole	MVC	↑ MVC possible	Consider dose reduction to MVC 150mg BID.
Anticonvulsants			
Carbamazepine **Phenobarbital** **Phenytoin**	MVC	↓ MVC possible	If used without a strong CYP3A inhibitor: MVC 600mg BID or use alternative antiepileptic agent.
Anti-mycobacterials			
Clarithromycin	MVC	↑ MVC possible	Dose: MVC 150mg BID
Rifabutin	MVC	↓ MVC possible	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%	Coadministration is not recommended. If coadministration is necessary use MVC 600mg BID. If coadministered with a strong CYP3A inhibitor use MVC 300mg BID.
Herbal Products			
St. John's wort	MVC	↓ MVC possible	Coadministration is not recommended.
Hormonal Contraceptives			
Hormonal Contraceptives	MVC	No significant effect on ethinyl estradiol or levonorgestrel	Safe to use in combination

Abbreviation: MVC = maraviroc.

Table 14e. Drug Interactions Between Integrase Inhibitor and Other Drugs

Concomitant Drug Class/Name	Integrase Inhibitor	Effect on Integrase Inhibitor or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comment
Acid Reducers			
Omeprazole	RAL	RAL AUC ↑ 212%, Cmax ↑ 315%, and Cmin ↑ 46%	No dosage adjustment recommended.
Anti-mycobacterials			
Rifampin	RAL	RAL AUC ↓ 40% and Cmin ↓ 61% with RAL 400mg Rifampin with RAL 800mg BID compared with RAL 400mg BID alone: RAL AUC ↑ 27% and Cmin ↓ 53%	Dose: RAL 800mg BID Monitor closely for virologic response.

Abbreviation: RAL = raltegravir

Table 15a. Interactions Among Protease Inhibitors (Updated December 1, 2009)

Drug Affected	Atazanavir	Fosamprenavir	Lopinavir/ Ritonavir	Nelfinavir	Ritonavir	Saquinavir	Tipranavir
Protease Inhibitors							
Darunavir (DRV)	Dose: ATV 300mg once daily + DRV 600mg BID + RTV 100mg BID	No data	**Should not be coadministered because doses are not established**	No data	Dose: (DRV 600mg + RTV 100mg) BID or (DRV 800mg + RTV 100mg) once daily	**Should not be coadministered because doses are not established**	No data
Fosamprenavir (FPV)	Dose: Insufficient data	•	**Should not be coadministered because doses are not established**	See FPV + NFV cell	Dose: (FPV 1,400mg + RTV 100mg or 200mg) once daily; or (FPV 700mg + RTV 100mg) BID	Dose: Insufficient data	**Should not be coadministered because doses are not established**
Indinavir (IDV)	**Should not be coadministered because of potential for additive hyperbilirubinema**	Dose: Not established	Dose: IDV 600mg BID + LPV/r 400/100mg BID	Dose: Limited data for IDV 1,200mg BID + NFV 1,250mg BID	Dose: IDV 800mg BID + RTV 100–200mg BID	Dose: Insufficient data	**Should not be coadministered because doses are not established**
Lopinavir/ Ritonavir (LPV/r)	Dose: ATV 300mg once daily + LPV/r 400/100mg BID	See LPV/r + FPV cell	•	See LPV/r + NFV cell	Lopinavir is coformulated with ritonavir as Kaletra	See LPV/r + SQV cell	**Should not be coadministered because doses are not established**
Nelfinavir (NFV)	No data	Dose: Insufficient data	Dose: No data with LPV/r tablets	•	See NFV + RTV cell	See NFV+SQV cell	**Should not be coadministered because doses are not established**
Ritonavir (RTV)	Dose: (ATV 300mg + RTV 100mg) once daily	See RTV + FPV cell	Lopinavir is coformulated with ritonavir as Kaletra.	Dose: Not established	•	Dose: (SQV 1,000mg + RTV 100mg) BID	Dose: (TPV 500mg + RTV 200mg) BID
Saquinavir (SQV)	Dose: Insufficient data	Dose: Insufficient data	Dose: SQV 1,000mg BID + LPV/r 400/100mg BID	Dose: SQV 1200mg BID + NFV 1,250mg BID	See SQV + RTV cell	•	**Should not be coadministered because doses are not established**

Table 15b. Interactions Between NNRTIs*, Maraviroc, Raltegravir, and PIs (Updated December 1, 2009)

*Delavirdine is not included in this table. Refer to the FDA package insert for information regarding delavirdine drug interactions.

		Efavirenz	Etravirine	Nevirapine	Maraviroc	Raltegravir
Atazanavir (ATV)	**Exposure**	With unboosted ATV ATV: AUC ↓ 74% EFV: no significant change With (ATV 300mg + RTV 100mg) once daily with food ATV concentrations similar to unboosted ATV without EFV	With unboosted ATV ETR: AUC ↑ 50%, Cmax ↑ 47%, and Cmin ↑ 58% ATV: AUC ↓ 17% and Cmin ↓ 47% With (ATV 300mg + RTV 100mg) once daily ETR: AUC, Cmax, and Cmin ↑ approximately 30% ATV: AUC ↓ 14% and Cmin ↓ 38%	With (ATV 300mg + RTV 100mg) once daily ATV: AUC ↓ 42% and Cmin ↓ 72% NVP: AUC ↑ 25%	With unboosted ATV MVC: AUC ↑ 257% With (ATV 300mg + RTV 100mg) once daily MVC: AUC ↑ 388%	With unboosted ATV RAL: AUC ↑ 72% With (ATV 300mg + RTV 100mg) once daily RAL: AUC ↑ 41%
	Dose	**Do not coadminister with unboosted ATV.** In treatment-naïve patients (ATV 400mg + RTV 100mg) once daily **Do not coadminister in treatment-experienced patients.**	**Do not coadminister with ATV +/− RTV.**	**Do not coadminister with ATV +/− RTV.**	MVC 150mg BID with ATV +/− RTV	Standard
Darunavir (DRV)	**Exposure**	With (DRV 300mg + RTV 100mg) BID DRV: AUC ↓ 13%, Cmin ↓ 31% EFV: AUC ↑ 21%	ETR 100mg BID with (DRV 600mg + RTV 100mg) BID DRV: no significant change ETR: AUC ↓ 37%, Cmin ↓ 49%	With (DRV 400mg + RTV 100mg BID) DRV: AUC ↑ 24%† NVP: AUC ↑ 27% and Cmin ↑ 47%	With (DRV 600mg + RTV 100mg) BID MVC: AUC ↑ 305% With (DRV 600mg + RTV 100mg) BID + ETR MVC: AUC ↑ 210%	With (DRV 600mg + RTV 100mg) BID RAL: AUC ↓ 29% and Cmin ↑ 38%
	Dose	Clinical significance unknown. Use standard doses and monitor closely. Consider monitoring levels.	Standard Despite decreased ETR, safety and efficacy established with this combination in a clinical trial	Standard	MVC 150mg BID	Standard
Efavirenz (EFV)	**Exposure**	•	↓ ETR possible	NVP: no significant change EFV: AUC ↓ 22%	MVC: AUC ↓ 45%	EFV: AUC ↓ 36%
	Dose		**Do not coadminister.**	**Do not coadminister.**	MVC: 600mg BID	Standard
Etravirine (ETR)	**Exposure**	↓ ETR possible	•	↓ ETR possible	MVC: AUC ↓ 53%, Cmax ↓ 60%	ETR: Cmin ↓ 17% RAL: Cmin ↓ 34%
	Dose	**Do not coadminister.**		**Do not coadminister**.	MVC 600mg BID	Standard
Fosamprenavir (FPV)	**Exposure**	With (FPV 1,400mg + RTV 200mg) once daily APV: Cmin ↓ 36%	With (FPV 700mg + RTV 100mg) BID APV: AUC ↑ 69%, Cmin ↑ 77%	With unboosted FPV 1,400mg BID APV: AUC ↓ 33% NVP: AUC ↑ 29% With (FPV 1,400mg + RTV 100mg) BID NVP: Cmin ↑ 19%	Unknown; ↑ MVC possible	No data
	Dose	(FPV 1,400mg + RTV 300mg) once daily; or (FPV 700mg + RTV 100mg) BID EFV standard	**Do not coadminister with FPV +/− RTV.**	(FPV 700mg + RTV 100mg) BID NVP standard	MVC 150mg BID	No data
Indinavir (IDV)	**Exposure**	IDV: ↓ 31%	IDV: ↓	IDV: ↓ 31% NVP: no effect	Unknown; ↑ MVC possible	No data
	Dose	IDV 1,000mg q8h or (IDV 800mg + RTV 100–200mg) BID EFV standard	**Do not coadminister.**	IDV 1,000mg q8h, or (IDV 800mg + RTV 100–200mg) BID NVP standard	MVC 150mg BID	No data

		Efavirenz	Etravirine	Nevirapine	Maraviroc	Raltegravir
Lopinavir/ Ritonavir (LPV/r)	**Exposure**	With LPV/r tablets 500/125mg BID‡ + EFV 600mg LPV levels similar to LPV/r 400/100mg BID without EFV	With LPV/r tablets ETR: levels ↓ 30%–45% (comparable to the decrease with DRV/r) LPV: levels ↓ 13%–20%.	With LPV/r capsules LPV: AUC ↓ 27% and Cmin ↓51%	MVC: AUC ↑ 295% With LPV/r + EFV MVC: AUC ↑153%	No data
	Dose	LPV/r tablets 500/125mg‡ BID; LPV/r oral solution 533/133mg BID EFV standard	Standard	LPV/r tablets 500/125mg‡ BID; LPV/r oral solution 533/133mg BID NVP standard	MVC 150mg BID	No data
Nelfinavir (NFV)	**Exposure**	NFV: AUC ↑ 20%	No data	NFV: Cmin ↓ 32% NVP: no significant effect	Unknown, possibly ↑ MVC concentration	No data
	Dose	Standard	**Do not coadminister.**	Standard	MVC 150mg BID	No data
Nevirapine (NVP)	**Exposure**	NVP: no significant change EFV: AUC ↓ 22%	↓ ETR possible	•	No significant change	No data
	Dose	**Do not coadminister.**	**Do not coadminister.**		Without PI MVC 300mg BID With PI (except TPV/r) MVC 150mg BID	No data
Raltegravir (RAL)	**Exposure**	RAL: AUC ↓ 36%	ETR: Cmin ↑ 17% RAL: Cmin ↓ 34%	No data	RAL: AUC ↓ 37% MVC: AUC ↓ 21%	•
	Dose	Standard	Standard	No data	Standard	
Ritonavir (RTV)	**Exposure**	Refer to information for boosted PI	Refer to information for boosted PI	Refer to information for boosted PI	With RTV 100 mg BID MVC: AUC ↑ 161%	With RTV 100mg BID RAL: AUC ↓ 16%
	Dose				MVC 150mg BID	Standard
Saquinavir (SQV)	**Exposure**	With SQV 1,200mg TID SQV: AUC ↓ 62% EFV: AUC ↓ 12%	With (SQV 1,000mg + RTV 100mg) BID SQV: AUC unchanged ETR: AUC ↓ 33%, Cmin ↓ 29% Reduced ETR levels similar to reduction with DRV/r	With SQV 600mg TID SQV: AUC ↓ 38% NVP: no significant change	With (SQV 1,000mg + RTV 100mg) BID MVC: AUC ↑ 877% With (SQV 1,000mg + RTV 100mg) BID + EFV MVC: AUC ↑ 400%	No data
	Dose	(SQV 1,000mg + RTV 100mg) BID	(SQV 1,000mg + RTV 100mg) BID	(SQV 1,000mg + RTV 100mg) BID	MVC 150mg BID	No data
Tipranavir (TPV)	**Exposure**	With (TPV 500mg + RTV 100mg) BID TPV: AUC ↓ 31%, Cmin ↓ 42% EFV: no significant change With (TPV 750mg + RTV 200mg) BID: TPV: no significant change EFV: no significant change	With (TPV 500mg + RTV 200mg) BID ETR: AUC ↓ 76%, Cmin ↓ 82% TPV: AUC ↑ 18%, Cmin ↑ 24%	With (TPV 250mg + RTV 200mg) BID and with (TPV 750mg + RTV 100mg) BID NVP: no significant change TPV: no data	With (TPV 500mg + RTV 200mg) BID MVC: no significant change in AUC TPV: no data	With (TPV 500mg + RTV 200mg) BID RAL: AUC ↓ 24%
	Dose	Standard	**Do not coadminister.**	Standard	MVC 300mg BID	Standard

† Based on between-study comparison.
‡Use a combination of two LPV/r 200mg/50mg tablets + one LPV/r 100mg/25mg tablet to make a total dose of LPV/r 500mg/150mg.

Preventing Secondary Transmission of HIV

(Updated December 1, 2009)

PREVENTION COUNSELING

Interventions to prevent transmission of HIV are key components of the management of HIV infection, yet multiple studies show that prevention is frequently neglected in clinical practice. Each patient encounter provides opportunities to reinforce HIV prevention messages—messages that patients often look to their providers to deliver, but may fail to receive *[1-2]*. Despite the challenges to providing effective prevention interventions in a busy practice setting, multiple approaches are available, including formal guidance from CDC for incorporating HIV prevention into medical care settings *[3]*. Such interventions have been demonstrated to be effective in changing sexual risk behavior *[4-6]*and can reinforce self-directed behavior change early in diagnosis *[7]*.

The CDC has identified prevention interventions for HIV-infected people that meet stringent criteria for efficacy and scientific rigor (CDC, 2009) and three that demonstrated efficacy in treatment settings (Options, Partnership for Health, and Positive Choices). The interventions are available through CDC trainings and materials, delivered as brief messages by providers or via laptop computer, and are readily implemented into busy clinics (http://www.cdc.gov/hiv/topics/research/prs/index.htm).

Evidence also exists regarding the efficacy of interventions to reduce injection drug use risk behavior. These include both behavioral interventions *[8-10]* and opiate substitution treatment with methadone *[11-12]*.

There is evidence of increases in HIV risk behaviors among infected persons coinciding with the availability of potent combination antiretroviral therapy. In some cohorts the rate of reported risk behaviors almost doubled compared with rates in the era prior to such therapies *[7]*. A meta-analysis of studies of HIV risk behaviors demonstrates that the prevalence of unprotected sex acts was increased in those who believed that receiving antiretroviral therapy or having a suppressed viral load protects against transmitting HIV *[13]*. Attitudinal shifts away from safer sexual practices since the availability of potent antiretroviral therapy underscore the role for provider-initiated HIV prevention counseling. With wider recognition of the concept that effective treatment may decrease the probability of transmission, it is particularly important for providers to help patients understand that a sustained viral load below the limits of detection will dramatically reduce but does not absolutely assure the absence of virus in the genital and blood compartments, and hence the inability to transmit virus to others *[13-14]*.

Additionally, given the role of sexually transmitted infections (STIs) as facilitators of HIV transmission, an essential adjunct to prevention counseling is the routine screening and symptom directed testing for STIs, as recommended by CDC *[3]*.

ANTIRETROVIRAL THERAPY AS PREVENTION

Antiretroviral therapy does have a role in preventing HIV transmission. Lower levels of plasma RNA have been associated with decreases in the concentration of virus in genital secretions *[15-16]*. Observational studies have demonstrated a decreased rate of HIV transmission among serodiscordant heterosexual couples following antiretroviral-induced viral suppression, in the absence of concomitant STIs. Multiple studies have demonstrated a direct correlation between HIV inoculum size (i.e., viral load) and probability of transmission *[17-18]*. Although some data suggest that the risk of heterosexual HIV transmission is low when an individual's viral load is <40 copies/ml, these data are contingent upon several assumptions, including: 1) completely suppressed viremia; 2) complete adherence to an effective antiretroviral regimen; and 3) the absence of a concomitant STI. The reduction of the viral load in the genital compartment notwithstanding, there is not yet published evidence from randomized clinical trials that antiretroviral therapy confirms the reduction or elimination of risk of HIV sexual transmission. Detection of HIV RNA in the genital secretions has been documented in individuals with controlled plasma HIV RNA *[19-20]*. Moreover, it is critical that any biological reduction in infectivity not be offset by increases in risk behavior (i.e., risk compensation).

SUMMARY

In summary, consistent and effective use of antiretroviral therapy, resulting in a sustained reduction in viral load, in conjunction with consistent condom usage, safer sexual and drug use practices, and detection and treatment of STIs are essential tools for prevention of sexual and blood-borne transmission of HIV. Given these important considerations, medical visits provide a vital

opportunity to reinforce HIV prevention messages, discuss sexual- and drug-related risk behaviors, diagnose and treat intercurrent STIs, and develop open communication between provider and patient.

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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.

Appendix A: Financial Disclosure for Members of the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents – February 2009

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Abbreviations: C = Co-Chair; ES = Executive Secretary; M = Member; N/A = not applicable

Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

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(Updated December 1, 2009)

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations **For dosage adjustment in renal or hepatic insufficiency, see Appendix, Table 7**	Elimination	Serum/ Intracellular Half-lives	Adverse Events
Abacavir (ABC)/ Ziagen **Also available as**:	Ziagen 300mg tablets or 20mg/mL oral solution	Ziagen 300mg BID or 600mg once daily Take without regard to meals	Metabolized by alcohol dehydrogenase and glucuronyl transferase Renal excretion of metabolites 82% Dosage adjustment for ABC is recommended in patients with hepatic insufficiency (see **Appendix, Table 7**)	1.5 hrs/ 12–26 hrs	• Hypersensitivity reaction symptoms may include fever, rash, nausea, vomiting, malaise or fatigue, or respiratory symptoms such as sore throat, cough, or shortness of breath. • Some cohort studies suggest increased risk of MI with recent or current use of ABC, but this is not substantiated in other studies.
Trizivir ABC with ZDV+3TC	Trizivir ABC 300mg + ZDV 300mg + 3TC 150mg	Trizivir 1 tablet BID			
Epzicom ABC with 3TC	Epzicom ABC 600mg + 3TC 300mg	Epzicom 1 tablet once daily			
Didanosine (ddI)/ Videx EC, generic didanosine enteric coated (dose same as Videx EC)	Videx EC 125, 200, 250, 400mg capsules Buffered tablets (non-EC) no longer available Videx 10mg/mL oral solution	**Body weight ≥ 60kg**: 400mg once daily*; with TDF, 250mg once daily **Body weight < 60kg**: 250mg once daily*; with TDF, 200mg once daily Take 1/2 hour before or 2 hours after a meal *Preferred dosing with oral solution is BID (total daily dose divided into 2 doses)	Renal excretion 50% Dosage adjustment in renal insufficiency recommended (see **Appendix, Table 7**)	1.5 hrs/ >20 hrs	• Pancreatitis • Peripheral neuropathy • Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity) • Potential association with noncirrhotic portal hypertension
Emtricitabine (FTC)/ Emtriva **Also available as:**	Emtriva 200mg hard gelatin capsule or 10mg/mL oral solution	Emtriva 200mg capsule once daily or 240mg (24 mL) oral solution once daily Take without regard to meals	Renal excretion 86% Dosage adjustment in renal insufficiency recommended (see **Appendix, Table 7**)	10 hrs/ >20 hrs	• Minimal toxicity • Hyperpigmentation/skin discoloration • Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue FTC.
Atripla FTC with EFV+TDF	Atripla FTC 200mg + EFV 600mg + TDF 300mg	Atripla 1 tablet at or before bedtime Take on an empty stomach to reduce side effects			
Truvada FTC with TDF	Truvada FTC 200mg + TDF 300mg	Truvada 1 tablet once daily			

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations **For dosage adjustment in renal or hepatic insufficiency, see Appendix, Table 7**	Elimination	Serum/ Intracellular Half-lives	Adverse Events
Lamivudine (3TC)/ Epivir **Also available as:**	Epivir 150, 300mg tablets or 10mg/mL oral solution	Epivir 150mg BID or 300mg once daily Take without regard to meals	Renal excretion 70% Dosage adjustment in renal insufficiency recommended (see **Appendix, Table 7**)	5–7 hrs/ 18–22 hrs	• Minimal toxicity • Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue 3TC.
Combivir 3TC with ZDV	Combivir 3TC 150mg + ZDV 300mg	Combivir 1 tablet BID			
Epzicom 3TC with ABC	Epzicom 3TC 300mg + ABC 600mg	Epzicom 1 tablet once daily			
Trizivir 3TC with ZDV+ABC	Trizivir 3TC 150mg + ZDV 300mg + ABC 300mg	Trizivir 1 tablet BID			
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* Take without regard to meals *WHO recommends 30mg BID dosing regardless of body weight.	Renal excretion 50% Dosage adjustment in renal insufficiency recommended (see **Appendix, Table 7**)	1.0 hr/ 7.5 hrs	• Peripheral neuropathy • Lipoatrophy • Pancreatitis • Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity) • Hyperlipidemia • Rapidly progressive ascending neuromuscular weakness (rare)
Tenofovir Disoproxil Fumarate (TDF)/ Viread **Also available as:**	Viread 300mg tablet	Viread 1 tablet once daily Take without regard to meals	Renal excretion Dosage adjustment in renal insufficiency recommended (see **Appendix, Table 7**)	17 hrs/ >60 hrs	• Asthenia, headache, diarrhea, nausea, vomiting, and flatulence • Renal insufficiency, Fanconi syndrome • Osteomalacia • Potential for decrease in bone mineral density • Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue TDF.
Atripla TDF with EFV+FTC	Atripla TDF 300mg + EFV 600mg + FTC 200mg	Atripla 1 tablet at or before bedtime Take on an empty stomach to reduce side effects			
Truvada TDF with FTC	Truvada TDF 300mg + FTC 200mg	Truvada 1 tablet once daily			
Zidovudine (AZT, ZDV)/ Retrovir, generic zidovudine **Also available as**:	Retrovir 100mg capsules, 300mg tablets, 10mg/mL intravenous solution, 10mg/mL oral solution	Retrovir 300mg BID or 200mg TID Take without regard to meals	Metabolized to AZT glucuronide (GAZT) Renal excretion of GAZT Dosage adjustment in renal insufficiency recommended (see **Appendix, Table 7**)	1.1 hrs/ 7 hrs	• Bone marrow suppression: macrocytic anemia or neutropenia • Gastrointestinal intolerance, headache, insomnia, asthenia • Nail pigmentation • Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity)
Combivir ZDV with 3TC	Combivir ZDV 300mg + 3TC 150mg	Combivir 1 tablet BID			
Trizivir ZDV with 3TC+ABC	Trizivir ZDV 300mg + 3TC 150mg + ABC 300mg	Trizivir 1 tablet BID			

Appendix B, Table 2. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) (Updated December 1, 2009)

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations For dosage adjustment in renal or hepatic insufficiency, see Appendix, Table 7	Elimination	Serum Half-life	Adverse Events
Delavirdine (DLV)/ Rescriptor	100, 200mg tablets	400mg TID; four 100mg tablets can be dispersed in >3 oz. of water to produce slurry; 200mg tablets should be taken as intact tablets Take without regard to meals Separate dose from antacids by 1 hour	CYP3A4 substrate and inhibitor; 51% excreted in urine (<5% unchanged) and 44% in feces	5.8 hrs	• Rash* • Increased transaminase levels • Headaches
Efavirenz (EFV)/ Sustiva **Also available as:**	50, 200mg capsules or 600mg tablets	600mg once daily at or before bedtime Take on an empty stomach to reduce side effects	Metabolized by CYPs 2B6 and 3A4 CYP3A4 mixed inducer/ inhibitor (more an inducer than an inhibitor)	40–55 hrs	• Rash* • Central nervous system symptoms† • Increased transaminase levels • False-positive results reported with some cannabinoid and benzodiazepine screening assays • Teratogenic in nonhuman primate and potentially teratogenic in humans
Atripla EFV with FTC + TDF	Atripla EFV 600mg + FTC 200mg + TDF 300mg	Atripla 1 tablet once daily at or before bedtime			
Etravirine (ETR)/ Intelence	100mg tablets	200mg BID Take following a meal	CYP3A4, 2C9, and 2C19 substrate 3A4 inducer; 2C9 and 2C19 inhibitor	41 +/– 20 hrs	• Rash * • Hypersensitivity reactions have been reported, characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure • Nausea
Nevirapine (NVP)/ Viramune	200mg tablets or 50mg/5 mL oral suspension	200mg once daily for 14 days (lead-in period); thereafter, 200mg BID Take without regard to meals Repeat lead-in period if therapy is discontinued for >7 days In patients who develop mild to moderate rash without constitutional symptoms, continue lead-in period until rash resolves but no longer than 28 days total.	CYP450 substrate and 3A inducer; 80% excreted in urine (glucuronidated metabolites, <5% unchanged); 10% in feces	25–30 hrs	• Rash, including Stevens-Johnson syndrome* • Symptomatic hepatitis, including fatal hepatic necrosis, has been reported‡

* During clinical trials, NNRTI was discontinued because of rash among 7% of NVP-treated, 4.3% of DLV-treated, 1.7% of EFV-treated, and 2% of ETR-treated patients. Rare cases of Stevens-Johnson syndrome have been reported with all NNRTIs; the highest incidence was seen with NVP.

† 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% compared with 26% among controls subjects; 2.6% of those persons on EFV 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 at significantly higher frequency in treatment-naïve female patients with pre-NVP CD4 counts >250 cells/mm3 or in treatment-naïve male patients with pre-NVP CD4 counts >400 cells/mm3. NVP should not be initiated in these patients unless the benefit clearly outweighs the risk. This toxicity has not been observed when NVP is given as single doses to mothers or infants for prevention of mother-to-child transmission of HIV.

Appendix B, Table 3. Characteristics of Protease Inhibitors (PIs) (Updated December 1, 2009)

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations For dosage adjustment in hepatic insufficiency, see Appendix, Table 7	Elimination	Serum Half-life	Storage	Adverse Events
Atazanavir (ATV)/ Reyataz	100, 150, 200, 300mg capsules	ARV-naïve pts: 400mg once daily or (ATV 300mg + RTV 100mg) once daily With 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, refer to Table 14a) Take with food	CYP3A4 inhibitor and substrate Dosage adjustment in hepatic insufficiency recommended (see Appendix, Table 7)	7 hrs	Room temperature (up to 25ºC or 77ºF)	• Indirect hyperbilirubinemia • Prolonged PR interval—first 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	75, 150, 400, 600mg tablets	ARV-naïve pts: (DRV 800mg + RTV 100mg) once daily ARV-experienced pts: (DRV 600mg + RTV 100mg) BID Unboosted DRV is **not** recommended Take with food	CYP3A4 inhibitor and substrate	15 hrs (when combined with RTV)	Room temperature (up to 25ºC or 77ºF)	• Skin rash (10%)—DRV has a sulfonamide moiety; Stevens-Johnson syndrome and 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 (a prodrug of amprenavir)	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 700mg + RTV 100mg) BID or • (FPV 1,400mg + RTV 300mg) once daily Take without regard to meals	Amprenavir is a CYP3A4 substrate, inhibitor, and inducer Dosage adjustment in hepatic insufficiency recommended (see Appendix, Table 7)	7.7 hrs (amprenavir)	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 pts with hemophilia • Nephrolithiasis
Indinavir (IDV)/ Crixivan	200, 333, 400mg capsules	800mg every 8 hrs Take 1 hour before or 2 hours after meals; may take with skim milk or low-fat meal With RTV: (IDV 800mg + RTV 100–200mg) BID Take without regard to meals	CYP3A4 inhibitor and substrate Dosage adjustment in hepatic insufficiency recommended (see Appendix, Table 7)	1.5–2 hrs	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

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations **For dosage adjustment in hepatic insufficiency, see Appendix, Table 7**	Elimination	Serum Half-life	Storage	Adverse Events
Lopinavir + Ritonavir (LPV/r)/ Kaletra	Tablets: (LPV 200mg + RTV 50mg) or (LPV 100mg + RTV 25mg) Oral solution: Each 5 mL contains (LPV 400mg + RTV 100mg) Oral solution contains 42% alcohol	LPV/r 400mg/100mg BID or LPV/r 800mg/200mg once daily Once-daily dosing is only recommended for PI-naïve pts and not for pregnant women or pts receiving EFV, NVP, FPV, or NFV With EFV or NVP (PI-naïve or PI-experienced pts): LPV/r 500mg/125mg tablets BID (use a combination of two LPV/r 200mg/50mg tablets + one LPV/r 100mg/25mg tablet to make a total dose of LPV/r 500mg/125mg.) or LPV/r 533mg/133mg oral solution BID Tablet: take without regard to meals Oral solution: take with food	CYP3A4 inhibitor and substrate	5–6 hrs	Oral tablet is stable at room temperature. Oral solution is stable at 2°–8°C until date on label and is stable when stored at room temperature (up to 25ºC or 77ºF) for 2 months.	• GI intolerance, nausea, vomiting, diarrhea • Asthenia • Hyperlipidemia (especially hypertriglyceridemia) • Elevated serum transaminases • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in pts with hemophilia • PR interval prolongation • QT interval prolongation and torsade de pointes
Nelfinavir (NFV)/ Viracept	250, 625mg tablets 50mg/g oral powder	1,250mg BID or 750mg TID Take with food	CYP2C19 and 3A4 substrate—metabolized to active M8 metabolite; CYP 3A4 inhibitor	3.5–5 hrs	Room temperature (15º–30ºC/59º–86ºF)	• Diarrhea • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in pts with hemophilia • Serum transaminase elevation
Ritonavir (RTV)/ Norvir	100mg capsules 80mg/mL oral solution	As pharmacokinetic booster for other PIs: 100–400mg per day in 1–2 divided doses (refer to other PIs for specific dosing recommendations) Take with food if possible; this may improve tolerability	CYP3A4 >2D6 substrate; potent 3A4, 2D6 inhibitor	3–5 hrs	Refrigerate capsules Capsules can be left at room temperature (up to 25ºC or 77ºF) for up to 30 days. Oral solution should **not** be refrigerated.	• GI intolerance, nausea, vomiting, diarrhea • Paresthesias—circumoral and extremities • Hyperlipidemia (especially hypertriglyceridemia) • Hepatitis • Asthenia • Taste perversion • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in pts with hemophilia
Saquinavir tablets and hard gel capsules (SQV)/ Invirase	500mg tablets or 200mg hard gel capsules	(SQV 1,000mg + RTV 100mg) BID Unboosted SQV is **not** recommended. Take within 2 hours after a meal	CYP3A4 inhibitor and substrate	1–2 hrs	Room temperature (15º–30ºC/59º–86ºF)	• GI intolerance, nausea, and diarrhea • Headache • Elevated transaminase enzymes • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in pts with hemophilia

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations **For dosage adjustment in hepatic insufficiency, see Appendix, Table 7**	Elimination	Serum Half-life	Storage	Adverse Events
Tipranavir (TPV)/ Aptivus	250mg capsules or 100mg/mL oral solution	(TPV 500mg + RTV 200mg) PO BID Unboosted TPV is **not** recommended. Take without regard to meals	Cytochrome P450 3A4 inducer and substrate Net effect when combined with RTV (CYP 3A4, 2D6 inhibitor)	6 hrs after single dose of TPV/r	Refrigerate capsules Capsules can be stored at room temperature (25ºC or 77ºF) for up to 60 days. Oral solution should **not** be refrigerated or frozen and should be used within 60 days after opening the bottle.	• Hepatotoxicity—clinical hepatitis, (including hepatic decompensation and hepatitis-associated fatalities) has been reported; monitor closely, especially in pts with underlying liver diseases. • Skin rash—TPV has a sulfonamide moiety; use with caution in pts with known sulfonamide allergy. • Rare cases of fatal and nonfatal intracranial hemorrhages have been reported. Most pts had underlying comorbidity, such as brain lesion, head trauma, recent neurosurgery, coagulopathy, hypertension, or alcoholism or were on medication with increased risk of bleeding. • Hyperlipidemia (especially hypertriglyceridemia) • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in pts with hemophilia

Appendix B, Table 4. Characteristics of Integrase Inhibitors (Updated December 1, 2009)

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations For dosage adjustment in hepatic insufficiency, see Appendix, Table 7	Serum half-life	Route of Metabolism	Adverse Events
Raltegravir (RAL)/ Isentress	400mg tablets	400mg BID With rifampin: 800mg BID Take without regard to meals	~9 hrs	UGT1A1-mediated glucuronidation	• Nausea • Headache • Diarrhea • Pyrexia • CPK elevation

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

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations	Serum half-life	Elimination	Storage	Adverse Events
Enfuvirtide (T20)/ Fuzeon	• Injectable—supplied as lyophilized powder • Each vial contains 108mg of T20; reconstitute with 1.1mL of sterile water for injection for delivery of approximately 90mg/1mL	90mg (1mL) subcutaneously BID	3.8 hrs	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). Reconsti-tuted solution should be stored under refrigeration at 2ºC–8ºC (36ºF–46Fº) and used within 24 hours.	• Local injection site reactions in 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 B, Table 6. Characteristics of CCR5 Antagonists (Updated January 29, 2008)

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations For dosage adjustment in hepatic insufficiency, see Appendix, Table 7	Serum Half-life	Elimination	Adverse Events
Maraviroc (MVC)/ Selzentry	150, 300mg tablets	• **150mg BID** when given with strong CYP3A inhibitors (with or without CYP3A inducers) including PIs (except TPV/r) • **300mg BID** when given with NRTIs, T-20, TPV/r, NVP, and other drugs that are not strong CYP3A inhibitors or inducers • **600mg BID** when given with CYP3A inducers, including EFV, ETR, etc. (without a CYP3A inhibitor) Take without regard to meals	14–18 hrs	CYP3A4 substrate	• Abdominal pain • Cough • Dizziness • Musculoskeletal symptoms • Pyrexia • Rash • Upper respiratory tract infections • Hepatotoxicity • Orthostatic hypotension

Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Updated December 1, 2009)

See reference section following tables for creatinine clearance (CrCl) calculation formulas and criteria for Child-Pugh classification.

Antiretrovirals Generic Name (abbreviation)/ Trade Name	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, or Epzicom is not recommended in patients with CrCl <50 mL/min. Use of Truvada is not recommended in patients with CrCl <30 mL/min.			
Abacavir (ABC)/ Ziagen	300mg PO BID	No dosage adjustment necessary	**Child-Pugh Score Dose** 5–6 200mg BID (use oral solution) > 6 Contraindicated
Didanosine enteric coated (ddI)/ Videx EC	**Body weight ≥60 kg**: 400mg PO once daily **Body weight <60 kg**: 250mg PO once daily	**Dose (once daily)** **CrCl (mL/min) ≥60 kg <60 kg** 30–59 200mg 125mg 10–29 125mg 125mg <10, HD, CAPD 125mg use oral solution	No dosage adjustment necessary
Didanosine oral solution (ddI)/ Videx	**Body weight ≥60 kg**: 200mg PO BID or 400mg PO once daily **Body weight <60 kg**: 250mg PO once daily or 125mg PO BID	**Dose (once daily)** **CrCl (mL/min) ≥60 kg <60 kg** 30–59 200mg 150mg 10–29 150mg 100mg <10, HD, CAPD 100mg 75mg	No dosage adjustment necessary
Emtricitabine (FTC)/ Emtriva	200mg oral capsule PO once daily or 240mg (24mL) oral solution PO once daily	**Dose** **CrCl (mL/min) Capsule Solution** 30–49 200mg q48h 120mg q24h 15–29 200mg q72h 80mg q24h <15 or HD 200mg q96h 60mg q24h Take dose after HD session on dialysis days	No dosage recommendation
Lamivudine (3TC)/ Epivir	300mg PO once daily or 150mg PO BID	**CrCl (mL/min) Dose** 30–49 150mg q24h 15–29 1 x 150mg, then 100mg q24h 4–14* 1 x 150mg, then 50mg q24h <5 or HD 1 x 50mg, then 25 mg q24h Take dose after HD session on dialysis days	No dosage adjustment necessary
Stavudine (D4T)/ Zerit	**Body weight ≥ 60 kg**: 40mg PO BID **Body weight <60 kg**: 30mg PO BID	**Dose** **CrCl (mL/min) ≥60 kg <60 kg** 26–50 20mg q12h 15mg q12h 10–25 or HD 20mg q24h 15 mg q24h Take dose after HD session on dialysis days	No dosage recommendation
Tenofovir (TDF)/ Viread	300mg PO once daily	**CrCl (mL/min) Dose** 30–49 300mg q48h 10–29 300mg twice weekly <10 not on HD no recommendation HD 300mg q7d Take dose after HD session on dialysis days	No dosage adjustment necessary
Emtricitabine (FTC) + **Tenofovir** (TDF) / Truvada	1 tablet PO once daily	**CrCl (mL/min) Dose** 30–49 1 tablet q48h <30 or HD not recommended	No dosage recommendation
Zidovudine (AZT, ZDV)/ Retrovir	300mg PO BID	**CrCl (mL/min) Dose** < 15 or HD 100mg TID or 300mg once daily	No dosage recommendation

* Error corrected January 15, 2010

Antiretrovirals Generic Name (abbreviation)/ Trade Name	Daily Dose	Dosing in Renal Insufficiency	Dosing in Hepatic Impairment
Non-Nucleoside Reverse Transcriptase Inhibitors			
Delavirdine (DLV)/ Rescriptor	400mg PO TID	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment
Efavirenz (EFV)/ Sustiva	600mg PO at or before bedtime	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment
Efavirenz (EFV) + **Emtricitabine** (FTC) + **Tenofovir** (TDF) / Atripla	1 tablet PO once daily	Atripla not recommended if CrCl <50 mL/min	
Etravirine (ETR)/ Intelence	200mg PO BID	No dosage adjustment necessary	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no dosage recommendation
Nevirapine (NVP)/ Viramune	200mg PO BID	**HD patients**: Some suggest additional 200mg after dialysis; however, pharmacokinetic data for this strategy are not available.	Child-Pugh Class B or C: contraindicated
Protease Inhibitors			
Atazanavir (ATV)/ Reyataz	400mg PO once daily or (ATV 300mg + RTV 100mg) PO 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 (Child-Pugh Score ≥7).
Darunavir (DRV)/ Prezista	(DRV 800mg + RTV 100mg) PO once daily (ARV-naïve pts) or (DRV 600mg + RTV 100mg) PO BID	No dosage adjustment necessary	Mild to moderate hepatic impairment: no dosage adjustment Severe hepatic impairment: not recommended
Fosamprenavir (FPV)/ Lexiva	1,400mg PO BID or (FPV 1,400mg + RTV 100–200mg) PO once daily or (FPV 700mg + RTV 100mg) PO BID	No dosage adjustment necessary	**Child-Pugh Score** **Dose** PI naïve only: 5–9 700mg BID 10–15 350mg BID PI naïve or PI experienced: 5–6 700mg BID + RTV 100mg once daily 7–8 450mg BID + RTV 100mg once daily 10–15 300mg BID + RTV 100mg once daily
Indinavir (IDV)/ Crixivan	800mg PO q8h	No dosage adjustment necessary	Mild to moderate hepatic insufficiency because of cirrhosis: 600mg q8h
Lopinavir/ritonavir (LPV/r) Kaletra	400/100mg PO BID or 800/200mg PO once daily (only for ARV-naïve patients)	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment
Nelfinavir (NFV)/ Viracept	1,250mg PO BID	No dosage adjustment necessary	Mild hepatic impairment: no dosage adjustment Moderate to severe hepatic impairment: do not use
Ritonavir (RTV)/ Norvir	As a PI-boosting agent: 100–400mg per day	No dosage adjustment necessary	Refer to recommendations for the primary PI
Saquinavir (SQV)/ Invirase	(SQV 1,000mg + RTV 100mg) PO BID	No dosage adjustment necessary	Mild to moderate hepatic impairment: use with caution Severe hepatic impairment: contraindicated
Tipranavir (TPV)/ Aptivus	(TPV 500mg + RTV 200mg) PO BID	No dosage adjustment necessary	Child-Pugh Class A: use with caution Child-Pugh Class B or C: contraindicated

Abbreviations: CAPD = chronic ambulatory peritoneal dialysis, HD = hemodialysis

Antiretrovirals Generic Name (abbreviation)/ Trade Name	Daily Dose	Dosing in Renal Insufficiency	Dosing in Hepatic Impairment
Fusion Inhibitors			
Enfuvirtide (T20)/ Fuzeon	90mg subcutaneous BID	No dosage adjustment necessary	No dosage recommendation
CCR5 Antagonists			
Maraviroc (MVC)/ Selzentry	The recommended dose differs based on concomitant medications because of drug interactions. See **Appendix B, 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 (RAL)/ Isentress	400mg BID	No dosage adjustment necessary	Mild to moderate hepatic insufficiency: no dosage adjustment necessary Severe hepatic insufficiency: no recommendation

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

Child-Pugh Score			
Component	**Points Scored**		
	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	2.8–3.5 g/dL	<2.8 g/dL
Total bilirubin or	<2 mg/dL (<34 μmol/L)	2–3 mg/dL (34 μmol/L to 50 μmol/L)	>3 mg/dL (>50 μmol/L)
Modified total bilirubin†	<4 mg/dL	4–7 mg/dL	>7 mg/dL
Prothrombin time (seconds prolonged) or	<4	4–6	>6
International normalized ratio (INR)	<1.7	1.7–2.3	>2.3

* 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 or atazanavir

Child-Pugh Classification	Total Score*
Class A	5–6 points
Class B	7–9 points
Class C	>9 points

* Sum of points for each component