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

**January 10, 2011**

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


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

# What's New in the Guidelines?

Key changes made to update the December 1, 2009, version of the guidelines are summarized below. Throughout the revised guidelines, significant updates are highlighted and fully discussed.

### Introduction

The Panel emphasizes its recognition of the importance of clinical research in generating evidence to address unanswered questions related to the optimal safety and efficacy of antiretroviral therapy (ART). The Panel encourages both the development of protocols and patient participation in well-designed, Institutional Review Board (IRB)-approved clinical trials.

### CD4 T-cell Count

The Panel recognizes that changes in CD4 cell count are seldom used in decision for ART changes in a patient on a suppressive ART regimen whose CD4 count is well above the threshold for opportunistic infection risk. In such patients, the Panel recommends that the CD4 count may be monitored less frequently, for example every 6 to 12 months (instead of every 3 to 6 months), unless there are changes in the patient's clinical status, such as new HIV-associated clinical symptoms or initiation of treatment with interferon, corticosteroids, or anti-neoplastic agents **(CIII)**.

### Viral Load Testing

The Panel recognizes that low-level positive viral load results (typically <200 copies/mL) have been commonly reported with some viral load assays. For the purpose of patient monitoring, the Panel defines virologic failure as a confirmed viral load >200 copies/mL, which eliminates most cases of viremia caused by isolated blips or assay variability.

### Drug-Resistance Testing

The Panel provides more specific recommendations on when to use genotypic testing to detect resistance to integrase strand transfer inhibitors (INSTIs).

- Because standard genotypic drug-resistance testing involves testing for mutations in the reverse transcriptase (RT) and protease (PR) genes, if transmitted INSTI resistance is a concern, providers may wish to supplement standard genotypic resistance testing with genotypic testing for resistance to this class of drugs **(CIII)**.
- In persons failing INSTI-based regimens, genotypic testing for INSTI resistance should be considered to determine whether to include a drug from this class in subsequent regimens **(BIII)**.

### What to Start: Initial Combination Regimens for the Antiretroviral-Naïve Patient

Changes to the "What to Start" recommendations include the following:

- A regimen consisting of maraviroc (MVC) + zidovudine/lamivudine (ZDV/3TC) is now listed as an "Acceptable Regimen" because FDA approval of MVC for use in ART-naïve patients was based on the results of a randomized controlled trial using this regimen **(CI).**
- "MVC + tenofovir/emtricitabine (TDF/FTC)" and "MVC + abacavir (ABC)/3TC" have been added as "Regimens that may be acceptable but more definitive data are needed" **(CIII).**
- In response to a recent change to the Invirase® product label based on findings from a healthy volunteer study that reported significant PR and QT interval prolongations, ritonavir-boosted saquinavir (SQV/r)-based regimens have been moved from "Alternative PI-based Regimens" to "Regimens that are Acceptable but Should be Used with Caution."

### Hepatitis B (HBV)/HIV Coinfection

This section has been revised to provide more specific recommendations for management of HIV patients coinfected with HBV, including recommendations for patients with 3TC/FTC-resistant HBV infection and for patients who cannot tolerate TDF-based regimens.

### *Mycobacterium Tuberculosis Disease with HIV Coinfection*

Based on recent randomized controlled trials showing survival and clinical benefits of starting ART earlier in treatment-naïve patients with active tuberculosis (TB) disease, the Panel provides the following recommendations on when to start ART in patients who are receiving treatment for active TB but are not yet on ART.

- All HIV-infected patients with diagnosed active TB should be treated with ART **(AI)**.
- For patients with CD4 count <200 cells/$mm^3$, ART should be initiated within 2–4 weeks of starting TB treatment **(AI)**.
- For patients with CD4 count 200–500 cells/$mm^3$, the Panel recommends initiating ART within 2–4 weeks, or at least by 8 weeks after commencement of TB therapy **(AIII)**.
- For patients with CD4 count >500 cells/$mm^3$, most panel members also recommend starting ART within 8 weeks of TB therapy **(BIII)**.

### *Adverse Effects of Antiretroviral Agents*

A new table format provides clinicians with a list of the most common and/or severe known antiretroviral (ARV)-associated adverse events listed by ARV drug class.

### *Additional Updates*

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

- Coreceptor Tropism Assays
- Treatment Goals
- Initiating Antiretroviral Therapy in Treatment-Naïve Patients
- What Not to Use
- Virologic and Immunologic Failure (previously titled “Management of Patients with Antiretroviral Treatment Failure”)
- Regimen Simplification
- Exposure-Response Relationship and Therapeutic Drug Monitoring for Antiretroviral Agents
- Acute HIV Infection
- HIV and Illicit Drug Users (with new Table)
- HIV-2 Infection
- Drug Interactions (and Tables)
- Drug Characteristics Tables (Appendices)

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Financial Disclosures for Members of DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents available at: **http://aidsinfo.nih.gov/contentfiles/AA_FinancialDisclosures.pdf**

# Guidelines Panel Members
# DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents

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***Acknowledgement:***
The Panel would also like to acknowledge *Nina H. Lin, M.D., (Massachusetts General Hospital & Harvard Medical School, Boston, MA)* for her assistance in the preparation of the Guidelines.

Updated January 10, 2011

# Introduction (Updated January 10, 2011)

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

The Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) is a working group of the Office of AIDS Research Advisory Council (OARAC). The primary goal of the Panel is to provide recommendations for HIV care practitioners based on current knowledge of antiretroviral (ARV) 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 ART, choice of the initial regimen in ART-naïve patients, drugs or combinations to be avoided, management of adverse effects and drug interactions, management of treatment failure, and special ART-related considerations in specific patient populations.

These guidelines generally represent the state of knowledge regarding the use of ARV agents. However, because the science evolves rapidly, the availability of new agents and new clinical data may change therapeutic options and preferences. Information included in these guidelines may not be consistent with approved labeling for the particular products or indications in question, and the terms "safe" and "effective" may not be synonymous with the Food and Drug Administration (FDA)-defined legal standards for product approval. The guidelines are updated frequently by the Panel (current and archived versions of the guidelines are available on the AIDS*info* Web site at **http://www.aidsinfo.nih.gov**). However, the guidelines cannot always keep pace with the rapid evolution of new data in this field, and they cannot provide guidance for all patients. Clinicians should exercise clinical judgment in management decisions tailored to unique patient circumstances.

The Panel recognizes the importance of clinical research in generating evidence to address unanswered questions related to the optimal safety and efficacy of ART. The Panel encourages both the development of protocols and patient participation in well-designed, Institutional Review Board (IRB)-approved clinical trials.

## GUIDELINES DEVELOPMENT PROCESS

Table 1 provides an outline of the composition of the Panel and guidelines process.

### Table 1. Outline of the Guidelines Development Process (Updated November 3, 2008)

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| Topic | Comment |
|---|---|
| **Goal of the guidelines** | Provide guidance to HIV care practitioners on the optimal use of ARV 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 1 representative from each of the following DHHS agencies: Centers for Disease Control and Prevention (CDC), FDA, Health Resource Services Administration (HRSA), and National Institutes of Health (NIH). These members are appointed by their respective agencies. Approximately 2/3 of the Panel members are nongovernmental scientific members. There are 4–5 community members with knowledge in HIV treatment and care. 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 vii** of this document. |

**Table 1. Outline of the Guidelines Development Process**
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| Topic | Comment |
|---|---|
| **Financial disclosure** | All members of the Panel submit a written financial disclosure annually reporting any association with manufacturers of ARV drugs or diagnostics used for management of HIV infections. A list of the latest disclosures is available on the AIDS*info* Web site (**http://aidsinfo.nih.gov/contentfiles/AA_Roster.pdf**). |
| **Users of the guidelines** | HIV treatment providers |
| **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 in the guidelines are generally 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 of Panel members with expertise in the area of interest. The members of the working group synthesize the available data and propose recommendations to the Panel. All proposals are discussed at monthly teleconferences and then voted on by the Panel before being endorsed as official recommendations. |
| **Other guidelines** | These guidelines focus on treatment for HIV-infected adults and adolescents. Separate guidelines outline the use of ART for other populations, such as pregnant women and children. 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 group of women 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 may also 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**.)

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

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

## References


1. Kitahata MM, Koepsell TD, Deyo RA, et al. Physicians' experience with the acquired immunodeficiency syndrome as a factor in patients' survival. *N Engl J Med.* 1996;334(11):701-706.
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.
3. Landon BE, Wilson IB, McInnes K, et al. Physician specialization and the quality of care for human immunodeficiency virus infection. *Arch Intern Med.* 2005;165(10):1133-1139.
4. Laine C, Markson LE, McKee LJ, et al. The relationship of clinic experience with advanced HIV and survival of women with AIDS. *AIDS.* 1998;12(4):417-424.
5. Kitahata MM, Van Rompaey SE, Dillingham PW, et al. Primary care delivery is associated with greater physician experience and improved survival among persons with AIDS. *J Gen Intern Med.* 2003;18(2):95-103.
6. Delgado J, Heath KV, Yip B, et al. Highly active antiretroviral therapy: physician experience and enhanced adherence to prescription refill. *Antivir Ther.* 2003;8(5):471-478.

# Baseline Evaluation (Updated January 10, 2011)

Each HIV-infected patient entering into care should have a complete medical history, physical examination, and laboratory evaluation and should be counseled regarding the implications of HIV infection. The goals of the initial evaluation are to confirm the presence of HIV infection, obtain appropriate baseline historical and laboratory data, ensure patient understanding about HIV infection and its transmission, and initiate care as recommended by established guidances such as the HIV primary care guidelines *[1]* and the guidelines for prevention and treatment of HIV-associated opportunistic infections *[2]*. Baseline information can then be used to define management goals and plans.

The following laboratory tests performed during initial patient visits can be used to stage HIV disease and to assist in the selection of antiretroviral (ARV) drug regimens:

- HIV antibody testing (if prior documentation is not available or if HIV RNA is below the assay's limit of detection) **(AI)**;
- CD4 T-cell count **(AI)**;
- Plasma HIV RNA (viral load) **(AI)**;
- Complete blood count, chemistry profile, transaminase levels, blood urea nitrogen (BUN) and creatinine, urinalysis, and serologies for hepatitis A, B, and C viruses **(AIII)**;
- Fasting blood glucose and serum lipids **(AIII)**; and
- Genotypic resistance testing at entry into care, regardless of whether ART will be initiated immediately **(AIII)**. For patients who have HIV RNA levels <500–1,000 copies/mL, amplification of virus for resistance testing may not always be successful **(BII)**.

In addition, other tests, including screening tests for sexually transmitted infections and tests for determining risk for opportunistic infections and need for prophylaxis, should be performed as recommended by HIV primary care and opportunistic infections guidelines *[1-2]*.

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

Education about HIV risk behaviors and effective strategies to prevent HIV transmission should be provided at each patient visit. (See **Preventing Secondary Transmission of HIV**.)

## 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. Centers for Disease Control and Prevention (CDC). 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 January 10, 2011)**

A number of laboratory tests are important for initial evaluation of HIV-infected patients upon entry into care, during follow-up if antiretroviral therapy (ART) has not been initiated, and prior to and after initiation or modification of therapy to assess virologic and immunologic efficacy of ART and to monitor for laboratory abnormalities that may be associated with antiretroviral (ARV) 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 (CD4 count) and plasma HIV RNA (viral load). Resistance testing should be used to guide selection of an ARV regimen in both ART-naïve and ART-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 (ABC). 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 January 10, 2011)

| | Entry into care | Follow-up before ART | ART initiation or modification[1] | 2–8 weeks post-ART initiation or modification | Every 3–6 months | Every 6 months | Every 12 months | Treatment failure | Clinically indicated |
|---|---|---|---|---|---|---|---|---|---|
| CD4 count | √ | every 3–6 months | √ | | √ | In clinically stable patients with suppressed viral load, CD4 count can be monitored every 6–12 months (see text) | | √ | √ |
| Viral load | √ | every 3–6 months | √ | √[2] | √[3] | | | √ | √ |
| Resistance testing | √ | | √[4] | | | | | √ | √ |
| HLA-B*5701 testing | | | √ if considering ABC | | | | | | |
| Tropism testing | | | √ if considering a CCR5 antagonist | | | | | √ if considering a CCR5 antagonist or for failure of CCR5 antagonist-based regimen | √ |
| Hepatitis B serology[5] | √ | | √ may repeat if HBsAg (-) and HBsAb (-) at baseline | | | | | | √ |
| Basic chemistry[6] | √ | every 6–12 months | √ | √ | √ | | | | √ |
| ALT, AST, T. bilirubin | √ | every 6–12 months | √ | √ | √ | | | | √ |
| CBC with differential | √ | every 3–6 months | √ | √ if on ZDV | √ | | | | √ |
| Fasting lipid profile | √ | if normal, annually | √ | √ consider 4–8 weeks after starting new ART | | √ if abnormal at last measurement | √ if normal at last measurement | | √ |
| Fasting glucose | √ | if normal, annually | √ | | √ if abnormal at last measurement | √ if normal at last measurement | | | √ |
| Urinalysis[7] | √ | | √ | | | √ if on TDF[8] | √ | | √ |
| Pregnancy test | | | √ if starting EFV | | | | | | √ |

[1]ARV modification may be done for treatment failure, adverse effects, or simplification.
[2]If HIV RNA is detectable at 2–8 weeks, repeat every 4–8 weeks until suppression to <200 copies/mL, then every 3–6 months.
[3]For adherent patients with suppressed viral load and stable clinical and immunologic status for >2–3 years, some experts may extend the interval for HIV RNA monitoring to every 6 months.
[4]For ART-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 ART, TDF + (FTC or 3TC) should be used as part of ARV regimen to treat both HBV and HIV infections. If HBsAg and HBsAb are 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 TDF; determination of renal function should include estimation of creatinine clearance using Cockcroft-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]*.
[8] More frequent monitoring may be indicated for patients with increased risk of renal insufficiency, such as patients with diabetes, hypertension, etc.

**Acronyms:** 3TC = lamivudine, ABC = abacavir, ALT = alanine aminotransferase, ART = antiretroviral therapy, AST = aspartate aminotranserase, CBC = complete blood count, EFV = efavirenz, FTC = emtricitabine, HBsAb = hepatitis B surface antibody, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, MDRD = modification of diet in renal disease (equation), TDF = tenofovir, ZDV = zidovudine

## References

1. Gupta SK, Eustace JA, Winston JA, et al. Guidelines for the management of chronic kidney disease in HIV-infected patients: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. *Clin Infect Dis.* 2005;40(11):1559-1585.

## CD4 T-CELL COUNT (Updated January 10, 2011)

The CD4 count serves as the major laboratory indicator of immune function in patients who have HIV infection. It is one of the key factors in deciding whether to initiate ART and prophylaxis for opportunistic infections, and it is the strongest predictor of subsequent disease progression and survival according to clinical trials and cohort studies *[1-2]*. A significant change (2 standard deviations) between two tests is approximately a 30% change in the absolute count or an increase or decrease in CD4 percentage by 3 percentage points.

- **Use of CD4 Count for Initial Assessment**. The CD4 count is one of the most important factors in the decision to initiate ART and/or prophylaxis for opportunistic infections. All patients should have a baseline CD4 count at entry into care **(AI)**. Recommendations for initiation of ART based on CD4 count are found in the **Initiating Antiretroviral Therapy in Antiretroviral-Naïve Patients** 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 *[3]*. Patients who initiate therapy with a low CD4 count or at an older age 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 ART in untreated patients, (2) assess immunologic response to ART, and (3) assess the need for initiation or discontinuation of prophylaxis for opportunistic infections **(AI)**.

The CD4 cell count response to ART varies widely, but a poor CD4 response is rarely an indication for modifying a virologically suppressive ARV regimen. In patients with consistently suppressed viral loads who have already experienced ART-related immune reconstitution, the CD4 cell count provides limited information, and frequent testing may cause unnecessary anxiety in patients with clinically inconsequential fluctuations. Thus, for the patient on a suppressive regimen whose CD4 cell count has increased well above the threshold for opportunistic infection risk, the CD4 count can be measured less frequently than the viral load. In such patients, CD4 count may be monitored every 6 to 12 months, unless there are changes in the patient's clinical status, such as new HIV-associated clinical symptoms or initiation of treatment with interferon, corticosteroids, or anti-neoplastic agents **(CIII)**.

**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 *[4-5]* or coinfection with human T-lymphotropic virus type I (HTLV-1) *[6]* may cause misleadingly elevated absolute CD4 counts. Alpha-interferon, on the other hand, may reduce the absolute CD4 number without changing the CD4 percentage *[7]*. In all these cases, CD4 percentage remains stable and may be a more appropriate parameter to assess the patient's immune function.

## References


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3. Kaufmann GR, Perrin L, Pantaleo G, et al. CD4 T-lymphocyte recovery in individuals with advanced HIV-1 infection receiving potent antiretroviral therapy for 4 years: the Swiss HIV Cohort Study. *Arch Intern Med.* 2003;163(18):2187-2195.
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## PLASMA HIV RNA TESTING (Updated January 10, 2011)

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 (ART) **(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 *[1]*. Thus, viral load testing serves as a surrogate marker for treatment response *[2]* and can be useful in predicting clinical progression *[3-4]*. 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.

Optimal viral suppression is generally defined as a viral load persistently below the level of detection (<20–75 copies/mL, depending on the assay used). However, isolated "blips" (viral loads transiently detectable at low levels, typically <400 copies/mL) are not uncommon in successfully treated patients and are not thought to represent viral replication or to predict virologic failure *[5]*. In addition, low-level positive viral load results (typically <200 copies/mL) appear to be more common with some viral load assays than others, and there is no definitive evidence that patients with viral loads quantified as <200 copies/mL using these assays are at increased risk for virologic failure *[6-8]*. For the purposes of clinical trials the AIDS Clinical Trials Group (ACTG) currently defines virologic failure as a confirmed viral load >200 copies/mL, which eliminates most cases of apparent viremia caused by blips or assay variability *[9]*. This definition may also be useful in clinical practice. (See **Virologic and Immunologic Failure**.)

For most individuals who are adherent to their antiretroviral (ARV) 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 longer 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 **(BIII)**.
- **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 **(BIII)**.
- **In Patients on a Stable ARV Regimen.** Viral load should be repeated every 3–4 months or as clinically indicated **(BII)**. Some clinicians may extend the interval to every 6 months for adherent patients who have suppressed viral loads for more than 2–3 years and whose clinical and immunologic status is stable **(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 **Drug Resistance Testing** and **Virologic and Immunologic Failure** **(AI)**.

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## DRUG-RESISTANCE TESTING (Updated January 10, 2011)

***Panel's Recommendations:***

- ***HIV drug-resistance testing is recommended for persons with HIV infection when they enter into care regardless of whether antiretroviral therapy (ART) will be initiated immediately or deferred (AIII). If therapy is deferred, repeat testing at the time of ART initiation should be considered (CIII).***
- ***Genotypic testing is recommended as the preferred resistance testing to guide therapy in antiretroviral (ARV)-naïve patients (AIII).***
- ***Standard genotypic drug-resistance testing in ARV-naïve persons involves testing for mutations in the reverse transcriptase (RT) and protease (PR) genes. If transmitted integrase strand transfer inhibitor (INSTI) resistance is a concern, providers may wish to supplement standard genotypic resistance testing with genotypic testing for resistance to this class of drug (CIII).***
- ***HIV drug-resistance testing should be performed to assist in the selection of active drugs when changing ARV regimens in persons with virologic failure and 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).***
- ***Drug-resistance testing should also be performed when managing suboptimal viral load reduction (AII).***
- ***In persons failing INSTI-based regimens, genotypic testing for INSTI resistance should be considered to determine whether to include a drug from this class in subsequent regimens (BIII).***
- ***Drug-resistance testing in the setting of virologic failure should be performed while the person is taking prescribed ARV drugs or, if not possible, within 4 weeks after discontinuing therapy (AII).***
- ***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 to genotypic testing is generally preferred for persons with known or suspected complex drug-resistance mutation patterns, particularly to protease inhibitors (PIs) (BIII).***
- ***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).***

***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***

### *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 reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). Testing for integrase and fusion inhibitor resistance can also be ordered separately from several commercial laboratories. No genotypic assays for assessing resistance to CCR5 antagonists are currently commercially available for clinical use in the United States. (See **Coreceptor Tropism Assays**.)

#### Genotypic Assays

Genotypic assays detect drug-resistance mutations present in relevant viral genes. Most genotypic assays involve sequencing of the RT and PR genes to detect mutations that are known to confer drug resistance. Genotypic assays that assess mutations in the integrase and gp41 (envelope) genes are 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 ARV 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 RT, PR, 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 tools 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 ARV drugs. RT and PR 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 viral replication by 50% (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. As a consequence, the proportion of virus with resistance mutations decreases 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 ARV 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 ARV 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 ART *[16-19]*. The likelihood that a patient will acquire drug-resistant virus is related to the prevalence of drug resistance in HIV-infected 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 ARV 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 *[16, 24]*.

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)** and a genotypic assay is preferred **(AIII)**. In this setting, treatment initiation should not be delayed by pending resistance testing results. Once results are obtained, the treatment regimen can be modified if warranted by the results. (See **Acute HIV Infection**.) 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 *[26-28]*. Therefore, if therapy is deferred, 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 ART, repeat resistance testing at the time treatment is started should be considered **(CIII)**.

Performing drug-resistance testing before ART initiation 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 *[29-31]*. 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, 32-34]*. In addition, a cost-effectiveness analysis of early genotypic resistance testing suggests that baseline testing in this population should be performed *[35]*. 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 ART should be considered because the patient may have acquired drug-resistant virus (i.e., superinfection) **(CIII)**.

Standard genotypic drug-resistance testing in ARV-naïve persons involves testing for mutations in the RT and PR genes. Although transmission of INSTI-resistant virus has rarely been reported, as use of INSTIs increases, the potential for transmission of INSTI-resistant virus may also increase. Therefore, providers may wish to supplement standard baseline genotypic resistance testing with genotypic testing for resistance to this class of drugs **(CIII).**

### Use of Resistance Assays in the Event of Virologic Failure

Resistance assays are useful in guiding decisions for patients experiencing virologic failure while on ART. Several prospective studies assessed the utility of resistance testing in guiding ARV drug selection in patients with virologic failure. These studies involved genotypic assays, phenotypic assays, or both *[6, 36-42]*. 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 *[43]*. Thus, resistance testing appears to be a useful tool in selecting active drugs when changing ARV regimens for virologic failure in persons with HIV RNA >1,000 copies/mL **(AI)**. (See **Virologic and Immunologic Failure**.) In persons with >500 but <1,000 copies/mL, testing may be unsuccessful but should still be considered **(BII)**. Drug-resistance testing is not usually recommended in persons with a plasma viral load <500 copies/mL because resistance assays cannot be consistently performed given low HIV RNA levels **(AIII)**.

Resistance testing also can help guide treatment decisions for patients with suboptimal viral load reduction **(AII)**. Virologic failure in the setting of combination ART is, for certain patients, associated with resistance to only one component of the regimen *[44-46]*. In that situation, substituting individual drugs in a failing regimen might be possible, although this concept will require clinical validation. (See **Virologic and Immunologic Failure**.)

Genotypic testing is generally preferred for virologic failure or suboptimal viral load reduction in persons failing their first or second ARV 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 to genotypic testing is generally preferred for persons with known or suspected complex drug-resistance mutation patterns, particularly to PIs **(BIII)**.

In patients failing INSTI-based regimens, testing for INSTI resistance should be considered to determine whether to include drugs from this class in subsequent regimens; genotypic testing is preferred **(BIII)**. Although it is not a drug-resistance assay, a coreceptor tropism assay should be performed whenever the use of a CCR5 antagonist is being considered **(AI)**. Coreceptor tropism testing should also be considered for patients who exhibit virologic failure on a CCR5 antagonist **(CIII)**. However, such testing may be of limited value because the absence of detectable CXCR4-

using virus does not exclude the possibility that CCR5 antagonist resistance may have developed. Assays for resistance to CCR5 inhibitors are not yet commercially available *[47]*. (See **Coreceptor Tropism Assays**.)

### Use of Resistance Assays in Pregnant Women

In pregnant women, the goal of ART is to maximally reduce plasma HIV RNA to provide appropriate maternal therapy and prevent mother-to-child transmission (MTCT) 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 **(AI)**. Phenotypic testing may provide additional information in those found to have complex drug-resistance mutation patterns, particularly to PIs **(BIII)**. Optimal prevention of perinatal transmission may require initiation of ART while results of resistance testing are pending. Once the results are available, the ARV regimen can be changed as needed.

## Table 4. Recommendations for Using Drug-Resistance Assays (Updated January 10, 2011)



| Clinical Setting/Recommendation | Rationale |
|---|---|
| **Drug-resistance assay recommended** | |
| **In acute HIV infection:** Drug-resistance testing is recommended regardless of whether ART is initiated immediately or deferred **(AIII)**. A genotypic assay is generally preferred **(AIII)**. | If ART 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 to modify or change regimens if results are obtained subsequent to treatment initiation.<br><br>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 ART is deferred, repeat resistance testing should be considered at the time therapy is initiated **(CIII)**. A genotypic assay is generally preferred **(AIII)**. | If ART 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 ART is initiated should be considered because the patient may have acquired a drug-resistant virus (i.e., superinfection). |
| **In ART-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 prior to the initiation of ART **(CIII)**. A genotypic assay is generally preferred **(AIII)**. | Repeat testing prior to initiation of ART should be considered because the patient may have acquired a drug-resistant virus (i.e., a superinfection).<br><br>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 an INSTI is considered for an ART-naïve patient and transmitted INSTI resistance is a concern, providers may wish to supplement standard resistance testing with a specific INSTI genotypic resistance assay **(CIII)**. | Standard genotypic drug-resistance assays test only for mutations in the RT and PR genes. |

**Table 4. Recommendations for Using Drug-Resistance Assays**
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| Clinical Setting/Recommendation | Rationale |
|---|---|
| **In patients with virologic failure:** Drug-resistance testing is recommended in persons on combination ART 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 ARV drugs or, if not possible, within 4 weeks after discontinuing therapy. |
| A standard genotypic resistance assay is generally preferred for those experiencing virologic failure on their first or second regimens **(AIII)**. | 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. |
| In patients failing INSTI-based regimens, genotypic testing for INSTI resistance should be considered to determine whether to include drugs from this class in subsequent regimens **(BIII)**. | Standard genotypic drug-resistance assays test only for mutations in the RT and PR genes. |
| Addition of phenotypic assay to genotypic assay is generally preferred for those with known or suspected complex drug-resistance patterns, particularly to PIs **(BIII)**. | Phenotypic testing can provide useful additional information for those with complex drug-resistance mutation patterns, particularly to PIs. |
| **In patients with suboptimal suppression of viral load:** Drug-resistance testing is recommended for persons with suboptimal suppression of viral load after initiation of ART **(AII)**. | Testing can help determine the role of resistance and thus assist the clinician 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 ART **(AIII)** and for those entering pregnancy with detectable HIV RNA levels while on therapy **(AI)**. | The goal of ART in HIV-infected pregnant women is to achieve maximal viral suppression for treatment of maternal HIV infection and for prevention of perinatal transmission of HIV. 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 ARV 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 (ABC)-containing regimen to reduce the risk of hypersensitivity reaction (HSR) (AI).***
- ***HLA-B*5701-positive patients should not be prescribed ABC (AI).***
- ***The positive status should be recorded as an ABC allergy in the patient's medical record (AII).***
- ***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 HSR (CIII).***

***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 ABC HSR is a multiorgan clinical syndrome typically seen within the initial 6 weeks of ABC 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 ABC. Discontinuing ABC usually promptly reverses HSR, whereas subsequent rechallenge can cause a rapid, severe, and even life-threatening recurrence *[1]*.

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 major histocompatibility complex (MHC) class I allele HLA-B*5701 *[2-3]*. Because the clinical criteria used for ABC HSR are overly sensitive and may lead to false-positive ABC HSR diagnoses, an ABC skin patch test (SPT) was developed as a research tool to immunologically confirm ABC HSR *[4]*. A positive ABC SPT is an ABC-specific delayed HSR 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 *[5]*. The ABC SPT could be falsely negative for some patients with ABC HSR and, at this point, is not recommended for use as a clinical tool. The PREDICT-1 study randomized patients before starting ABC either to be prospectively screened for HLA-B*5701 (with HLA-B*5701–positive patients not offered ABC) or to standard of care at the time of the study (i.e., no HLA screening, with all patients receiving ABC) *[6]*. 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 and 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 of ABC HSR (100% sensitivity in black and white populations) *[7]*.

On the basis of the results of these studies, the Panel recommends screening for HLA-B*5701 before starting patients on an ABC-containing regimen **(AI)**. HLA-B*5701–positive patients should not be prescribed ABC **(AI)**, and the positive status should be recorded as an ABC allergy in the patient's medical record **(AII)**. HLA-B*5701 testing is needed only once in a patient's lifetime; thus, efforts to carefully record and maintain the test 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 January 10, 2011)

***Panel's Recommendations:***

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

***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***

HIV enters cells by a complex process that involves 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]*. CCR5 inhibitors (i.e., maraviroc [MVC]), 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 MVC, 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 (ARV)-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 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 MVC 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 *[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. In patients with plasma HIV-1 RNA below the limit of detection, coreceptor usage can be determined from proviral DNA obtained from peripheral blood mononuclear cells; however, the clinical utility of this assay remains to be determined *[11]*.

### *Genotypic Assays*

Genotypic determination of HIV-1 coreceptor usage is based on sequencing the V3-coding region of HIV-1 *env*, the principal determinant of coreceptor usage. A variety of algorithms and bioinformatics programs can be used to predict coreceptor usage from the V3 sequence. When compared to the phenotypic assay, genotypic methods show high specificity (~90%) but only modest sensitivity (~50%–70%) for the presence of a CXCR4-utilizing virus. Given these performance characteristics, these assays may not be sufficiently robust to completely rule out the presence of an X4 or D/M variant *[12]*.

Recent studies in which V3 genotyping was performed on samples from patients screening for clinical trials of MVC suggest that genotyping performed as well as phenotyping in predicting the response to MVC *[13-14]*. On the basis of these data, accessibility, and cost, European guidelines currently favor genotypic testing for determining coreceptor usage. An important caveat to these results is that the majority of patients who received MVC were first shown to have R5 virus by a phenotypic assay (*Trofile*). Consequently, the opportunity to assess treatment response to MVC in patients whose virus was considered R5 by genotype but D/M or X4 by phenotype was limited to a relatively small number of patients. It is also important to note that the genotyping approaches used in these studies are not routinely available from clinical laboratories in the United States at this time.

Given the uncertainty regarding the genotypic assays and fewer logistical barriers to obtaining a phenotype in the United States than elsewhere, the Panel recommends that a phenotype be used as the preferred coreceptor tropism screening test in the United States.

### *Use of Coreceptor Tropism Assays in Clinical Practice*

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

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

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# Treatment Goals (Updated January 10, 2011)

Eradication of HIV infection cannot be achieved with available antiretroviral (ARV) regimens even when new, potent drugs are added to a regimen already suppressing plasma viral load below the limits of detection with commercially available assays *[1]*. This is chiefly because the pool of latently infected CD4 T-cells is established during the earliest stages of acute HIV infection *[2]* and persists with a long half-life, despite prolonged suppression of plasma viremia *[3-7]*. Therefore the primary goals for initiating antiretroviral therapy (ART) are to:

- reduce HIV-associated morbidity and prolong the duration and quality of survival,
- restore and preserve immunologic function,
- maximally and durably suppress plasma HIV viral load (see **Plasma HIV RNA Testing**), and
- prevent HIV transmission.

Adoption of treatment strategies recommended in these guidelines has reduced HIV-related morbidity and mortality *[8-11]* and has reduced perinatal *[12]* and, probably, behavior-associated transmission of HIV *[13-16]*. HIV suppression with ART may also decrease inflammation and immune activation thought to contribute to higher rates of cardiovascular and other end-organ damage reported in HIV-infected cohorts. (See **Initiating Antiretroviral Therapy**.) 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 *[17-18]*.

Achieving viral suppression requires the use of ARV regimens with at least two, and preferably three, active drugs from two or more drug classes. Baseline resistance testing and patient characteristics should guide the specific regimen design. (See **What to Start: Initial Combination Regimens for the Antiretroviral-Naïve Patient**.) When initial suppression is not achieved or is lost, rapidly changing to a new regimen with at least two active drugs is required. (See **Virologic and Immunologic Failure**.) The increasing number of drugs and drug classes makes viral suppression below detection limits an appropriate goal in all patients, even those with primary or acquired drug resistance.

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

- high potency of ARV regimen,
- excellent adherence to treatment regimen *[19]*,
- low baseline viremia *[20]*,
- higher baseline CD4 count (>200 cells/mm$^3$) *[21]*, and
- rapid reduction of viremia in response to treatment *[20, 22]*.

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 *[23]*.

## 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 ARV regimens are recommended for use. (See **What to Start**.) Many of these regimens have comparable efficacy but vary to some degree in dosing frequency and symmetry, pill burden, drug interactions, and potential side effects. A regimen should be tailored to each patient to enhance adherence and thus improve long-term treatment success. Individual regimen choice 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 6%–16% prevalence of HIV drug resistance in ART-naïve patients *[24-28]*, and some studies suggest that the presence of transmitted drug-resistant viruses may lead to suboptimal virologic responses *[29]*. Therefore, pretreatment genotypic resistance testing should be used to guide selection of the most optimal initial ARV regimen. (See **Drug-Resistance Testing**.)

### *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 access to medication and inadequate treatment education and support. Conditions that promote adherence should be maximized prior to and after initiation of ART. (See **Adherence to Antiretroviral Therapy**.)

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# Initiating Antiretroviral Therapy in Treatment-Naïve Patients (Updated January 10, 2011)

***Panel's Recommendations:***

- ***Antiretroviral therapy (ART) should be initiated in all patients with a history of an AIDS-defining illness or with a CD4 count <350 cells/mm$^3$ (AI).***
- ***ART is also recommended for patients with CD4 counts between 350 and 500 cells/mm$^3$ (A/B$^*$-II).***
- ***ART should be initiated, regardless of CD4 count, in patients with the following conditions: HIV-associated nephropathy (HIVAN) (AII) and hepatitis B virus (HBV) coinfection when treatment of HBV is indicated (AIII).***
- ***A combination antiretroviral (ARV) drug regimen is also recommended for pregnant women who do not meet criteria for treatment with the goal to prevent perinatal transmission (AI).***
- ***For patients with CD4 counts >500 cells/mm$^3$, Panel members are evenly divided: 50% favor starting ART at this stage of HIV disease (B); 50% view initiating therapy at this stage as optional (C) (B/C-III).***
- ***Patients initiating ART should be willing and able to commit to lifelong treatment and should understand the benefits and risks of therapy and the importance of adherence (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***

$^*$ ***Panel members are divided on the strength of this recommendation: 55% voted for strong recommendation (A) and 45% voted for moderate recommendation (B).***

The primary goal of ART is to reduce HIV-associated morbidity and mortality. This is best accomplished by using ART 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 ART, 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 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 ART in patients with CD4 counts ≤350 cells/mm$^3$. 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 ART in reducing AIDS- and non-AIDS-associated morbidity and mortality, the Panel now recommends ART 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 ART 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 ART 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 ARV regimens that are more effective, more convenient, and better tolerated than ARV combinations no longer in use; and (4) increasing evidence that effective ART reduces HIV transmission **(BIII)**.

The other 50% of the Panel members feel that current evidence does not definitively demonstrate clear benefit of ART 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 ART, 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 ART 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 ART improves survival and delays disease progression in these patients *[1-3]*. Long-term data from multiple observational cohort studies evaluating earlier ART (>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 ART at CD4 counts of 200–350 cells/mm$^3$ or to defer treatment until their CD4 counts 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 ART with CD4 counts of 200–350 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 multinational trial enrolling more than 5,400 participants with CD4 counts >350 cells/mm$^3$. Participants were randomized to continuous ART or to treatment interruption until CD4 count dropped to <250 cells/mm$^3$. In a subgroup analysis involving the 249 study participants who were ART 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 ART 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 cells/mm$^3$ to provide data that directly address the question of when to start therapy in patients with CD4 counts of 350–500 cells/mm$^3$. 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% confidence interval [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 counts were <350 cells/mm$^3$ had an increased risk of death compared with 2,084 patients who initiated therapy with CD4 counts 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 to <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 initiation of ART in patients with CD4 counts between 350 and 500 cells/mm$^3$. Panel members are 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 counts >500 cells/mm$^3$ or after CD4 counts dropped below this threshold. The adjusted mortality rates were significantly higher among the 6,935 patients who deferred therapy until CD4 count fell to <500 cells/mm$^3$ compared with rates in the 2,200 patients who started therapy while CD4 count was > 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 ART.

In contrast, analysis of the ART-CC cohort failed to identify a benefit for patients initiating ART with CD4 counts > 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 <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 ART in HIV-infected persons with a CD4 count >500 cells/mm$^3$ **(BIII)**.

The other 50% of the Panel members are reluctant to broadly recommend starting ART 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 that concerns remain over the unknown overall benefit and long-term risks with earlier treatment.

When discussing starting ART 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 ART, 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]*. ART 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)**.

### Coinfection 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]*. ART may attenuate liver disease progression in persons coinfected with HBV and/or HCV by preserving or restoring immune function and reducing HIV-related immune activation and inflammation *[25-27]*. ARV drugs active against both HIV and HBV (e.g., tenofovir disoproxil fumarate [TDF], lamivudine [3TC], emtricitabine [FTC]) may also prevent the development of significant liver disease by directly suppressing HBV replication *[28-29]*. Although ARV 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 ARV-induced liver injury; however, the majority of coinfected persons do not develop clinically significant liver injury, particularly those receiving recommended ARV regimens *[31-33]*. Some studies suggest that the rate of hepatotoxicity is greater in persons with more advanced HIV disease. Nevirapine (NVP) 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, ART 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]*. Studies link exposure to specific ARV 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 ART 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 ART *[46]*. In other studies, ART 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

*[42, 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 ART 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 ART 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 *[42, 47, 50-53]*. The ANRS C04 Study 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 ART 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, human papilloma virus [HPV], Epstein-Barr virus [EBV], human herpes virus-8 [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 ART 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 malignancies **(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 ART 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 ART *[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 ARV 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 ART **(CIII)**.

### Age and treatment-related immune reconstitution

The CD4 cell response to ART 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 HIV 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]*. ART 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 ART 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 the degree of residual inflammation and/or T-cell dysfunction during ART appears to be 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 ART reduces transmission of HIV. The most dramatic and well-established example of this effect is the use of ART in pregnant women to prevent mother-to-child transmission (MTCT) 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 ART during pregnancy has reduced the HIV transmission rate from approximately 20%–30% to <2% *[81]*. Thus, use of combination ARV drug regimens is recommended for all HIV-infected pregnant women to prevent MTCT of HIV **(AI)**, even if the mother does not meet the criteria for initiation of therapy for treatment of her HIV infection. Following delivery, considerations regarding continuation of the ARV regimen for maternal therapeutic indications are the same as for other nonpregnant individuals. For detailed recommendations, see ***Perinatal Guidelines*** *[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 ART, suggest that suppression of viremia in ART-adherent patients with no concomitant sexually transmitted infections (STIs) substantially reduces the risk of HIV transmission *[88-93]*. Based on these studies, the use of effective ART 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 ART, there are also potential limitations to this approach. Concerns about long-term toxicity and the development of ARV resistance have served as a rationale for the deferral of HIV therapy. Earlier initiation of ART 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 ART for most patients.

Although newer ARV 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 ART initiation at CD4 counts >350 cells/$mm^3$ (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 ART remain.

### *Antiretroviral Drug Toxicities and Quality of Life*

Earlier initiation of ART extends exposure to ARV 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 nucleoside reverse transcriptase inhibitor (NRTI) and protease inhibitor (PI) classes *[38, 94]*. In the SMART study, continuous exposure to ART has been associated with significantly greater loss of bone density compared with interruption or deferral of therapy *[46]*. There may be unknown complications related to cumulative use of ARV drugs for many decades. A list of known ARV-associated toxicities can be found in **Adverse Effects of Antiretroviral Agents**.

Although ART 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 ARV drugs now used in first-line regimens can cause side effects that may reduce quality of life. Efavirenz (EFV), for example, can cause neurocognitive or psychiatric side effects, and all the PIs 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 regimens if treatment is initiated far in advance of an immediate risk of HIV-associated morbidity and mortality. The greater convenience and potency of current ARV regimens facilitate adherence and reduce the risk of ARV 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 poor adherence, such as untreated major psychiatric disorders, active substance abuse, social circumstances, patient concerns about side effects, and poor adherence to clinic visits, have been identified. 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 **Adherence.**

### *Cost*

Although ART 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 non-ARV drugs and hospitalization. However, no cost comparisons have been reported between those starting ART 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 ARV drugs in patients with higher CD4 counts. 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:

- ART should be initiated in all patients with a history of an AIDS-defining illness or with a CD4 count of <350 cells/mm$^3$ **(AI)**.
- ART is also recommended for patients with CD4 counts between 350 and 500 cells/mm$^3$ **(A/B-II)**.*
- ART should also be initiated, regardless of CD4 count, in patients with the following conditions: HIVAN **(AII)** and HBV coinfection when treatment of HBV is indicated **(AIII)**.
- A combination ARV drug regimen is also recommended for pregnant women who do not meet criteria for treatment with the goal to prevent perinatal transmission **(AI)**.
- For patients with CD4 counts >500 cells/mm$^3$, 50% of the Panel members favor starting ART (B); the other 50% of members view treatment as optional (C) in this setting **(B/C-III)**.
- Patients initiating ART should be willing and able to commit to lifelong treatment and should understand the benefits and risks of therapy and the importance of adherence (**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.

* The Panel is divided on the strength of this recommendation: 55% of Panel members voted for strong recommendation **(A)** and 45% voted for moderate recommendation **(B)**.

### *Conditions Favoring More Rapid Initiation of Therapy*

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

- Pregnancy **(AI)** (Clinicians should refer to the ***Perinatal Guidelines*** for more detailed recommendations for the management of HIV-infected pregnant women.) *[82]*
- 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)**
- HIVAN **(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 ART may improve outcomes by improving immune responses, the benefits of ART 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 ART *[101-102]* **(CIII)**.

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

In patients who have active tuberculosis, initiating ART within the first 1–2 months of treatment for tuberculosis appears to confer a significant survival advantage *[103-104]*. (See ***Mycobacterium Tuberculosis* Disease with HIV Coinfection**.)

Clinicians should refer to the ***Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents*** *[105]* for more detailed discussion on when to initiate ART 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 to adherence are being addressed. However, increased urgency for ART (see above) may override potential predictors of poor adherence.

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 ART 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 ART.
- Patients taking medications that have clinically significant drug interactions with ART and for whom alternative therapy is not available.

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

There are some less common situations in which ART 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 gain survival or quality-of-life benefits from ART. 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 ART 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 ART. However, it should be noted that ART 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 ARV-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 ART. However, some nonprogressors have high viral loads, and 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 diagnosed 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 Centers for Disease Control and Prevention (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 *[113-116]*. 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

The current recommendations are based on increasing evidence that supports earlier initiation of ART than was advocated in previous guidelines. The strength of the recommendations varies with the quality and availability of existing evidence. 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 January 10, 2011)

***Panel's Recommendations:***

- ***The Panel recommends the following as preferred regimens for antiretroviral (ARV)-naïve patients:***
  - ***efavirenz/tenofovir/emtricitabine (EFV/TDF/FTC) (AI)***
  - ***ritonavir-boosted atazanavir + tenofovir/emtricitabine (ATV/r + TDF/FTC) (AI)***
  - ***ritonavir-boosted darunavir + tenofovir/emtricitabine (DRV/r + TDF/FTC) (AI)***
  - ***raltegravir + tenofovir/emtricitabine (RAL + TDF/FTC) (AI)***
- ***A list of Panel-recommended alternative and acceptable regimens can be found in Table 5a and Table 5b.***
- ***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.***

***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***

There are more than 20 approved ARV 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 (INSTIs).

The Panel provides recommendations for preferred, alternative, and acceptable regimens; regimens that may be acceptable but more definitive data are needed; and regimens that may be acceptable but should be used with caution (**Tables 5a and 5b**). Potential advantages and disadvantages of the components recommended as initial therapy for ARV-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**.

## CONSIDERATIONS WHEN SELECTING A FIRST ANTIRETROVIRAL REGIMEN FOR ANTIRETROVIRAL THERAPY-NAÏVE PATIENTS

### *Data Used for Making Recommendations*

The Panel reviews clinical trial data published in peer-reviewed journals and data prepared by manufacturers for Food and Drug Administration (FDA) review. In selected cases, data presented in abstract format in major scientific meetings also are reviewed. The first criterion for selection is published information from a randomized, prospective clinical trial with an adequate sample size that demonstrates durable viral suppression and immunologic enhancement (as evidenced by increase in CD4 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, alternative, or acceptable ratings in **Tables 5a and 5b**. "Preferred regimens" are those studied in randomized controlled trials and shown to have optimal and durable virologic efficacy, favorable tolerability and toxicity profiles, and ease of 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 may actually be the preferred regimen in certain situations. Some regimens are classified as "Acceptable Regimens" because of reduced virologic activity, lack of efficacy data from large clinical trials, or other factors (such as greater toxicities, requiring additional testing, pill burden, or drug interaction potential) compared with preferred or alternative regimens.

Lastly, the Panel classified several regimens as "regimens that are acceptable but should be used with caution" because of some safety or efficacy concerns explained in **Table 5b.**

### *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 count if considering nevirapine (NVP);
- HLA-B*5701 testing if considering abacavir (ABC);
- coreceptor tropism assay if considering maraviroc (MVC);
- 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 ARV agents can be found in **Appendix B, Tables 1–6**. Additionally, **Appendix B, Table 7** provides clinicians with ARV dosing recommendations for patients who have renal or hepatic insufficiency.

Possible regimens include combinations of two NRTIs with an NNRTI, a PI (preferably boosted with ritonavir [RTV]), an INSTI (namely raltegravir [RAL]) or a CCR5 antagonist (namely MVC). In clinical trials, NNRTI-, PI-, INSTI-, or CCR5 antagonist-based regimens have all resulted in suppression of HIV RNA levels and CD4 cell increases in a large majority of patients *[1-7]*. Some comparative data are available. (See below.)

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

# Table 5a. Preferred and Alternative Antiretroviral Regimens for Antiretroviral Therapy-Naïve Patients (Updated January 10, 2011)

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 ARV 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)<br>**The preferred regimens for nonpregnant patients are arranged by order of FDA approval of components other than nucleosides, thus, by duration of clinical experience.** | |
|---|---|
| **NNRTI-Based Regimen**<br>• EFV/TDF/FTC[1] **(AI)**<br><br>**PI-Based Regimens** *(in alphabetical order)*<br>• ATV/r + TDF/FTC[1] **(AI)**<br><br>• DRV/r (once daily) + TDF/FTC[1] **(AI)**<br><br>**INSTI-Based Regimen**<br>• RAL + TDF/FTC[1] **(AI)**<br><br>**Preferred Regimen[2] for Pregnant Women**<br>• LPV/r (twice daily) + ZDV/3TC[1] **(AI)** | **Comments**<br>**EFV** should not be used during the first trimester of pregnancy or in women trying to conceive or not using effective and consistent contraception.<br><br>**ATV/r** should not be used in patients who require >20 mg omeprazole equivalent per day. Refer to **Table 15a** 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)*<br>• EFV + (ABC or ZDV)/3TC[1] **(BI)**<br><br>• NVP + ZDV/3TC[1] **(BI)**<br><br>**PI-Based Regimens** *(in alphabetical order)*<br>• ATV/r + (ABC or ZDV)/3TC[1] **(BI)**<br><br>• FPV/r (once or twice daily) + either [(ABC or ZDV)/3TC[1]] or TDF/FTC[1] **(BI)**<br><br>• LPV/r (once or twice daily) + either [(ABC or ZDV)/3TC[1]] or TDF/FTC[1] **(BI)** | **Comments**<br>**NVP**<br>• NVP should not be used in patients with moderate to severe hepatic impairment (Child-Pugh B or C)[3]<br>• NVP should not be used in women with pre-ARV CD4 count >250 cells/mm$^3$ or men with pre-ARV CD4 count >400 cells/mm$^3$.<br><br>**ABC**<br>• ABC should not be used in patients who test positive for HLA-B*5701.<br>• Use ABC with caution in patients with high risk of cardiovascular disease or with pretreatment HIV RNA >100,000 copies/mL. (See text.)<br><br>**Once-daily LPV/r** is not recommended in pregnant women. |

[1]3TC may substitute for FTC or vice versa.
[2]For more detailed recommendations on ARV use in an HIV-infected pregnant woman, refer to the ***Perinatal Guidelines*** available at **http://aidsinfo.nih.gov/guidelines**.
[3]Refer to **Appendix B, Table 7** for the criteria for Child-Pugh classification.

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.

**Acronyms**: 3TC = lamivudine, ABC = abacavir, ATV = atazanavir, ATV/r = atazanavir/ritonavir, DRV = darunavir, DRV/r = darunavir/ritonavir, EFV = efavirenz, FPV = fosamprenavir, FPV/r = fosamprenavir/ritonavir, FTC = emtricitabine, INSTI = integrase strand transfer inhibitor, LPV = lopinavir, LPV/r = lopinavir/ritonavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleos(t)ide reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, RAL = raltegravir, TDF = tenofovir, ZDV = zidovudine

## Table 5b. Acceptable Antiretroviral Regimens for Treatment-Naïve Patients (Updated January 10, 2011)

| **Acceptable Regimens (CI)** (Regimens that may be selected for some patients but are less satisfactory than preferred or alternative regimens) **and Regimens that may be Acceptable but more definitive data are needed (CIII)** | |
|---|---|
| **NNRTI-Based Regimen**<br>• EFV + ddI + (3TC or FTC) **(CI)**<br><br>**PI-Based Regimens**<br>• ATV + (ABC or ZDV)/3TC[1] **(CI)**<br>• DRV/r + (ABC or ZDV)/3TC[1] **(CIII)**<br><br>**INSTI-Based Regimen**<br>• RAL + (ABC or ZDV)/3TC[1] **(CIII)**<br><br>**CCR5 Antagonist-Based Regimens**<br>• MVC + ZDV/3TC[1] **(CI)**<br>• MVC + TDF/FTC[1] or ABC/3TC[1] **(CIII)** | **Comments**<br>**EFV + ddI + (FTC or 3TC)** has only been studied in small clinical trials.<br><br>**ATV/r** is generally preferred over ATV. Unboosted ATV may be used when RTV boosting is not possible.<br><br>**MVC**<br>Tropism testing should be performed before initiation of therapy; only patients found to have only CCR5-tropic virus are candidates for MVC. |
| **Regimens that may be acceptable but should be used with caution** (Regimens that have demonstrated virologic efficacy in some studies but have safety, resistance, or efficacy concerns. See comments below.) | |
| **NNRTI-Based Regimens**<br>• NVP + ABC/3TC[1] **(CIII)**<br><br>• NVP + TDF/FTC[1] **(CIII)**<br><br>**PI-Based Regimens**<br>• FPV + [(ABC or ZDV)/3TC[1] or TDF/FTC[1]] **(CIII)**<br><br>• SQV/r + TDF/FTC[1] **(CI)**<br>• SQV/r + (ABC or ZDV)/3TC[1] **(CIII)** | **Comments**<br>Use **NVP** and **ABC** together with caution because both can cause HSRs within first few weeks after initiation of therapy.<br><br>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.<br><br>**FPV/r** is generally preferred over unboosted FPV. Virologic failure with unboosted FPV-based regimen may select mutations that confer cross resistance to DRV.<br><br>**SQV/r**<br>• SQV/r was associated with PR and QT prolongation in a healthy volunteer study.<br>• Baseline ECG is recommended before initiation of SQV/r.<br>• SQV/r is not recommended in patients with any of the following:<br>1. pretreatment QT interval >450 msec<br>2. refractory hypokalemia or hypomagnesemia<br>3. concomitant therapy with other drugs that prolong QT interval<br>4. complete AV block without implanted pacemaker<br>5. risk of complete AV block |

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

**Acronyms**: 3TC = lamivudine, ABC = abacavir, ATV = atazanavir, ATV/r = atazanavir/ritonavir, AV = atrioventricular, ddI = didanosine, DRV = darunavir, DRV/r = darunavir/ritonavir, ECG = electrocardiogram, EFV = efavirenz, FPV = fosamprenavir, FPV/r = fosamprenavir/ritonavir, FTC = emtricitabine, HSR = hypersensitivity reaction, INSTI = integrase strand transfer inhibitor, msec = millisecond, MVC = maraviroc, NNRTI = non-nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, RAL = raltegravir, RTV = ritonavir, SQV = saquinavir, SQV/r = saquinavir/ritonavir, TDF = tenofovir, ZDV = zidovudine

### *NNRTI- versus PI- versus INSTI- versus CCR5 Antagonist-Based Regimens*

EFV-based regimens have been compared with a variety of other regimens in clinical trials, including boosted or unboosted PI-based, RAL-based, and MVC-based regimens *[3-9]*. No regimen has proven superior to EFV-based regimens with respect to virologic responses.

*NNRTI- versus PI-Based Regimens*

RTV-boosted PI-based regimens have shown good virologic and immunologic responses but are often associated with more gastrointestinal symptoms, whereas EFV-based regimens are associated with more rash and central nervous system adverse effects. Both types of regimens may be associated with hepatic transaminase elevations *[10]*.

Drug resistance to most PIs requires multiple mutations in the HIV protease gene, and it seldom develops after early virologic failure *[11]*, especially when RTV boosting is used. Resistance to EFV or NVP, however, is conferred by a single mutation in the reverse transcriptase gene, and it develops rapidly after virologic failure *[11]*. An estimated 8% of newly infected patients in the United States carry NNRTI-resistant viruses *[12]*. Because of the concern for primary resistance in the ART-naïve population, genotypic testing results should be used to guide the selection of the initial ARV regimen. (See **Drug-Resistance Testing**.) In terms of convenience, the coformulated tablet of TDF, FTC, and EFV allows for once-daily dosing with a single tablet. Most PI-based regimens include RTV, 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 with older PIs (for example, nelfinavir [NFV]or indinavir [IDV]). Drug-drug interactions are important with both kinds of regimens, but more clinically significant interactions are seen with RTV-boosted PI regimens.

*Other Treatment Options*

Another option for initial therapy is the combination of TDF, FTC, and RAL *[6]*. This combination has shown similar virologic efficacy as compared with a combination of TDF, FTC, and EFV up to 96 weeks *[13]* and is generally well tolerated. There are no clinical trial data comparing INSTI-based with PI-based regimens. RAL 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. MVC has been approved for use in ART-naïve patients, based on data from the MERIT study comparing MVC/zidovudine (ZDV)/lamivudine (3TC) with EFV/ZDV/3TC *[7]*.

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 [DLV], EFV, etravirine [ETR], and NVP) 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 ART-naïve patients *[12, 14-16]* and the low genetic barrier of NNRTIs for development of resistance. Resistance testing should be performed for ART-naïve patients to guide therapy selection. (See **Drug-Resistance Testing**.) The first three approved NNRTIs (i.e., DLV, EFV, NVP) require only a single mutation to confer resistance, and cross resistance affecting these three NNRTIs is common. ETR, an NNRTI approved for ART-experienced patients, has *in vitro* activity against some viruses with mutations that confer resistance to DLV, EFV, and NVP *[17]*.

On the basis of clinical trial results and safety data, the Panel recommends either EFV or NVP as the NNRTI for initial ART. In most instances, EFV is preferred, based on its potency and tolerability (as discussed below). EFV 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.

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

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

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

### *EFV as Preferred NNRTI*

Large randomized, controlled trials and cohort studies of ART-naïve patients have demonstrated potent viral suppression in EFV-treated patients; a substantial proportion of these patients had HIV RNA <50 copies/mL during up to 7 years of follow-up *[1-2, 18]*. Studies that compared EFV-based regimens with other regimens demonstrated the combination of EFV with two NRTIs was superior virologically to some PI-based regimens, including indinavir (IDV) *[3]*, ritonavir-boosted lopinavir (LPV/r) *[4]*, and nelfinavir (NFV) *[8]* and to triple-NRTI–based regimens of ABC, ZDV, and 3TC or ABC, TDF, and 3TC *[19-20]*. EFV-based regimens also had comparable virologic activity when compared with NVP- *[21-22]*, atazanavir (ATV)- *[5]*, RAL- *[6]*, or MVC-based *[7]* regimens.

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

The 2NN trial compared EFV with NVP, both given with stavudine (d4T) and 3TC, in ART-naïve patients. Virologic responses were similar for both drugs, although NVP was associated with greater toxicity and did not meet criteria for noninferiority compared with EFV *[21]*.

Two major limitations of EFV are its central nervous system adverse effects, which usually resolve over a few weeks, and its potential teratogenic effects. In animal reproductive studies, EFV caused major congenital anomalies in the central nervous system in nonhuman primates at drug exposure levels similar to those achieved in humans *[23]*. Several cases of neural tube defects in human newborns of mothers exposed to EFV during the first trimester of pregnancy have been reported *[24-25]*. Therefore, EFV is not recommended in pregnant women during the first trimester of pregnancy or in women with high pregnancy potential (women 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 EFV and dual-NRTI combinations (ABC, didanosine [ddI], d4T, TDF, or ZDV together with FTC or 3TC) show durable virologic activity, although there may be differences among the various combinations chosen. (See **Dual-NRTI Options**.) A single tablet coformulated with TDF, FTC, and EFV provides one-tablet, once-daily dosing and is currently the preferred NNRTI-based regimen **(AI)**.

### *NVP as Alternative NNRTI*

In the 2NN trial, 70% of participants in the EFV arm and 65.4% in the twice-daily NVP 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 NVP *[21]*. Two deaths were attributed to NVP use. One resulted from fulminant hepatitis and one from staphylococcal sepsis as a complication of Stevens-Johnson syndrome.

In a randomized controlled trial, NVP was found to be noninferior to boosted ATV when combined with TDF/FTC *[26]*. This study enrolled only women and men with CD4 counts <250 cells/mm$^3$ and <400 cells/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 ART-naïve participants who receive NVP plus TDF and either 3TC or FTC *[27-29]*. Pending published results from randomized trials, clinicians should closely monitor virologic responses if using this combination **(CIII)**.

Serious hepatic events have been observed when NVP was initiated in ART-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. Retrospective analysis of reported events suggests that women with higher CD4 counts appear to be at highest risk *[30-31]*. 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 NVP initiation compared with women with CD4 counts ≤250 cells/mm$^3$ (11.0% vs. 0.9%). An increased risk was also seen in men with pretreatment CD4 counts >400 cells/mm$^3$ compared with men with pretreatment CD4 counts ≤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 NVP *[31-32]*. In contrast, other studies have not shown an association between baseline CD4 counts and severe NVP hepatotoxicity *[33-34]*. Symptomatic hepatic events have not been reported with single-dose NVP given to mothers or infants for prevention of perinatal HIV infection.

On the basis of the earlier safety data, the Panel recommends that NVP may be considered as an alternative to EFV as initial therapy for women with pretreatment CD4 counts ≤250 cells/mm$^3$ or in men with CD4 counts ≤400 cells/mm$^3$. Patients who experience CD4 count increases to levels above these thresholds as a result of NVP-containing therapy can safely continue therapy without an increased risk of adverse hepatic events *[35]*.

At the initiation of NVP, a 14-day lead-in period at a dosage of 200 mg once daily should be instituted before increasing to the maintenance dosage of 200 mg twice daily. Some experts recommend monitoring serum transaminases at baseline, prior to and 2 weeks after dose escalation, and then monthly for the first 18 weeks. Clinical and laboratory parameters should be assessed at each visit.

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

### *Summary: PI-Based Regimens*

PI-based regimens have demonstrated more virologic potency and durability and higher barriers to resistance than NNRTI- and INSTI-based regimens. In patients who experience virologic failure while on 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 an ART-naïve patient, clinicians should consider factors such as dosing frequency, food requirements, pill burden, daily RTV dose, drug interaction potential, baseline lipid profile, toxicity profile of the individual PI, and pregnancy status. (See the ***Perinatal Guidelines*** for specific recommendations in pregnancy *[36]*.)

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 RTV used as a pharmacokinetic boosting agent. Some studies have suggested that LPV/r, IDV, fosamprenavir (FPV), or FPV/r may be associated with increased rates of myocardial infarction (MI) or stroke *[37-38]*. It should be noted that in both studies, there were too few patients receiving ATV/r or DRV/r to be included in the analysis. Ritonavir-boosted saquinavir (SQV/r) can prolong the PR and QT intervals on electrocardiogram (ECG). The degree of QT prolongation is greater than that seen with some other boosted PIs. Therefore, SQV/r should be used with caution in patients at risk of or who use concomitant drugs that may potentiate these ECG abnormalities *[39]*.

The potent inhibitory effect of RTV on the cytochrome P (CYP) 450 3A4 isoenzyme has allowed the addition of low-dose RTV to other PIs as a pharmacokinetic booster to increase drug exposure and prolong plasma half-life of the active PI. This allows for reduced dosing frequency and/or pill burden, which may improve overall adherence to the regimen. The increased trough concentration ($C_{min}$) may improve the ARV activity of the primary PI, which can be beneficial when the patient harbors HIV strains with reduced susceptibility to the PI *[40-42]* and also may contribute to the lower risk of resistance upon virologic failure compared with 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 RTV. In patients without pre-existing PI resistance, there is growing support for the use of once-daily

boosted PI regimens that use only 100 mg per day of RTV because they tend to cause fewer gastrointestinal side effects and less metabolic toxicity than regimens that use RTV at a dose of 200 mg per day. In the case of RTV-boosted darunavir (DRV) (800/100 mg once daily) and ATV (300/100 mg once daily), there are large head-to-head trials demonstrating noninferiority or superiority compared with LPV/r, with less gastrointestinal and lipid toxicity.

The Panel uses the following criteria to distinguish between preferred versus alternative PIs in ART-naïve patients: (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) RTV-boosted PI with no more than 100 mg of RTV per day; (3) once-daily dosing; (4) low pill count; and (5) good tolerability. Using these criteria, the Panel recommends ATV + RTV (once daily) **(AI)** and DRV + RTV (once daily) **(AI)** as preferred PIs.

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

**RTV-Boosted ATV (ATV/r).** RTV boosting of ATV, given as two pills once daily, enhances the concentrations of ATV and improves virologic activity compared with unboosted ATV in a clinical trial *[43]*.

The CASTLE study compared once-daily ATV/r with twice-daily LPV/r, each in combination with TDF/FTC, in 883 ARV-naïve participants. In this open-label, noninferiority study, analysis at 48 weeks *[44]* and at 96 weeks *[45]* showed similar virologic and CD4 responses of the two regimens. More hyperbilirubinemia and less gastrointestinal toxicity were seen in the ATV/r arm. This study supports the designation of ATV/r + TDF/FTC as a preferred regimen.

The main adverse effect associated with ATV/RTV is indirect hyperbilirubinemia, with or without jaundice or scleral icterus, but without concomitant hepatic transaminase elevations. Several cases of nephrolithiasis have also been reported in patients who received RTV-boosted or unboosted ATV *[46]*. ATV/RTV 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 ATV. **Table 15a** provides recommendations for how to use RTV-boosted ATV with these agents.

**RTV-Boosted DRV (DRV/r).** The ARTEMIS study compared DRV/r (800/100 mg once daily, three pills per day) with LPV/r (once or twice daily), both in combination with TDF/FTC, in a randomized, open-label, noninferiority trial. The study enrolled 689 ART-naïve participants. At 48 weeks, DRV/r was noninferior to LPV/r. The virologic response rates were lower in the LPV/r arm among those participants whose baseline HIV RNA levels were >100,000 copies/mL. Grades 2 to 4 adverse events, primarily diarrhea, were seen more frequently in LPV/r recipients *[47]*. At 96 weeks, virologic response to DRV/r was superior to response with LPV/r *[48]*.

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

**RTV-Boosted FPV (FPV/r) (once or twice daily).** FPV/r is recommended as an alternative PI. The KLEAN trial compared twice-daily FPV/r with LPV/r, each in combination with ABC and 3TC, in ART-naïve patients. At Weeks 48 and 144, similar percentages of subjects achieved viral loads of <400 copies/mL *[49-50]*. Clinical and laboratory adverse events did not differ between the regimens. In this study of ART-naïve participants, twice-daily FPV/r was noninferior to twice-daily LPV/r. In the KLEAN study, the occurrence of metabolic adverse effects was similar with boosted FPV and with LPV/r. Based on the above criteria for preferred PIs that favor once-daily regimens with no more than 100 mg/day of RTV, twice-daily FPV is now considered an alternative choice.

In a study comparing once-daily FPV/r (1,400 mg with RTV 200 mg once daily) with NFV *[51]*, similar virologic efficacy was reported in both arms. A comparative trial of once-daily FPV/r (1,400/100 mg) with once-daily ATV/r, both in combination with TDF/FTC, was conducted in 106 ARV-naïve participants *[52]*. Similar virologic and CD4 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, FPV/r regimens, with once- or twice-daily dosing, are recommended as alternatives.

**RTV-Boosted LPV (LPV/r) (coformulated) (BI).** LPV/r is the only available coformulated boosted PI. It can be given once or twice daily. However, the need for 200 mg/day of RTV, and the higher rate of gastrointestinal side

effects and hyperlipidemia when compared with boosted PIs using RTV 100 mg/day, make it an alternative rather than preferred PI for ART-naïve patients. Early studies showed that LPV/r was superior to NFV in maintaining suppressed viral loads *[53]*. A 7-year follow-up study of LPV/r and two NRTIs showed sustained virologic suppression in patients who were maintained on the originally assigned regimen *[54]*. Results of clinical trials that compared LPV/r with ATV/r, DRV/r, FPV/r, or SQV/r are discussed in the respective sections of this document. The ACTG 5142 study showed that the regimen of twice-daily LPV/r plus two NRTIs had decreased virologic efficacy when compared with EFV plus two NRTIs. However, the CD4 response was greater with LPV/r, and there was less drug resistance associated with virologic failure *[4]*.

Several trials have evaluated different formulations and dosages of LPV/r administered once or twice daily *[47, 55-56]*. In the largest trial that compared once-daily with twice-daily LPV/r, both in combination with TDF/FTC, 664 ART-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 *[57]*. At Week 48, 77% of once-daily and 76% of twice-daily LPV/r 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 LPV/r include insulin resistance and hyperlipidemia, especially hypertriglyceridemia; these required pharmacologic management in some patients. In the D:A:D and French observational cohorts, cumulative use of LPV/r was associated with a slightly increased risk of MI *[37-38]*. Once-daily LPV/r should not be used in patients who have HIV mutations associated with PI resistance because higher LPV trough levels may be required to suppress resistant virus. LPV/r given twice daily is the preferred PI for use in pregnant women *[36]*. Once-daily dosing should not be used in this situation, especially during the third trimester, when LPV levels are expected to decline. For more detailed information regarding ART drug choices and related issues in pregnancy, see the ***Perinatal Guidelines*** *[36]*.

### *Acceptable PI-Based Component*

**ATV**. Unboosted ATV is given once daily and has fewer adverse effects on lipid profiles than other available PIs. Three studies compared ATV-based combination regimens with either NFV- or EFV-based regimens. These studies established similar virologic efficacy among ATV 400 mg once daily and both comparator treatment groups in ARV-naïve patients after 48 weeks of therapy *[5, 43, 58-59]*. The ACTG 5175 trial compared three regimens in ART-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 ATV + enteric-coated ddI + FTC because of an inferior virologic response when compared with the other two arms—once-daily EFV plus either ZDV/3TC (twice daily) or TDF/FTC (once daily) *[60]*. If unboosted ATV is prescribed for an ART-naïve patient, clinicians should consider using a dual-NRTI backbone other than ddI + FTC (or 3TC).

Unboosted ATV may be an initial therapy for patients when a once-daily regimen without RTV is desired and for patients with underlying risk factors indicating that hyperlipidemia may be particularly undesirable. ATV should be used with RTV-boosting if TDF or EFV are used concomitantly because these two agents can lower the concentrations of ATV. ATV 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 ATV absorption. Proton pump inhibitors should not be used in patients who are taking unboosted ATV. $H_2$ antagonists and antacids should be used with caution and with careful dose separation. (See **Tables 14 and 15a**.)

### *PI Components that May be Acceptable but Should be Used with Caution (in alphabetical order, by active PI component)*

**FPV.** In a study comparing unboosted FPV given twice daily with NFV, more participants randomized to FPV achieved viral suppression at 48 weeks than participants assigned to NFV, and greater differences were seen in those who had pretreatment viral loads >100,000 copies/mL *[61]*. However, virologic failure on unboosted FPV may select for resistance mutations that confer cross resistance to DRV *[62-63]*, a PI with an important role in management of ART-experienced patients. As such, FPV/r is preferred over unboosted FPV, and the unboosted strategy should be used with caution.

**RTV-Boosted SQV (SQV/r).** The GEMINI study compared SQV/r (1,000/100 mg twice daily) with LPV/r, both given twice daily, in combination with TDF/FTC given once daily, in 337 ART-naïve participants who were monitored over 48 weeks. Similar levels of viral suppression and increases in CD4 counts were seen in both arms *[64]*. Triglyceride levels were higher in the LPV/r arm. The SQV/r regimen has a higher pill burden and requires twice-daily dosing and 200 mg of RTV. In a healthy volunteer study, SQV/r use was associated with increases in both QT and PR intervals. The degree of QT prolongation was greater than that seen with some other boosted PIs. Rare cases of torsades de pointes and complete heart block have been reported in post-marketing surveillance. Based on these findings, an ECG is recommended prior to initiation of SQV/r. SQV/r is not recommended for patients with any of the following conditions: documented congenital or acquired QT prolongation, pretreatment QT interval of >450 milliseconds (msec), refractory hypokalemia or hypomagnesemia, complete atrioventricular (AV) block without implanted pacemakers, at risk of complete AV block, or receiving other drugs that prolong QT interval *[39]*. Based on these restrictions and because there are several other preferred or alternative PI options, the Panel recommends that SQV/r may be acceptable but should be used with caution in selected ARV-naïve patients. (See **Table 5b** for rating.)

## INSTI-BASED REGIMENS (INSTI + 2 NRTIs)

**RAL.** RAL is an INSTI that is approved for use in ART-naïve patients, based on results of STARTMRK, a Phase III study that compared RAL (400 mg twice daily) with EFV (600 mg once daily), each in combination with TDF/FTC, in ART-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 RAL and EFV, respectively, p <0.001 for noninferiority). CD4 counts rose by 189 cells/$mm^3$ in the RAL group versus 163 cells/$mm^3$ in the EFV 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 *[13]*. Based on these data, the Panel recommends RAL + TDF/FTC (or 3TC) as a preferred regimen for ART-naïve patients **(AI)**.

Comparisons of RAL-based regimen with other regimens in ART-naïve subjects have not yet been reported, and there is less experience with RAL than with EFV or boosted PIs for initial therapy. In addition, RAL must be administered twice daily, a potential disadvantage when compared with some other regimens. RAL, like EFV, has a lower genetic barrier to resistance than RTV-boosted PIs, and resistance mutations were observed at approximately the same frequency in the comparative trial. RAL use with other dual NRTIs (such as ABC/3TC or ZDV/3TC) may be acceptable, but more definitive data for these regimens are needed **(CIII)**.

## CCR5 ANTAGONIST-BASED REGIMENS (CCR5-A + 2 NRTIs)

The MERIT study compared the CCR5 antagonist MVC with EFV, both in combination with ZDV/3TC, in a randomized, double-blinded trial in ART-naïve participants *[7]*. Only participants who had CCR5-tropic virus and had no evidence of resistance to any drugs used in the study were enrolled (n = 721). At 48 weeks, virologic suppression (defined as HIV RNA <400 copies/mL) was seen in 70.6% of MVC recipients and in 73.1% of EFV recipients, and HIV RNA <50 copies/mL was observed in 65.3% of MVC recipients and in 69.3% of EFV recipients. The HIV RNA <50 copies/mL results did not meet the criteria set by the investigators to demonstrate noninferiority for MVC in this study. CD4 count increased by an average of 170 cells/$mm^3$ in the MVC arm and by 144 cells/$mm^3$ in the EFV arm. Through 48 weeks, more participants discontinued MVC compared with EFV because of lack of efficacy (11.9% vs. 4.2%), whereas fewer participants discontinued MVC because of toxicity (4.2% vs. 13.6%). Follow-up results at 96 weeks demonstrated durable responses *[65]*. In a post-hoc reanalysis using a more sensitive viral tropism assay, 15% of patients with non-R5 screening virus were excluded from analysis, and their retrospective exclusion resulted in similar response rates in both arms, using either the HIV RNA criteria of <400 or <50 copies/mL. Based on the results, FDA approved MVC for use in regimens for ART-naïve patients. Because MVC requires twice-daily dosing, requires an expensive tropism assay prior to use, and there is little experience with regimens other than ZDV/3TC, the Panel recommends MVC + ZDV/3TC as an acceptable regimen for use in ART-naïve patients **(CI)**. Although the MERIT trial used ZDV/3TC as its NRTI backbone, many clinicians would favor the combination of MVC with TDF/FTC or ABC/3TC pending further data **(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 RTV), an INSTI, or a CCR5 antagonist. Most dual-NRTI combinations used in clinical practice consist of a primary NRTI plus 3TC or FTC. Both 3TC and FTC have few adverse effects but may select for the M184V resistance mutation, which confers high-level resistance to both drugs; a modest decrease in susceptibility to ddI and ABC; and improved susceptibility to ZDV, d4T, and TDF *[66]*.

All NRTIs except ddI can be taken without food restrictions. Adherence may be additionally improved with once-daily dosing (available for all NRTIs except d4T and ZDV) and with fixed-dosage combinations, such as ABC/3TC, TDF/FTC (with or without EFV), or ZDV/3TC.

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*

**TDF/FTC (coformulated).** TDF 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 TDF/FTC and TDF/FTC/EFV are both administered as one tablet once daily and are designed to improve adherence.

TDF, when used with either 3TC or FTC as part of an EFV-based regimen in ART-naïve patients, demonstrated potent virologic suppression *[18]* and was superior to ZDV/3TC in virologic efficacy up to 144 weeks *[67]*. In the 934 study, more participants in the ZDV/3TC arm developed loss of limb fat (as assessed by dual-energy x-ray absorptiometry [DXA]) and anemia at 96 and 144 weeks compared with the TDF/FTC arm *[67]*. Emergence of the M184V mutation was less frequent than with ZDV/3TC, and no participant had developed the K65R mutation after 144 weeks of therapy, in contrast to other studies in which TDF was combined with 3TC. TDF with FTC or 3TC has been studied in combination with several boosted PIs and RAL in randomized clinical trials; all such trials demonstrate good virologic benefit *[6, 44, 47, 52, 56]*.

TDF/FTC was compared with ABC/3TC in the ACTG 5202 study *[68]* and the HEAT trial *[69]*. Inferior virologic responses were observed in participants randomized to ABC/3TC who had a pretreatment HIV RNA >100,000 copies/mL. This was not confirmed by the results from the HEAT trial. (See the ABC/3TC section below for more detailed discussion.)

One randomized controlled trial found NVP to be noninferior to boosted ATV when combined with TDF/FTC *[26]*. Three small studies (n <100) have suggested more virologic failures than would be expected in ART-naïve participants who receive NVP plus TDF and either 3TC or FTC *[27-29]*. 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 TDF use *[70-71]*. Risk factors may include advanced HIV disease, greater treatment experience, and pre-existing renal impairment *[72]*. Renal function, urinalysis, and electrolytes should be monitored in patients who are on TDF. In patients who have some degree of pre-existing renal insufficiency (creatinine clearance [CrCl] <50 mL/min), TDF 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 ABC) may be preferred over dose-adjusted TDF in this setting.

TDF concentrations can be increased by some PIs, and studies have suggested a greater risk of renal dysfunction when TDF is used in PI-based regimens *[70, 73-76]*. TDF has been used in combination with PIs without renal toxicity in several clinical trials that involved patients who had CrCl >50–60 mL/min. Furthermore, in two randomized studies comparing TDF/FTC to ABC/3TC, participants receiving TDF/FTC experienced a significantly greater decline in bone mineral density *[77-78]*.

TDF plus either FTC or 3TC 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., 3TC or FTC) can lead to HBV resistance and is not recommended. (See **Hepatitis B (HBV)/HIV Coinfection**.)

### *Alternative Dual NRTIs (in alphabetical order)*

**ABC/3TC (coformulated) for Patients Who Test Negative for HLA-B*5701.** ABC has the potential for serious hypersensitivity reactions (HSRs). Clinically suspected HSRs have been observed in 5%–8% of patients who start ABC. The risk of this reaction is highly associated with the presence of the HLA-B*5701 allele *[79-80]*. (See **HLA-B*5701 Screening**.) HLA-B*5701 testing should precede the use of ABC. ABC should not be given to patients who test positive for HLA-B*5701, and based on test results, ABC hypersensitivity should be noted on the patient's allergy list. Patients 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 ABC/3TC and ZDV/3TC (both given twice daily and combined with EFV), participants from both arms achieved similar virologic responses. The ABC-treated participants experienced a greater CD4 T-cell increase at 48 weeks *[81]*. The fixed-dose combination of ABC/3TC 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 ABC/3TC versus TDF/FTC when used in combination with either EFV or RTV-boosted ATV. 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 ABC/3TC arm compared with the TDF/FTC arm *[68]*. Participants who had HIV RNA levels <100,000 copies/mL at study screening remained randomized and on study; a subsequent analysis of virological responses in this lower viral load stratum showed no significant differences between ABC/3TC and TDF/FTC *[82]*. In another study (HEAT), 688 participants received ABC/3TC or TDF/FTC in combination with once-daily LPV/r. 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) *[69]*. The ASSERT study compared open label ABC/3TC with TDF/FTC in 385 HLA-B5701-negative, ART-naïve patients; all study subjects also received EFV. At 48 weeks, a lower proportion of the ABC/3TC-treated subjects had HIV RNA <50 copies/mL (59%) compared with those receiving TDF/FTC (71%, difference 11.6%, 95% confidence interval [CI] 2.2 to 21.1) *[83]*.

An association between ABC use and MI was first reported in the D:A:D cohort. This large, multinational observational study group found that recent (within 6 months) or current use of ABC, but not TDF, predicted an increased risk of MI, particularly in participants with pre-existing cardiac risk factors *[37, 84]*. In contrast, a pooled analysis of 52 clinical trials involving more than 9,500 participants who had received ABC showed no increase in MI risk *[85]*. Several additional retrospective studies have subsequently addressed this issue, but no consensus has been reached, either on the association or a possible mechanism *[86]*.

Pending additional data, ABC/3TC 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 ABC/3TC remains a good alternative dual-NRTI option for some ART-naïve patients.

**ZDV/3TC (coformulated).** The dual-NRTI combination of ZDV/3TC has extensive durability, safety, and tolerability experience *[3, 5, 8, 19, 87-89]*. A fixed-dose combination of ZDV/3TC is available for one-tablet, twice-daily dosing. Selection of the 3TC-associated M184V mutation has been associated with increased susceptibility to ZDV. In a comparative trial of ABC/3TC versus ZDV/3TC (both given twice daily and combined with EFV), even though virologic responses were similar in both arms, the CD4 count increase was greater in the ABC/3TC-treated patients than in the ZDV/3TC-treated patients *[81]*.

Bone marrow suppression, manifested by macrocytic anemia and/or neutropenia, is seen in some patients. ZDV 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 ZDV had less limb fat at 96 and 144 weeks than those who took TDF, and there was a significant loss of fat among ZDV recipients between 48, 96, and 144 weeks *[67]*. In ACTG 5142, limb fat was lowest in patients treated with d4T, but those treated with ZDV had less limb fat than those treated with TDF *[10]*. Primarily because of its greater toxicity compared with TDF/FTC, ZDV/3TC is now considered an alternative rather than a preferred dual-NRTI option **(BI)**.

ZDV/3TC 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 ARV drug choices and related issues in pregnancy, see the ***Perinatal Guidelines*** *[36]*.

### *Acceptable Dual NRTI*

**ddI + (FTC or 3TC).** The FTC-301A trial tested ddI + FTC with EFV in ART-naïve patients and demonstrated potent virologic suppression *[90]*. The GESIDA 3903 study compared ddI/3TC with ZDV/3TC, combined with EFV *[91]*. At 48 weeks, virologic response for ddI/3TC was noninferior to ZDV/3TC.

The ACTG 5175 trial compared three regimens in ART-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 of ATV + enteric-coated ddI + FTC because of an inferior virologic response compared with the other two arms (once-daily EFV plus either ZDV/3TC twice daily or TDF/FTC once daily) *[60]*. Alternative PIs should be considered if ddI + (FTC or 3TC) are used. ddI use also is associated with an increased risk of pancreatitis, peripheral neuropathy, other mitochondria-associated toxicities, and possibly noncirrhotic portal hypertension *[92]*. In the D:A:D study of MI risk, the use of ddI within the previous 6 months was associated with an increased risk of MI, compared with the use of other NRTIs *[84]*. This increase in cardiovascular risk was not seen in other cohort studies *[93]*.

Based on the limited clinical trial experience with the use of ddI + 3TC (or FTC) with another ARV drug other than EFV, the unfavorable results from ACTG 5175, and the many side effects associated with ddI, the Panel considers it an acceptable but inferior option and only to be used with EFV **(CI)**.

**NRTIs and Hepatitis B Virus (HBV).** Three of the current NRTIs—FTC, 3TC, and TDF—have activity against HBV. Most HBV/HIV coinfected patients should use coformulated TDF/FTC (or TDF + 3TC) as their NRTI backbone to provide additional activity against HBV and to avoid selection of HBV mutation that confers resistance to 3TC/FTC. 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 TDF, 3TC, or FTC *[94-96]*. 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**.)

## ALL-NRTI REGIMENS

Several clinical trials that studied triple-NRTI regimens have shown suboptimal virologic activity *[19-20, 97-100]*.

**ABC/3TC/ZDV (coformulated).** ABC/3TC/ZDV is the only triple-NRTI combination for which randomized, controlled trials are available. ABC/3TC/ZDV demonstrated comparable ARV activity to IDV-based *[88-89]* and NFV-based regimens *[100]* but was inferior virologically to an EFV-based regimen *[19]*. 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.

**ZDV/3TC + TDF.** The DART study demonstrated that the combination of ZDV/3TC + TDF has antiviral activity *[101]*; however, comparative data with standard regimens are not available and therefore this combination **cannot be recommended** in routine clinical practice **(BIII)**.

**ZDV/3TC + ABC + TDF.** A quadruple-NRTI regimen of ZDV/3TC + ABC + TDF first showed comparable virologic responses to an EFV-based regimen in a small pilot study *[102]*. A larger study randomized 322 subjects to receive TDF/FTC combined with EFV, ATV/RTV, or a quadruple-NRTI regimen with ZDV and ABC. 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 lower with the quadruple-NRTI regimen and the rate of serious toxicity was twice as high as that observed with the EFV-based regimen *[103]*. Thus, this regimen **cannot be recommended (BI)**.

# Table 6. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (Updated January 10, 2011)



| ARV Class | ARV Agent(s) | Advantages | Disadvantages |
|---|---|---|---|
| **NNRTI (in alphabetical order)** | | **NNRTI Class Advantages:**<br>• Long half-lives | **NNRTI Class Disadvantages:**<br>• Low genetic barrier to resistance (single mutation confers resistance for EFV, NVP, and DLV); greater risk of resistance at the time of failure or treatment interruption<br>• Potential for cross resistance<br>• Skin rash<br>• Potential for CYP450 drug interactions (See Tables 14, 15b, and 16b.)<br>• Transmitted resistance to NNRTIs more common than resistance to PIs |
| | **EFV** | • Virologic responses equivalent or superior to all comparators to date<br>• Lowest pill burden; once-daily dosing<br>• Fixed-dose combination with TDF/FTC | • Neuropsychiatric side effects<br>• 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.<br>• Dyslipidemia |
| | **NVP** | • No food effect<br>• 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)<br>• Higher incidence of hepatotoxicity than with other NNRTIs, including serious and even fatal cases of hepatic necrosis<br>• Contraindicated in patients with moderate or severe (Child-Pugh B or C) hepatic impairment<br>• Some data suggest that ART-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 is not recommended in these patients unless benefit clearly outweighs risk.<br>• Early virologic failure of NVP + TDF + (FTC or 3TC) in small clinical trials<br>• Fewer clinical trial data than for EFV |
| **PI (in alphabetical order)** | | **PI Class Advantages:**<br>• Higher genetic barrier to resistance<br>• PI resistance uncommon with failure (boosted PIs) | **PI Class Disadvantages:**<br>• Metabolic complications (e.g., dyslipidemia, insulin resistance, hepatotoxicity)<br>• Gastrointestinal adverse effects<br>• CYP3A4 inhibitors and substrates: potential for drug interactions (more pronounced with RTV-based regimens) (See Tables 14 and 15a.) |
| | **ATV** | • Fewer adverse effects on lipids than other PI<br>• Once-daily dosing<br>• Low pill burden (two pills per day)<br>• Good GI tolerability<br>• Signature mutation (I50L) not associated with broad PI cross resistance | • Indirect hyperbilirubinemia sometimes leading to jaundice or scleral icterus<br>• PR interval prolongation: generally inconsequential unless combined with another drug with similar effect<br>• Cannot be coadministered with TDF, EFV, or NVP (See ATV/r.)<br>• Nephrolithiasis<br>• Skin rash<br>• Food requirement<br>• Absorption depends on food and low gastric pH (See Table 15a for detailed information regarding interactions with H2 antagonists, antacids, and PPIs.) |
| | **ATV/r** | • RTV boosting: higher trough ATV concentration and greater antiviral effect<br>• Once-daily dosing<br>• Low pill burden (two pills per day) | • More adverse effects on lipids than unboosted ATV<br>• More hyperbilirubinemia and jaundice than unboosted ATV<br>• Food requirement<br>• Absorption depends on food and low gastric pH (See Table 15a for interactions with $H_2$ antagonists, antacids, and PPIs.)<br>• RTV boosting required with TDF and EFV. With EFV, use ATV 400 mg and RTV 100 mg once daily (PI-naïve patients only).<br>• Should not be coadministered with NVP |

**Table 6. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy**
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| ARV Class | ARV Agent(s) | Advantages | Disadvantages |
|---|---|---|---|
| | **DRV/r** | • Once-daily dosing | • Skin rash<br>• Food requirement |
| | **FPV** | • No food effect | • Skin rash<br>• Potential for PI resistance with failure, including emergence of mutations that can cause DRV cross resistance |
| | **FPV/r** | • Twice-daily dosing resulted in efficacy comparable to LPV/r<br>• RTV boosting: higher trough APV concentration and greater antiviral effect<br>• Once-daily dosing possible with RTV 100 mg or 200 mg daily<br>• No food effect | • Skin rash<br>• Hyperlipidemia<br>• Once-daily dosing results in lower APV concentrations than twice-daily dosing<br>• For FPV 1,400 mg + RTV 200 mg: requires 200 mg of RTV and no coformulation<br>• Fewer data on FPV 1,400 mg + RTV 100 mg dose than on DRV/r and ATV/r |
| | **LPV/r** | • Coformulated<br>• No food requirement<br>• Recommended PI in pregnant women (twice daily only)<br>• Greater CD4 count increase than with EFV-based regimens | • Requires 200 mg per day of RTV<br>• Lower drug exposure in pregnant women—may need dose increase in third trimester<br>• Once-daily dosing not recommended in pregnant women<br>• Once-daily dosing: lower trough concentration than twice-daily dosing<br>• Possible higher risk of MI associated with cumulative use of LPV/r<br>• 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. |
| | **SQV/r** | • Efficacy similar to LPV/r with less hyperlipidemia | • Highest pill burden among available PI regimens (6 pills per day)<br>• Requires 200 mg of RTV<br>• Food requirement<br>• PR and/or QT interval prolongations in a healthy volunteer study<br>• Pretreatment ECG recommended<br>• SQV/r is not recommended for patients with any of the following conditions: (1) congenital or acquired QT prolongation; (2) pretreatment ECG >450 msec; (3) on concomitant therapy with other drugs that prolong QT interval; (4) complete AV block without implanted pacemakers; (5) risk of complete AV block. |
| **INSTI** | **RAL** | • Virologic response noninferior to EFV<br>• Fewer drug-related adverse events and lipid changes than EFV<br>• No food effect<br>• Fewer drug-drug interactions than PI- or NNRTI-based regimens | • Less long-term experience in ART-naïve patients than with boosted PI- or NNRTI-based regimens<br>• Twice-daily dosing<br>• Lower genetic barrier to resistance than with boosted PI-based regimens<br>• No data with NRTIs other than TDF/FTC in ART-naïve patients |
| **CCR5 Antagonist** | **MVC** | • Virologic response noninferior to EFV in post-hoc analysis of MERIT study (See text.)<br>• Fewer adverse effects than EFV | • Requires viral tropism testing prior to initiation of therapy with additional cost and possible delay in initiation of therapy<br>• More MVC-treated than EFV-treated patients discontinued therapy due to lack of efficacy in MERIT study<br>• Less long-term experience in ART-naïve patients than with boosted PI- or NNRTI-based regimens<br>• Limited experience with 2-NRTI other than ZDV/3TC<br>• Twice-daily dosing<br>• CYP 3A4 substrate, dosing depends on presence or absence of concomitant CYP3A4 inducer(s) or inhibitor(s) |
| **Dual NRTIs** | | **Dual-NRTI Class Advantage:**<br>Established backbone of combination ART | **Dual-NRTI Class Disadvantage:**<br>Rare but serious cases of lactic acidosis with hepatic steatosis reported with d4T, ddI, and ZDV |

**Table 6. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy**


| | | | |
|---|---|---|---|
| **Dual-NRTI pairs (in alphabetical order)** | **ABC/3TC** | • Virologic response noninferior to ZDV/3TC<br>• Better CD4 count response than with ZDV/3TC<br>• Once-daily dosing<br>• Coformulation<br>• No food effect<br>• No cumulative TAM-mediated resistance | • Potential for ABC HSR in patients with HLA-B*5701<br>• Potential for increased cardiovascular events, especially in patients with cardiovascular risk factors<br>• 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. |
| | **ddI + (3TC or FTC)** | • Once-daily dosing<br>• No cumulative TAM-mediated resistance | • Peripheral neuropathy, pancreatitis<br>• Reports of noncirrhotic portal hypertension<br>• Food effect; must be taken on an empty stomach<br>• Requires dosing separation from some PIs<br>• Increase in toxicities when used with ribavirin, TDF, d4T, or hydroxyurea<br>• 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. |
| | **TDF/FTC or TDF + 3TC** | • Better virologic responses than with ZDV/3TC<br>• 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.<br>• Active against HBV; recommended dual-NRTI for HBV/HIV coinfection<br>• Once-daily dosing<br>• No food effect<br>• Coformulated (TDF/FTC) and (EFV/TDF/FTC)<br>• No cumulative TAM-mediated resistance | • Potential for renal impairment, including rare reports of Fanconi syndrome and acute renal insufficiency<br>• Early virologic failure of NVP + TDF + (FTC or 3TC) in small clinical trials<br>• Potential for decrease in bone mineral density |
| | **ZDV/3TC** | • Coformulated (ZDV/3TC and ZDV/3TC/ABC)<br>• No food effect (although better tolerated with food)<br>• Preferred 2 NRTI in pregnant women | • Bone marrow suppression, especially anemia and neutropenia<br>• GI intolerance, headache<br>• Mitochondrial toxicity, including lipoatrophy, lactic acidosis, hepatic steatosis<br>• Inferior to TDF/FTC in combination with EFV<br>• Diminished CD4 T-cell responses compared with ABC/3TC |

**Acronyms**: 3TC = lamivudine, ABC = abacavir, ART = antiretroviral therapy, ARV = antiretroviral, ATV = atazanavir, ATV/r = atazanavir/ritonavir, AV = atrioventricular, CYP = cytochrome P, ddI = didanosine, DLV = delavirdine, DRV/r = darunavir/ritonavir, ECG = electrocardiogram, EFV = efavirenz, FPV = fosamprenavir, FPV/r = fosamprenavir/ ritonavir, FTC = emtricitabine, GI = gastrointestinal, HBV = hepatitis B virus, HSR = hypersensitivity reaction, INSTI = integrase strand transfer inhibitor, LPV/r = lopinavir/ritonavir, MI = myocardial infarction, msec = milliseconds, MVC = maraviroc, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, PPI = proton pump inhibitor, SQV/r = saquinavir/ritonavir, TAM = thymidine analogue mutation, TDF = tenofovir, ZDV = zidovudine

## Table 7. Antiretroviral Components Not Recommended as Initial Therapy
**(Updated December 1, 2009)**

| **ARV Drugs or Components** (in alphabetical order) | **Reasons for NOT recommending as initial therapy** |
|---|---|
| ABC/3TC/ZDV (coformulated) as triple-NRTI combination regimen **(BI)** | • Inferior virologic efficacy |
| ABC + 3TC + ZDV + TDF as quadruple-NRTI combination **(BI)** | • Inferior virologic efficacy |
| ABC + ddI **(BIII)** | • Insufficient data in ART-naïve patients |
| ABC + TDF **(BIII)** | • Insufficient data in ART-naïve patients |
| DRV (unboosted) | • Use without RTV has not been studied |
| DLV **(BII)** | • Inferior virologic efficacy<br>• Inconvenient (three times daily) dosing |
| ddI + TDF **(BII)** | • High rate of early virologic failure<br>• Rapid selection of resistance mutations<br>• Potential for immunologic nonresponse/CD4 T-cell decline<br>• Increased ddI drug exposure and toxicities |
| T-20 **(BIII)** | • No clinical trial experience in ART-naïve patients<br>• Requires twice-daily subcutaneous injections |
| ETR **(BIII)** | • Insufficient data in ART-naïve patients |
| IDV (unboosted) **(BIII)** | • Inconvenient dosing (three times daily with meal restrictions)<br>• Fluid requirement |
| IDV (RTV-boosted) **(BIII)** | • High incidence of nephrolithiasis |
| NFV **(BI)** | • Inferior virologic efficacy<br>• High incidence of diarrhea |
| RTV as sole PI **(BIII)** | • High pill burden<br>• Gastrointestinal intolerance |
| SQV (unboosted) **(BI)** | • Inferior virologic efficacy |
| d4T + 3TC **(BI)** | • Significant toxicities including lipoatrophy; peripheral neuropathy; and hyperlactatemia, including symptomatic and life-threatening lactic acidosis, hepatic steatosis, and pancreatitis |
| TPV (ritonavir-boosted) **(BI)** | • Inferior virologic efficacy |

**Acronyms**: 3TC = lamivudine, ABC = abacavir, ARV = antiretroviral, d4T = stavudine, ddI = didanosine, DLV = delavirdine, DRV = darunavir, ETR = etravirine; IDV = indinavir, IDV/r = ritonavir-boosted indinavir, NFV = nelfinavir, NRTI = nucleoside reverse transcriptase inhibitor, RTV = ritonavir, SQV = sacquinavir, T-20 = enfuvirtide, TDF = tenofovir, TPV = tipranavir, ZDV = zidovudine

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# What Not to Use (January 10, 2011)

Some antiretroviral (ARV) 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 nucleoside reverse transcriptase inhibitor (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 (PMTCT), zidovudine (ZDV) monotherapy is not recommended but 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 preferred. (See ***Perinatal Guidelines*** *[1]*, available at **http://aidsinfo.nih.gov**.)

Single-drug treatment regimens with a ritonavir (RTV)-boosted protease inhibitor (PI), either lopinavir (LPV) *[2]*, atazanavir (ATV) *[3]*, or darunavir (DRV) *[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 **(AI)** *[6]*.

**Triple-NRTI regimens.** In general, triple-NRTI regimens other than abacavir/lamivudine/zidovudine (ABC/3TC/ZDV) **(BI)** and possibly lamivudine/zidovudine + tenofovir (3TC/ZDV + TDF) **(BII) should not be used** because of suboptimal virologic activity *[7-9]* or lack of data **(AI)**.

## ANTIRETROVIRAL COMPONENTS NOT RECOMMENDED

**Atazanavir (ATV) + indinavir (IDV).** 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 (ddI) + stavudine (d4T).** The combined use of ddI and d4T 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 the deaths of several HIV-infected pregnant women secondary to severe lactic acidosis with or without hepatic steatosis and pancreatitis *[14]*. Therefore, the combined use of ddI and d4T **is not recommended (AII)**.

**Didanosine (ddI) + tenofovir (TDF).** Use of ddI + TDF may increase ddI concentrations *[15]* and serious ddI-associated toxicities including pancreatitis and lactic acidosis *[16-17]*. These toxicities may be lessened by ddI dose reduction. The use of this combination has also been associated with immunologic nonresponse or CD4 cell decline despite viral suppression *[18-19]*, high rates of early virologic failure *[20-21]*, and rapid selection of resistance mutations *[20, 22]*. Because of these adverse outcomes, this dual-NRTI combination **is not generally recommended (AII)**. Clinicians caring for patients who are clinically stable on regimens containing ddI + TDF should consider altering the NRTIs to avoid this combination.

**Two-non-nucleoside reverse transcriptase inhibitor (2-NNRTI) combinations.** In the 2NN trial, ARV-naïve participants were randomized to receive once- or twice-daily nevirapine (NVP) versus efavirenz (EFV) versus EFV plus NVP, all combined with d4T and 3TC *[23]*. A higher frequency of clinical adverse events that led to treatment discontinuation was reported in participants randomized to the two-NNRTI arm. Both EFV and NVP may induce metabolism of etravirine (ETR), which leads to reduction in ETR drug exposure *[24]*. Based on these findings, the Panel **does not recommend using two NNRTIs in combination in any regimen (AI)**.

**Efavirenz (EFV) in first trimester of pregnancy and in women with significant childbearing potential.** EFV 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 EFV *[25-26]*. EFV **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 ARV 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 ***Perinatal Guidelines*** *[1]*, available at **http://aidsinfo.nih.gov**.)

**Emtricitabine (FTC) + lamivudine (3TC).** 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 *[27]*. These two agents **should not be used** as a dual-NRTI combination **(AIII)**.

**Etravirine (ETR) + unboosted PI.** ETR may induce the metabolism and significantly reduce the drug exposure of unboosted PIs. Appropriate doses of the PIs have not been established *[24]* **(AII)**.

**Etravirine (ETR) + ritonavir (RTV)-boosted atazanavir (ATV) or fosamprenavir (FPV).** ETR may alter the concentrations of these PIs. Appropriate doses of the PIs have not been established *[24]* **(AII)**.

**Etravirine (ETR) + ritonavir (RTV)-boosted tipranavir (TPV).** RTV-boosted TPV significantly reduces ETR concentrations. These drugs **should not be coadministered** *[24]* **(AII)**.

**Nevirapine (NVP) initiated in ARV-naïve women with CD4 counts >250 cells/mm$^3$ or in ARV-naïve men with CD4 counts >400 cells/mm$^3$.** Greater risk of symptomatic hepatic events, including serious and life-threatening events, has been observed in these patient groups. NVP **should not be initiated** in these patients **(BI)** unless the benefit clearly outweighs the risk *[28-30]*. Patients who experience CD4 count increases to levels above these thresholds as a result of antiretroviral therapy (ART) can be safely switched to NVP *[31]*.

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

**Stavudine (d4T) + zidovudine (ZDV).** These two NRTIs **should not be used** in combination because of antagonism demonstrated *in vitro [32]* and *in vivo [33]* **(AII)**.

## Table 8. Antiretroviral Regimens or Components That Should Not Be Offered At Any Time
**(Updated January 10, 2011)**

| | Rationale | Exception |
|---|---|---|
| **Antiretroviral Regimens Not Recommended** | | |
| **Monotherapy with NRTI (AII)** | • Rapid development of resistance<br>• Inferior ARV activity when compared with combination of three or more ARV agents | • No exception |
| **Dual-NRTI regimens (AI)** | • Rapid development of resistance<br>• Inferior ARV activity when compared with combination of three or more ARV agents | • No exception |
| **Triple-NRTI regimens (AI) except for ABC/ZDV/3TC (BI) or possibly TDF + ZDV/3TC (BII)** | • High rate of early virologic nonresponse seen when triple-NRTI combinations, including ABC/TDF/3TC and TDF/ddI/3TC, were used as initial regimen in ART-naïve patients.<br>• Other triple-NRTI regimens have not been evaluated. | • ABC/ZDV/3TC (BI) and possibly TDF + ZDV/3TC (BII) in patients in whom other combinations are not desirable |
| **Antiretroviral Components Not Recommended as Part of an Antiretroviral Regimen** | | |
| **ATV + IDV (AIII)** | • Potential additive hyperbilirubinemia | • No exception |
| **ddI + d4T (AII)** | • High incidence of toxicities: peripheral neuropathy, pancreatitis, and hyperlactatemia<br>• Reports of serious, even fatal, cases of lactic acidosis with hepatic steatosis with or without pancreatitis in pregnant women | • When no other ARV options are available and potential benefits outweigh the risks **(BIII)** |
| **ddI + TDF (AII)** | • Increased ddI concentrations and serious ddI-associated toxicities<br>• Potential for immunologic nonresponse and/or CD4 cell count decline<br>• High rate of early virologic failure<br>• Rapid selection of resistance mutations at failure | • Clinicians caring for patients who are clinically stable on regimens containing TDF + ddI should consider altering the NRTIs to avoid this combination. |
| **2-NNRTI combination (AI)** | • When EFV combined with NVP, higher incidence of clinical adverse events seen when compared with either EFV- or NVP-based regimen.<br>• Both EFV and NVP may induce metabolism and may lead to reductions in ETR exposure; thus, they should not be used in combination with ETR. | • No exception |
| **EFV in first trimester of pregnancy or in women with significant childbearing potential (AIII)** | • Teratogenic in nonhuman primates | • When no other ARV options are available and potential benefits outweigh the risks **(BIII)** |
| **FTC + 3TC (AIII)** | • Similar resistance profiles<br>• No potential benefit | • No exception |
| **ETR + unboosted PI (AII)** | • ETR may induce metabolism of these PIs; appropriate doses not yet established | • No exception |
| **ETR + RTV-boosted ATV or FPV (AII)** | • ETR may alter the concentrations of these PIs; appropriate doses not yet established | • No exception |
| **ETR + RTV-boosted TPV (AII)** | • ETR concentration may be significantly reduced by RTV-boosted TPV | • No exception |
| **NVP in ARV-naïve women with CD4 count >250 cells/mm$^3$ or men with CD4 count >400 cells/mm$^3$ (BI)** | • High incidence of symptomatic hepatotoxicity | • If no other ARV option available; if used, patient should be closely monitored |
| **d4T + ZDV (AII)** | • Antagonistic effect on HIV-1 | • No exception |
| **Unboosted DRV, SQV, or TPV (AII)** | • Inadequate bioavailability | • No exception |

**Acronyms:**
3TC = lamivudine, ABC = abacavir, ATV = atazanavir, d4T = stavudine, ddI = didanosine, DRV = darunavir, EFV = efavirenz, ETR = etravirine, FPV = fosamprenavir, FTC = emitricitabine, IDV = indinavir, NVP = nevirapine, RTV = ritonavir, SQV = saquinavir, TDF = tenofovir, TPV = tipranavir, ZDV = zidovudine

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# Management of the Treatment-Experienced Patient

## VIROLOGIC AND IMMUNOLOGIC FAILURE (Updated January 10, 2011)

***Panel's Recommendations:***

- ***Assessing and managing an antiretroviral (ARV)-experienced patient experiencing failure of antiretroviral therapy (ART) is complex. Expert advice is critical and should be sought.***
- ***Evaluation of virologic failure should include an assessment of the severity of the patient's HIV disease, ART history, use of concomitant medications with consideration of adverse drug interactions with ARV agents, HIV RNA and CD4 T-cell count trends over time, and prior drug-resistance testing results.***
- ***Drug-resistance testing should be obtained while the patient is taking the failing ARV regimen or within 4 weeks of treatment discontinuation (AII).***
- ***The goal of treatment for ARV-experienced patients with drug resistance who are experiencing virologic failure is to re-establish virologic suppression (e.g., HIV RNA <48 copies/mL) (AI).***
- ***To design a new regimen, the patient's treatment history and past and current resistance test results should be used to identify at least two (preferably three) fully active agents to combine with an optimized background ARV regimen (AI). A fully active agent is one that is likely to have ARV activity on the basis of the patient's treatment history, drug-resistance testing, and/or a novel mechanism of action.***
- ***In general, adding a single, fully active ARV in a new regimen is not recommended because of the risk of rapid development of resistance (BII).***
- ***In patients with a high likelihood of clinical progression (e.g., CD4 count <100 cells/mm$^3$) and limited drug options, adding a single drug may reduce the risk of immediate clinical progression, because even transient decreases in HIV RNA and/or transient increases in CD4 cell counts have been associated with clinical benefits (CI).***
- ***For some highly ART-experienced patients, maximal virologic suppression is not possible. In this case, ART should be continued (AI) with regimens designed to minimize toxicity, preserve CD4 cell counts, and avoid clinical progression.***
- ***Discontinuing or briefly interrupting therapy in a patient with viremia may lead to a rapid increase in HIV RNA and a decrease in CD4 cell count and increases the risk of clinical progression. Therefore, this strategy is not recommended (AI).***
- ***In the setting of virologic suppression, there is no consensus on how to define or treat immunologic failure.***

***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***

### *Virologic Definitions*

***Virologic suppression:*** A confirmed HIV RNA level below the limit of assay detection (e.g., <48 copies/mL).

***Virologic failure:*** The inability to achieve or maintain suppression of viral replication (to an HIV RNA level <200 copies/mL).

***Incomplete virologic response:*** Two consecutive plasma HIV RNA levels >200 copies/mL after 24 weeks on an ARV regimen. Baseline HIV RNA may affect the time course of response, and some regimens will take longer than others to suppress HIV RNA levels.

***Virologic rebound:*** Confirmed detectable HIV RNA (to >200 copies/mL) after virologic suppression.

***Persistent low-level viremia:*** Confirmed detectable HIV RNA levels that are <1,000 copies/mL.

***Virologic blip:*** After virologic suppression, an isolated detectable HIV RNA level that is followed by a return to virologic suppression.

## *Causes of Virologic Failure*

Virologic failure in a patient can occur for multiple reasons. Data from older patient cohorts suggested that suboptimal adherence and drug intolerance/toxicity accounted for 28%–40% of virologic failure and regimen discontinuations *[1-2]*. More recent data suggest that most virologic failure on first-line regimens occurred due to either pre-existing (transmitted) drug resistance or suboptimal adherence *[3]*. Factors associated with virologic failure include:

- Patient characteristics
  - 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., active substance abuse, depression)
  - presence of drug-resistant virus, either transmitted or acquired
  - prior treatment failure
  - incomplete medication adherence and missed clinic appointments

- ARV regimen characteristics
  - 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 virologic potency
  - prescription errors

- Provider characteristics, such as experience in treating HIV disease

- Other or unknown reasons

## *Management of Patients with Virologic Failure*

### Assessment of Virologic Failure

If virologic failure is suspected or confirmed, a thorough work-up is indicated, addressing the following factors:
- change in HIV RNA and CD4 T-cell counts over time
- occurrence of HIV-related clinical events
- ARV 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 medications
- concomitant medications and supplements (with consideration for adverse drug-drug interactions)
- comorbidities (including substance abuse)

In many cases, the cause(s) of virologic failure will be identified. In some cases, no obvious cause(s) may be identified. It is important to distinguish among the reasons for virologic failure because the approaches to subsequent therapy differ. The following potential causes of virologic failure should be explored in depth.

- **Adherence.** Assess the patient's adherence to the regimen. For incomplete adherence, identify and address the underlying cause(s) (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). (See **Adherence**.)

- **Medication Intolerance.** Assess the patient's tolerance of the current regimen and the severity and duration of side effects, keeping in mind that even minor side effects can impact adherence. Management strategies for intolerance in the absence of drug resistance may include:
  - using symptomatic treatment (e.g., antiemetics, antidiarrheals)
  - changing one ARV to another within the same drug class, if needed (e.g., change to tenofovir [TDF] or abacavir [ABC] for zidovudine [ZDV]-related toxicities; change to nevirapine [NVP] or etravirine [ETR] for efavirenz [EFV]-related toxicities) *[4-5]*
  - changing from one drug class to another (e.g., from a non-nucleoside reverse transcriptase inhibitor [NNRTI] to a protease inhibitor [PI], from enfuvirtide [T-20] to raltegravir [RAL]) if necessary and no prior drug resistance is suspected

- **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 ARV agents and/or concomitant medications, if possible. Therapeutic drug monitoring (TDM) may be helpful if pharmacokinetic drug-drug interactions or impaired drug absorption leading to decreased ARV exposure is suspected. (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 if the plasma HIV RNA level is >500 copies/mL **(AII)**. (See **Drug-Resistance Testing**.) Evaluate the degree of drug resistance and consider the patient's prior treatment history and prior resistance test results. Drug resistance tends to be cumulative for a given individual; thus, all prior treatment history and resistance test results should be taken into account. Routine genotypic or phenotypic testing gives information relevant for selecting nucleoside reverse transcriptase inhibitors (NRTIs), NNRTIs, and PIs. Additional drug-resistance tests for patients experiencing failure on fusion inhibitors and/or integrase strand transfer inhibitors (INSTIs) and viral tropism tests for patients experiencing failure on a CCR5 antagonist also are available. (See **Drug-Resistance Testing**.)

### Changing ART

There is no consensus on the optimal time to change therapy for virologic failure. The goal of ART is to suppress HIV replication to a level where drug-resistance mutations do not emerge. However, the specific level of viral suppression needed to achieve durable virologic suppression remains unknown. Selection of drug resistance does not appear to occur in patients with persistent HIV RNA levels suppressed to <48 copies/mL *[6]*, although this remains controversial *[7]*.

The clinical implications of HIV RNA in the range of >48 to <200 copies/mL in a patient on ART are controversial. Unlike the case with higher levels of HIV RNA, most, if not all, circulating virus from individuals with this level of HIV RNA results from the release of HIV from long-lived latently infected cells and does not signify ongoing viral replication with the emergence of drug-resistant virus *[8]*. Although some studies have suggested that viremia at this low level predicts subsequent failure *[9]* and can be associated with the evolution of drug resistance *[10]*, a large retrospective analysis showed that using an HIV RNA threshold for virologic failure of <200 copies/mL had the same predictive value as using a threshold of <50 copies/mL *[11]*.

Newer technologies (e.g., Taqman assay) have made it possible to detect HIV RNA in more patients with low level viremia (<200 copies/mL) than was possible with previous assays. Use of these newer assays has resulted in more confirmatory viral load testing than may be necessary *[12-14]*.

Persistent HIV RNA levels >200 copies/mL often are associated with evidence of viral evolution and drug-resistance mutation accumulation *[15]*; this is particularly common when HIV RNA levels are >500 copies/mL *[16]*. Persistent plasma HIV RNA levels in the 200 to 1,000 copies/mL range should therefore be considered as virologic failure.

Viremia "blips" (e.g., viral suppression followed by a detectable HIV RNA level and then subsequent return to undetectable levels) usually are not associated with subsequent virologic failure *[17]*.

## Management of Virologic Failure

Once virologic failure is confirmed, generally the regimen should be changed as soon as possible to avoid progressive accumulation of resistance mutations *[18]*.

Ideally, a new ARV regimen should contain at least two, and preferably three, fully active drugs on the basis of drug treatment history, resistance testing, or new mechanistic class **(AI)** *[19-27]*. Some ARV drugs (e.g., NRTIs) may contribute partial ARV activity to a regimen, despite drug resistance *[28]*, while others (e.g., T-20, NNRTIs, RAL) likely do not provide partial activity *[28-30]*. 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. In addition, archived drug-resistance mutations may not be detected by standard drug-resistance tests, emphasizing the importance of considering treatment history and prior drug-resistance tests. Drug potency and viral susceptibility are more important than the number of drugs prescribed.

Early studies of ART-experienced patients identified factors associated with better virologic responses to subsequent regimens *[31-32]*. These factors included lower HIV RNA level and/or higher CD4 cell count at the time of therapy change, using a new (i.e., not yet taken) class of ARV drugs, and using ritonavir (RTV)-boosted PIs in PI-experienced patients.

More recent clinical trials support the strategy of conducting reverse transcriptase (RT) and protease (PT) resistance testing (both genotype and phenotype) while an ART-experienced patient is taking a failing ARV regimen, designing a new regimen based on the treatment history and resistance testing results, and selecting at least two and preferably three active drugs for the new treatment regimen *[20-21, 23-24, 33]*. Higher genotypic and/or phenotypic susceptibility scores (quantitative measures of drug activity) are associated with better virologic responses *[23-24]*. Patients who receive more active drugs have a better and more prolonged virologic response than those with fewer active drugs in the regimen. Active ARV drugs include those with activity against drug-resistant viral strains, including newer members of existing classes (the NNRTI—ETR, the PIs—darunavir [DRV] and tipranavir [TPV]) and drugs with new mechanisms of action (the fusion inhibitor—T-20, the CCR5 antagonist—maraviroc [MVC] in patients with R5 but not X4 virus, and the INSTI—RAL). Drug-resistance tests for patients experiencing failure on fusion inhibitors (FIs) and/or INSTIs and viral tropism tests for patients experiencing failure on a CCR5 antagonist also are available. (See **Drug-Resistance Testing**.)

### *Clinical Scenarios of Virologic Failure*

- ***Low-level viremia (HIV RNA <1,000 copies/mL).*** Assess adherence. Consider variability in HIV RNA assays. Patients with HIV RNA <48 copies/mL or isolated increases in HIV RNA ("blips") do not require a change in treatment *[13]* **(AII)**. There is no consensus regarding how to manage patients with HIV RNA levels >48 copies/mL and <200 copies/mL; HIV RNA levels should be followed over time to assess the need for changes (**AIII**). Patients with persistent HIV RNA levels >200 copies/mL often select out drug-resistant viral variants, particularly when HIV RNA levels are >500 copies/mL. Persistent plasma HIV RNA levels in the 200 to 1,000 copies/mL range should be considered as possible virologic failure; resistance testing should be attempted if the HIV RNA level is >500 copies/mL. For individuals with sufficient therapeutic options, consider treatment change **(BIII)**.

- ***Repeated detectable viremia (HIV RNA >1,000 copies/mL) and NO drug resistance identified.*** Consider the timing of the drug-resistance test (e.g., was the patient off ARV 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)**.

- ***Repeated detectable viremia (HIV RNA >1,000 copies/mL) and drug resistance identified.*** The goals in this situation are to resuppress HIV RNA levels maximally (i.e., to <48 copies/mL) and to prevent further selection of resistance mutations. With the availability of multiple new ARVs, including some with new mechanisms of action, this goal is now possible in many patients, including those with extensive treatment experience and drug resistance. With virologic failure, consider changing the treatment regimen sooner, rather than later, to minimize continued selection of resistance mutations. In a patient with ongoing viremia and evidence of resistance, some drugs in a regimen (e.g., NNRTI, T-20, RAL) should be discontinued promptly to decrease the risk of selecting additional drug-resistance mutations in order to preserve the activity of these drug classes in future regimens. A new regimen should include at least two, and preferably three, fully active agents **(AII)**.

- ***Highly drug resistant HIV.*** There is a subset of patients who have experienced toxicity and/or 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 suboptimal ARV 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. If maximal virologic suppression cannot be achieved, the goals are to preserve immunologic function and to prevent clinical progression (even with ongoing viremia). 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)**. Even partial virologic suppression of HIV RNA >0.5 $\log_{10}$ copies/mL from baseline correlates with clinical benefits *[34]*. There is evidence from cohort studies that continuing therapy, even in the presence of viremia and the absence of CD4 T-cell count increases, reduces the risk of disease progression *[35]*. Other cohort studies suggest continued immunologic and clinical benefits if the HIV RNA level is maintained <10,000–20,000 copies/mL *[36-37]*. However, these potential benefits all must be balanced with the ongoing risk of accumulating additional resistance mutations.

  In general, adding a single, fully active ARV in a new regimen is **not** recommended because of the risk of rapid development of resistance **(BII)**. However, in patients with a high likelihood of clinical progression (e.g., CD4 cell count <100 cells/$mm^3$) and limited drug options, adding a single drug may reduce the risk of immediate clinical progression, because even transient decreases in HIV RNA and/or transient increases in CD4 cell counts have been associated with clinical benefits **(CI)**. Weighing the risks (e.g., selection of drug resistance) and benefits (e.g., ARV activity) of using a single active drug in the heavily ART 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 research studies or expanded access programs, or single-patient access of investigational new drug(s) (IND), as specified in Food and Drug Administration (FDA) regulations: **http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm163982.htm**).

  Discontinuing or briefly interrupting therapy in a patient with viremia may lead to a rapid increase in HIV RNA and a decrease in CD4 T-cell count and increases the risk of clinical progression *[38-39]*. Therefore, this strategy is **not** recommended **(AI)**. See **Discontinuation or Interruption of Antiretroviral Therapy**.

- ***Prior treatment and suspected drug resistance, now presenting to care in need of therapy with limited information (i.e., incomplete or absence of self-reported history, medical records, or previous resistance data).*** 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 ARV regimen and assess drug resistance in 2–4 weeks to help guide the choice of the next regimen; another strategy is to start two or three drugs known to be active based on treatment history (e.g., MVC with R5 virus, RAL if no prior INSTI).

## *Immunologic Failure: Definition, Causes, and Management*

**Immunologic failure** can be defined as the failure to achieve and maintain an adequate CD4 response despite virologic suppression. Increases in CD4 counts in ARV-naïve patients with initial ARV regimens are approximately 150 cells/$mm^3$ over the first year *[40]*. A CD4 count plateau may occur after 4–6 years of treatment with suppressed viremia *[41-45]*.

No accepted specific definition for immunologic failure exists, although some studies have focused on patients who fail to increase CD4 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 counts above pretherapy levels by a certain threshold (e.g., >50 or 100 cells/mm$^3$) over a given time period. The former criterion may be preferable because of data linking these thresholds with the risk of non-AIDS clinical events *[46]*.

The proportion of patients experiencing immunologic failure depends on how failure is defined, the observation period, and the CD4 count when treatment was started. In the longest study conducted to date, the percentage of patients with suppressed viremia who reached a CD4 count >500 cells/mm$^3$ through 6 years of treatment was 42% in those starting treatment with a CD4 count <200 cells/mm$^3$, 66% in those starting with a CD4 count 200–350 cells/mm$^3$, and 85% in those starting with a CD4 count >350 cells/mm$^3$ *[41]*.

A persistently low CD4 count while on suppressive ART is associated with a small, but appreciable, risk of AIDS- and non-AIDS-related morbidity and mortality *[47-48]*. For example, in the FIRST study *[49]*, a low CD4 count on therapy was associated with an increased risk of AIDS-related complications (adjusted hazard ratio of 0.56 per 100 cells/mm$^3$ higher CD4 count). Similarly, a low CD4 count was associated with an increased risk of non-AIDS events, including cardiovascular, hepatic, and renal disease and cancer. Other studies support these associations *[50-53]*.

Factors associated with poor CD4 T-cell response:
- CD4 count <200/mm$^3$ when starting ART
- Older age
- Coinfection (e.g., hepatitis C virus [HCV], HIV-2, human T-cell leukemia virus type 1 [HTLV-1], HTLV-2)
- Medications, both ARVs (e.g., ZDV *[54]*, TDF + didanosine [ddI] *[55-57]*) and other medications.
- Persistent immune activation
- Loss of regenerative potential of the immune system
- Other medical conditions

**Assessment of Immunologic Failure.** CD4 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., cancer chemotherapy, interferon, prednisone, ZDV; combination of TDF and ddI), 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.** No consensus exists on when or how to treat immunologic failure. Given the risk of clinical events, it is reasonable to focus on patients with CD4 counts <200 cells/mm$^3$ because patients with higher CD4 counts have a lower risk of clinical events. It is not clear that immunologic failure in the setting of virologic suppression should prompt a change in the ARV regimen. Because ongoing immune activation 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 *[58]*. Others suggest changing the regimen to another regimen (e.g., from NNRTI-based to PI-based, INSTI-based, or CCR5 antagonist-based regimens), but this strategy has not shown clear benefit.

An immune-based therapy, interleukin-2, demonstrated CD4 count increases but no clinical benefit in two large randomized studies *[59]* and therefore is not recommended **(AI)**. Other immune-based therapies (e.g., gene therapies, growth hormone, cyclosporine, interleukin-7) are under investigation. Currently, immune-based therapies **should not** be used unless in the context of a clinical trial **(AIII)**.

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## REGIMEN SIMPLIFICATION (Updated January 10, 2011)

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 (ART) may be considered candidates for regimen simplification, 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 review consideration of changes in treatment for reducing ongoing adverse effects. Regimens used in simplification strategies generally should be those that have proven high efficacy in antiretroviral (ARV)-naïve patients (see **What to Start**) or that would be predicted to be highly active for a given patient based on the individual's past treatment history and resistance profile.

### *Rationale*

The major rationales behind regimen simplification are to improve the patient's quality of life, maintain long-term adherence, avoid toxicities that may develop with prolonged ARV use, 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 ARV agents developed earlier in the HIV epidemic, many ARV medications approved in recent years have sufficiently long half-lives to allow for once-daily dosing, and most also do not have dietary restrictions. Patients on regimens initiated earlier in the era of potent combination ART with drugs that pose a high 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 is relatively low in patients after simplification 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 patients who were treated with presumably nonsuppressive mono- or dual-nucleoside reverse transcriptase inhibitor (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 who achieve viral suppression after having had documented or suspected drug resistance. Often, these patients are on regimens selected when management of drug resistance, understanding of potentially adverse drug-drug interactions, and understanding of treatment options were relatively limited. Regimen simplification may also be considered for patients on two ritonavir (RTV)-boosted protease inhibitors (PIs). Although successful in suppressing viral replication, this treatment may cause patients to be on regimens that are cumbersome, costly, 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 are easier to take without sacrificing ARV activity. Specific situations in which drug simplification could be considered in ART-experienced patients with viral drug resistance are outlined below. Simplifying regimens in patients who have extensive prior treatment histories is complicated. In such a case, a patient's treatment history, treatment responses and tolerance, and resistance test results should be thoroughly reviewed before designing a new regimen. Expert consultation should be considered whenever possible.

### *Types of Treatment Simplification*

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

- ***NRTI Substitutions*** *(e.g., changing from zidovudine [ZDV] or stavudine [d4T] to tenofovir [TDF] or abacavir [ABC])**:*** 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 Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)*** *(e.g., from nevirapine [NVP] to efavirenz [EFV])**:*** 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 (such as from twice-daily to once-daily RTV-boosted lopinavir [LPV/r] or RTV-boosted darunavir [DRV/r]) or, in the case of atazanavir (ATV), to administration without RTV boosting *[6]*. (Unboosted ATV is presently not a preferred PI component and not recommended if the patient is taking TDF or if the patient has HIV with reduced susceptibility to ATV.) 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 patients without PI-resistant virus. However, these switches are not recommended in patients who have a history of documented or suspected PI resistance because convincing data in this setting are lacking.

**Out-of-Class Substitutions.** One common out-of-class substitution for regimen simplification involves a change from a PI-based to an NNRTI-based regimen. An important study in this regard was the NEFA trial, which evaluated substitution of a PI-based regimen in virologically suppressed patients with NVP, EFV, or ABC *[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 ABC than in patients switched to EFV or NVP. The increased risk of treatment failure was particularly high in patients 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 the integrase strand transfer inhibitor (INSTI) raltegravir (RAL) and the CCR5 antagonist maraviroc (MVC), also offer opportunities for out-of-class substitutions, particularly in patients who have a history of virus resistant to older HIV drugs. Three randomized studies have evaluated replacing a boosted PI with RAL in virologically suppressed patients. In two of these studies *[9-10]*, the switch to RAL was associated with an increased risk of virologic failure in patients with documented or suspected pre-existing NRTI resistance; a third study did not find this higher risk, possibly due to a longer period of virologic suppression before the change *[11]*. Overall, these results suggest that in ART-experienced patients, RAL should be used with caution as a substitute for a boosted PI. This strategy should be avoided in patients with documented NRTI resistance unless there are other fully active drugs in the regimen.

Because enfuvirtide (T-20) requires twice-daily injections, causes injection-site reactions, and is more expensive than other available ARV agents, patients who are virologically suppressed on T-20-containing regimens may wish to substitute T-20 with an active oral agent. Because the majority of patients on T-20 have highly drug-resistant virus, substitution must be with another fully active agent. Data from one randomized trial and one observational study suggest that RAL can safely substitute for T-20 in patients not previously treated with INSTI *[12-13]*. 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 *[14]*.

Other newer agents that might be considered as substitutes for T-20 are etravirine (ETR) or MVC. Use of ETR in this setting would optimally be considered only when viral susceptibility to ETR can be assured from resistance testing performed prior to virologic suppression and after carefully assessing for possible deleterious drug-drug interactions

(e.g., ETR cannot be administered with several PIs [see **Table 16b**]). In the ETR early access program, switching from T-20 to ETR showed promise in maintaining viral suppression at 24 weeks, but only 37 subjects were included in this report *[15]*. MVC is only active in those with documented R5-only virus, a determination that cannot routinely be made in those with undetectable HIV RNA on a stable regimen. Although there is a commercially available proviral DNA assay to assess viral tropism in virologically suppressed patients, there are no clinical data on whether results of this test predict the successful use of MVC as a substitute for another active drug.

**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. In early studies, this approach was 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 an RTV-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 lower cost. In a randomized clinical trial *[18]*, low-level viremia was more common in those on maintenance LPV/r alone than on a three-drug combination regimen. Viral suppression was achieved by resuming the NRTIs. Studies of DRV/r 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 outside of a clinical trial.

### *Monitoring After Treatment Simplification*

Patients should be evaluated 2–6 weeks after treatment simplification 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 change in therapy. 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 January 10, 2011)

***Panel's Recommendations:***

- ***Therapeutic drug monitoring (TDM) for antiretroviral (ARV) agents is not recommended for routine use in the management of the HIV-infected adult (CIII).***
- ***TDM may be considered in selected clinical scenarios, as discussed in the text below.***

***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***

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

TDM is a strategy applied to certain antiarrhythmics, anticonvulsants, antineoplastics, and antibiotics that utilizes measured drug concentrations to design dosing regimens to improve the likelihood of the desired therapeutic and safety outcomes. 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.

Several ARV 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 (ART) derives from 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]*.

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

Multiple factors limit the routine use of TDM in HIV-infected adults *[4-5]*. These factors include:

- 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 for all ARV drugs that is associated with achieving the desired therapeutic response and/or reducing the frequency of drug-associated adverse reactions;
- intrapatient variability in ARV drug concentrations;
- lack of widespread availability of clinical laboratories that perform quantitation of ARV concentrations under rigorous quality assurance/quality control standards; and
- shortage of experts to assist with interpretation of ARV concentration data and application of such data to revise patients' dosing regimens.

**Exposure-Response Relationships and TDM with Different ARV Classes**

*Protease Inhibitors (PIs), Non-Nucleoside Reverse Transcriptase Inhibitors ( NNRTIs), and Integrase Inhibitors*. Relationships between the systemic exposure to PIs and NNRTIs and treatment response have been reviewed in various publications *[4-7]*. Although there are limitations and unanswered questions, the consensus among clinical pharmacologists from the United States and Europe is that the data provide a framework for the potential implementation of TDM for PIs and NNRTIs. However, information on relationships between concentrations and drug-associated toxicities are sparse. Clinicians who use TDM as a strategy to manage either ARV response or toxicities should consult the most current data on the proposed therapeutic concentration range. Exposure-response data for darunavir (DRV), etravirine (ETR), and raltegravir (RAL) are accumulating but are not sufficient to recommend minimum trough concentrations. The median trough concentrations for these agents in HIV-infected persons receiving the recommended dose are included in **Table 9b**.

*CCR5 Antagonists*. Trough maraviroc (MVC) concentrations have been shown to be an important predictor of virologic success in studies conducted in ART-experienced persons *[8-9]*. Clinical experience in the use of TDM for MVC, 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 9b**).

*Nucleoside Reverse Transcriptase Inhibitors (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**. Multiple scenarios exist in which both ARV concentration data and expert opinion may be useful in patient management. Consultation with a clinical pharmacologist or a clinical pharmacist with HIV expertise may be advisable in these cases. These scenarios include the following:

- **Suspect clinically significant drug-drug or drug-food interactions** that may result in reduced efficacy or increased dose-related toxicities;
- **Changes in pathophysiologic states** that may impair gastrointestinal, hepatic, or renal function, thereby potentially altering drug absorption, distribution, metabolism, or elimination;
- **Pregnant women** who may be at risk of 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;
- **Heavily pretreated patients** experiencing virologic failure and who may have viral isolates with reduced susceptibility to ARVs;
- **Use of alternative dosing regimens and ARV combinations** for which safety and efficacy have not been established in clinical trials;
- **Concentration-dependent, drug-associated toxicities**; and
- **Lack of expected virologic response** in medication-adherent persons.

**TDM**

- **For patients who have drug-susceptible virus**. **Table 9a** includes a synthesis of recommendations *[2-7]* for minimum target trough PI and NNRTI concentrations in persons with drug-susceptible virus.
- **For ART-experienced patients with virologic failure (see Table 9b)**. Fewer data are available to formulate suggestions for minimum target trough concentrations in ART-experienced patients who have viral isolates with reduced susceptibility to ARV agents. Concentration recommendations for tipranavir (TPV) and MVC were derived only from studies in ART-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 ARV 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 DRV in ART-experienced persons *[10-11]*. Exposure-response data for DRV, ETR, and RAL are accumulating but are not sufficient to recommend minimum trough concentrations. The median trough concentrations for these agents in HIV-infected persons receiving the recommended dose are included in **Table 9b**.

**Using Drug Concentrations to Guide Therapy**. There are several challenges and considerations for implementation of TDM in the clinical setting. Use of TDM to monitor ARV 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 information. In addition, as knowledge of associations between ARV concentrations and virologic response continues to accumulate, clinicians who employ a TDM strategy for patient management should consult the most current literature.

## Table 9a. Trough Concentrations of Antiretroviral Drugs for Patients Who Have Drug-Susceptible Virus **(Updated January 10, 2011)**

| Drug | Concentration (ng/mL) |
|---|---|
| **Suggested minimum target trough concentrations in patients with HIV-1 susceptible to the ARV drugs** *[2-9]* | |
| Fosamprenavir (FPV) | 400<br>(measured as amprenavir concentration) |
| Atazanavir (ATV) | 150 |
| Indinavir (IDV) | 100 |
| Lopinavir (LPV) | 1,000 |
| Nelfinavir[1] (NFV) | 800 |
| Saquinavir (SQV) | 100–250 |
| Efavirenz (EFV) | 1,000 |
| Nevirapine (NVP) | 3,000 |

[1]Measurable active (M8) metabolite

## Table 9b. Trough Concentrations of Antiretroviral Drugs for Treatment-Experienced Patients with Virologic Failure (Updated January 10, 2011)

| Drug | Concentration (ng/mL) |
|---|---|
| **Suggested minimum target trough concentrations for ART-experienced patients who have resistant HIV-1 strains** | |
| Maraviroc (MVC) | >50 |
| Tipranavir (TPV) | 20,500 |
| **Median (Range) Trough Concentrations from Clinical Trials** *[12-14]* | |
| Darunavir (DRV) (600 mg twice daily) | 3,300 (1,255–7,368) |
| Etravirine (ETR) | 275 (81–2,980) |
| Raltegravir (RAL) | 72 (29–118) |

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# DISCONTINUATION OR INTERRUPTION OF ANTIRETROVIRAL THERAPY

**(Updated November 3, 2008)**

Discontinuation of antiretroviral therapy (ART) may result in viral rebound, immune decompensation, and clinical progression. Unplanned interruption of ART may become necessary because of severe drug toxicity, intervening illness, surgery that precludes oral therapy, or unavailability of antiretroviral (ARV) medication. Some investigators have studied planned treatment discontinuation strategies in situations or for reasons that include: in patients who achieve viral suppression and wish to enhance adherence; to 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 ART vary and may include drug toxicity; intercurrent illnesses that preclude oral intake, such as gastroenteritis or pancreatitis; surgical procedures; or unavailability of drugs. Stopping ARV 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, all drugs should be stopped simultaneously. 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 cannot 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 ARV 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 a non-nucleoside reverse transcriptase inhibitor [NNRTI]). Options in this circumstance are discussed below. (See **Discontinuation of efavirenz, etravirine, or nevirapine**.)

## *Interruption of Therapy after Pregnancy*

ARV drugs for prevention of perinatal transmission of HIV are recommended for all pregnant women, regardless of whether they have indications for ART for their own health. Following delivery, considerations regarding continuation of the ARV regimen for maternal therapeutic indications are the same as for other nonpregnant individuals. The decision of whether to continue therapy after delivery should take into account current recommendations for initiation of ART, current and nadir CD4 T-cell counts and trajectory, HIV RNA levels, adherence issues, and patient preference.

## *Planned Long-Term Therapy Interruptions*

Planned therapy interruptions have been contemplated in various scenarios, listed below. Research is ongoing in several of the scenarios. Therapy interruptions **cannot 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**.)

- **In patients who have had exposure to multiple ARV agents, have experienced ARV treatment failure, and have few treatment options available because of extensive resistance mutations**—interruption is **not recommended** unless 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 *[1-4]*. The largest of these studies showed negative clinical impact of treatment interruption in these patients *[1]*. The Panel notes that partial virologic suppression from combination therapy has been associated with clinical benefit *[5]*; therefore, interruption of therapy is not recommended.
- **In patients on ART who have maintained a CD4 count above the level currently recommended for treatment initiation and irrespective of whether their baseline CD4 counts were either above or below that recommended threshold**—interruption is also **not recommended** unless 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 ART 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. In the SMART study, the largest of such trials with more than 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 all cause mortality compared with the trial arm of continuous ART *[6]*. In the TRIVACAN study, the same CD4 count thresholds were used for stopping and restarting treatment *[7]*. 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 twofold increase in rates of World Health Organization (WHO) Stage 4 events/deaths in the 12-week ART cycling group among African patients achieving a CD4 count >300/$mm^3$ compared with the continuous ART group *[8]*. Observational data from the EuroSIDA cohort noted a twofold increase in risk of death after a treatment interruption of ≥3 months. Factors linked to increased risk of death or progression included lower CD4 counts, higher viral loads, and a prior history of AIDS *[9]*. Other studies have reported no major safety concerns *[10-12]*, 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 *[13-14]*. There is concern that CD4 counts <500 cells/$mm^3$ are associated with a range of non-AIDS clinical events (e.g., cancer and heart, liver, and kidney disease) *[6, 15-16]*.

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 of 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 ARV-specific issues should be taken into consideration. These include:

- **Discontinuation of efavirenz (EFV), etravirine (ETR), or nevirapine (NVP).** The optimal interval between stopping EFV, ETR, or NVP and other ARV drugs is not known. The duration of detectable levels of EFV or NVP after discontinuation ranges from less than 1 week to more than 3 weeks *[17-18]*. Simultaneously stopping all drugs in a regimen containing these agents may result in functional monotherapy with the NNRTIs because NNRTIs have much longer half-lives 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 *[18-19]*. Some experts recommend stopping the NNRTI but continuing the other ARV 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 4 or 7 days of zidovudine (ZDV) + lamivudine (3TC) after a single dose of NVP reduced the risk of postnatal NVP resistance from 60% to 10%–12% *[20]*. Use of nucleoside reverse transcriptase inhibitors (NRTIs) with a longer half-life such as tenofovir (TDF) plus emtricitabine (FTC) has also been shown to decrease

NVP resistance after single-dose treatment *[21]*. The findings may, however, differ in patients on chronic NVP treatment. An alternative strategy is to substitute a protease inhibitor (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 an NNRTI- to a PI-based regimen prior to interruption had a lower rate of NNRTI-resistant mutation after interruption and a greater chance of resuppression of HIV RNA after restarting therapy than those who stopped all the drugs simultaneously or stopped the NNRTI before the 2-NRTI *[22]*. 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 ETR and treatment interruption is lacking but its long half-life of approximately 40 hours suggests that stopping ETR needs to be done carefully using the same suggestions for NVP and EFV for the time being.

- **Discontinuation and reintroduction of NVP**. Because NVP is an inducer of the drug-metabolizing hepatic enzymes, administration of full therapeutic doses of NVP without a 2-week, low-dose escalation phase will result in excess plasma drug levels and potentially increase the risk of toxicity. Therefore, in a patient who has interrupted treatment with NVP for more than 2 weeks, NVP should be reintroduced with a dose escalation period of 200 mg once daily for 14 days and then a 200 mg twice-daily regimen **(AII)**.
- **Discontinuation of FTC, 3TC, or TDF in patients with hepatitis B virus (HBV) coinfection**. Patients with HBV coinfection (hepatitis B surface antigen [HbsAg] or hepatitis B e antigen [HBeAg] positive) and receiving one or a combination of these NRTIs may experience an exacerbation of hepatitis upon drug discontinuation *[23-24]*. (See **Hepatitis B (HBV)/HIV Coinfection**.)

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# Considerations for Antiretroviral Use in Special Patient Populations

## ACUTE HIV INFECTION (Updated January 10, 2011)

***Panel's Recommendations:***

- ***It is unknown if treatment of acute HIV infection results in long-term virologic, immunologic, or clinical benefit; treatment should be considered optional at this time (CIII).***
- ***Therapy should also be considered optional for patients with HIV seroconversion in the previous 6 months (CIII).***
- ***All pregnant women with acute or recent HIV infection should start a combination antiretroviral (ARV) regimen as soon as possible to prevent mother-to-child transmission (MTCT) of HIV (AI).***
- ***If the clinician and patient elect to treat acute HIV infection, 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 be helpful in guiding the selection of an ARV regimen that can provide the optimal 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).***
- ***Because clinically significant resistance to protease inhibitors (PIs) is less common than resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) in antiretroviral therapy (ART)-naïve persons who harbor drug-resistant virus, a ritonavir (RTV)-boosted PI-based regimen should be used if therapy is initiated before drug-resistance test results are available (AIII).***

***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***

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 symptoms are similar to those for influenza, infectious mononucleosis, or other illnesses. Additionally, acute infection can occur asymptomatically. **Table 10** provides practitioners with guidance 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 is typically 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 because 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. Interest in routine screening for antibody-negative acute infection has led to select centers performing virologic testing on all antibody-negative specimens, including the use of pooled HIV RNA testing on all seronegative serum samples *[8]*. In addition, a combination HIV antigen/antibody test

(ARCHITECT), recently licensed by the Food and Drug Administration (FDA), could be used for this purpose. Patients diagnosed with acute HIV infection by a virologic test while still antibody negative or indeterminate should have confirmatory serologic testing performed over the next 3 months **(AI)**. (See **Table 10**.)

### *Performance of Resistance Testing*

Data from the United States and Europe demonstrate that transmitted virus may be resistant to at least one ARV drug in 6%–16% of patients *[9-11]*. If the decision is made to initiate therapy in a person with acute HIV infection, genotypic resistance testing at baseline to guide the selection of an ARV regimen will likely optimize virologic response; this strategy is therefore recommended **(AIII)**. (See **Drug-Resistance Testing**.) 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 ART has a beneficial effect on laboratory markers of disease progression *[12-16]*. 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 of viral transmission during this highly infectious stage of disease. 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 ART *[17-18]*.
- **Potential Risks of Treating Acute HIV Infection.** The potential disadvantages of initiating therapy include exposure to ART without a known clinical benefit, which could result in drug toxicities, development of drug resistance, continuous need for therapy with strict adherence, and adverse effect on quality of life.

Some of the potential benefits associated with treatment during acute infection remain uncertain and of unknown clinical relevance, while the risks are largely consistent with those for initiating therapy in chronically infected asymptomatic patients with high CD4 counts. 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).** Because acute or recent HIV infection is associated with a high risk of MTCT of HIV, all HIV-infected pregnant women should start a combination ARV regimen as soon as possible to prevent perinatal transmission of HIV **(AI)** *[19]*. Following delivery, considerations regarding continuation of the ARV regimen as therapy for the mother are the same as for treatment of other nonpregnant individuals. 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 ART in this setting. Information regarding such trials can be obtained at **www.clinicaltrials.gov** or from local HIV treatment experts.

### *Treatment for Recent but Nonacute HIV Infection or Infection of Undetermined Duration*

In addition to patients with acute HIV infection, some HIV 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 *[20]*. In the case of pregnancy, use of a combination ARV regimen to prevent MTCT of HIV is recommended **(AI)**. For nonpregnant patients the current guidelines have provided a rationale for recommending initiation of ART in ART-naïve patients with CD4 count between 350 and 500 cells/mm$^3$ as well as a recommendation to consider therapy for those with CD4 count >500 cells/mm$^3$. (See **Initiating Antiretroviral Therapy**.) Although these recommendations are primarily based upon data from patients with chronic infection, the potential benefit of early treatment on immune recovery and on attenuation of the pathologic effects of viremia-associated inflammation and coagulation could apply to those with early HIV infection as well. Based upon all of

these considerations it is reasonable that clinicians share with patients the potential rationale for initiating ART during early HIV infection and offer treatment to those who are willing and able to commit to lifelong treatment.

### *Treatment Regimen for Acute or Recent HIV Infection*

If the clinician and patient have made the decision to initiate ART for acute or recent HIV infection, the goal of therapy is to suppress plasma HIV RNA levels to below detectable levels **(AIII)**. Data are insufficient to draw firm conclusions regarding specific drug combinations to use in acute HIV infection. Potential combinations of agents should be those used in chronic infection. (See **What to Start**.) However, because clinically significant resistance to PIs is less common than resistance to NNRTIs in ART-naïve persons, an RTV-boosted PI-based regimen should be used if therapy is initiated before drug-resistance test results are available **(AIII)**. If resistance test results or resistance pattern of the source virus are known, this information should be used to guide the selection of the ARV regimen.

### *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 at 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 counseling patients prior to initiation of therapy. Patients need to know that there are limited data regarding the benefits of stopping treatment, whereas strong data from studies in patients with chronic HIV infection show that stopping ART may be harmful *[21]*.

## Table 10. Identifying, Diagnosing, and Managing Acute HIV-1 Infection (Updated January 10, 2011)

- **Suspecting acute HIV infection:** Signs or symptoms of acute HIV infection with recent (within 2–6 weeks) high risk of exposure to HIV*
  - 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:** Epstein-Barr virus (EBV)- and non-EBV (e.g., cytomegalovirus [CMV])-related infectious mononucleosis syndromes, influenza, viral hepatitis, streptococcal infection, syphilis

- **Evaluation/diagnosis of acute/primary HIV infection**
  - HIV antibody enzyme immunoassay (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.
  - When acute HIV infection is diagnosed by a positive virologic test (such as HIV RNA or p24 antigen) that was preceded by a negative HIV antibody test, a confirmatory HIV antibody test should be performed over the next 3 months to confirm seroconversion.

- **Considerations for antiretroviral therapy:**
  - All pregnant women with acute or recent HIV infection should start on a combination ARV regimen as soon as possible because of the high risk of MTCT of HIV **(AI)**.
  - Treatment of acute and early HIV infection in nonpregnant persons is considered optional **(CIII)**.
  - Potentially unique benefits associated with ART during acute and early infection exist, although they remain unproven.
  - The risks of ART during acute and early infection are consistent with those for initiating ART in chronically infected asymptomatic patients with high CD4 counts.
  - If therapy is initiated, the goal should be for maintenance of maximal viral suppression.
  - Enrollment in a 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. The p24 antigen is less sensitive but more specific than HIV RNA tests; HIV RNA tests are generally preferred. HIV RNA tests include quantitative branched DNA (bDNA), reverse transcriptase-polymerase chain reaction (RT-PCR), or qualitative transcription-mediated amplification (APTIMA, GenProbe).

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## HIV-INFECTED ADOLESCENTS AND YOUNG ADULTS (Updated January 10, 2011)

Older children and adolescents now make up the largest percentage of HIV-infected children cared for at pediatric HIV clinics in the United States. The Centers for Disease Control and Prevention (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 13–24 years of age *[1]*. Recent trends in HIV prevalence reveal that the disproportionate burden of HIV/AIDS among racial minorities is even greater among youth 13–19 years of age than among young adults 20–24 years of age *[2]*. Furthermore, trends for all HIV/AIDS diagnoses in 33 states from 2001 to 2006 decreased for all transmission categories except among men who have sex with men (MSM). Notably, among all black MSM, the largest increase in HIV/AIDS diagnoses occurred among youth 13–24 years of age *[3]*. 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 antiretroviral therapy (ART) and what antiretroviral (ARV) medications should be used.

Most adolescents who acquire HIV are infected through high-risk behaviors. Many of them are recently infected and unaware of their HIV infection status. Thus, many 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 among HIV-infected adolescents and young adults presenting for care identified primary genotypic resistance mutations to ARV 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 *[4]*. This transmission dynamic reflects that a substantial proportion of youth's sexual partners are likely older and may be more ART experienced; thus, awareness of the importance of baseline resistance testing among recently infected youth naïve to ART is imperative.

A limited but increasing number of HIV-infected adolescents are long-term survivors of HIV infection acquired perinatally or in infancy through blood products. Such adolescents are usually heavily ART experienced and may have a unique clinical course that differs from that of adolescents infected later in life *[5]*. If these heavily ART-experienced adolescents harbor resistant virus, optimal ARV regimens should be based on the same guiding principles as for heavily ART-experienced adults. (See **Virologic and Immunogic Failure**.)

Adolescents are developmentally at a difficult crossroad. Their needs for autonomy and independence and their evolving decisional capacity intersect and compete with concrete thinking processes, risk-taking behaviors, preoccupation with self-image, and the need to "fit in" with their peers. This makes it challenging to attract and sustain adolescents' focus on maintaining their health, particularly for those with chronic illnesses. These challenges are not specific to any particular transmission mode or stage of disease. Thus, irrespective of disease duration or mode of HIV transmission, every effort must be made to engage them in care so they can improve and maintain their health for the long term.

### *Antiretroviral Therapy Considerations in Adolescents*

Adult guidelines for ART are usually appropriate for postpubertal adolescents, because the clinical course of HIV-infected adolescents who were infected sexually or through injection drug use during adolescence is more similar to that of adults than to that of children. Adult guidelines can also be useful for postpubertal youth who were perinatally infected because these patients often have treatment challenges associated with the use of long-term ART that mirror those of ART-experienced adults, such as extensive resistance, complex regimens, and adverse drug effects.

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 *[6-7]*. 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 children who were infected with HIV perinatally *[8]*, 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 ARV 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 following adult or pediatric dosing guidelines and adolescents

who have 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 in 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*** *[9]*.

### *Adherence Concerns in Adolescents*

HIV-infected adolescents are especially vulnerable to specific adherence problems based on their psychosocial and cognitive developmental trajectory. 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;
- mood disorders and other mental illness;
- lack of familial and social support;
- absence of or inconsistent access to care or health insurance; and
- incumbent risk of inadvertent parental disclosure of the youth's HIV infection status if parental health insurance is used.

In selecting treatment regimens for adolescents, clinicians must balance the goal of prescribing a maximally potent ART 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 inconspicuous *[10]*. 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 *[11-13]*. Directly observed therapy might be considered for selected HIV-infected adolescents such as those with mental illness *[14-18]*.

### *Difficult Adherence Problems*

Because adolescence 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 who, while needing therapy, pose significant concerns regarding their 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 adherence-related problems are 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 made carefully in context with the individual's 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*** *[9]*.

### *Special Considerations in Adolescents*

Sexually transmitted infections (STIs), in particular human papilloma virus (HPV), should also be addressed in all adolescents. For a more detailed discussion on STIs, see the most recent CDC guidelines *[19]* and the pediatric opportunistic infection treatment guidelines on HPV among HIV-infected adolescents *[20]*. Family planning counseling, including a discussion of the risks of perinatal transmission of HIV and methods to reduce risks, should be provided to all youth. Providing gynecologic care for the HIV-infected female adolescent is especially important. Contraception, including the interaction of specific ARV drugs on hormonal contraceptives, and the potential for pregnancy also may alter choices of ART. As an example, efavirenz (EFV) 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** and the ***Perinatal Guidelines*** *[21]*.

### *Transitioning Care*

Given 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 abuse treatment, mental health, treatment education, and adherence counseling are all found in one clinic setting. In contrast, some 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 perinatally infected—who would likely have more disease burden history, complications, and chronicity; less functional autonomy; greater need for ART; and higher mortality risk; and (2) those more recently infected due to high-risk behaviors. Thus, these subgroups have unique biomedical and psychosocial considerations and needs.

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 lack of information, stigma or disclosure concerns, and differences in practice styles; (3) preparing youth for life skills development, including counseling them on the appropriate use of a primary care provider and appointment management, the importance of prompt symptom recognition and reporting, and 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 January 10, 2011)

### *Treatment Challenges of HIV-Infected IDUs*

Injection drug use is the second-most common mode of HIV transmission in the United States. In addition, noninjection illicit drug use may facilitate sexual transmission of HIV. Injection and noninjection 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 stimulants (e.g., cocaine and amphetamines); 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 of 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 because 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 injection and noninjection drug users 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 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, and endocarditis. Other morbidities such as alteration in levels of consciousness and neurologic and renal disease are not uncommon. Furthermore, these comorbidities are associated with a higher risk of drug overdoses in IDUs with HIV disease, due in part to respiratory, hepatic, and neurological impairments *[4]*. Successful HIV therapy for IDUs often rests upon acquiring familiarity with and providing care for these comorbid conditions and overdose prevention support.

IDUs have less access to HIV care and are less likely to receive antiretroviral therapy (ART) than other populations *[5-6]*. Factors associated with low rates of ART among IDUs include active drug use, younger age, female gender, suboptimal health care, recent incarceration, lack of access to rehabilitation programs, and lack of expertise among health care providers *[5-6]*. The typically unstable, chaotic life patterns of many IDUs; the powerful pull of addictive substances; and common misperceptions about the dangers, impact, and benefits of ART all contribute to decreased adherence *[7]*. The chronic and relapsing nature of substance abuse as a biologic and medical disease, compounded by the high rate of mental illness that antedates and/or is exacerbated by illicit substance use, additionally complicate the relationship between health care workers and IDUs *[8-9]*. The first step in provision of care and treatment for these individuals is to recognize the existence of a substance abuse problem. Whereas this is often open and obvious, patients may hide such behaviors from clinicians. Assessment of a patient for 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 ART in IDUs 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 ART. 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 *[9]*, 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 Opioid Substitution Therapy*

IDUs are more likely to experience an increased frequency of side effects and toxicities of ART. Although not systematically studied, this is likely because underlying hepatic, renal, neurologic, psychiatric, gastrointestinal, and hematologic disorders are highly prevalent among IDUs. Selection of ARV agents in this population should be made with consideration of these comorbid conditions. Opioid substitution therapies such as methadone and buprenorphine/naloxone and extended release naltrexone are commonly used for management of opioid dependence in HIV infected-patients.

**Methadone and ART.** Methadone, an orally administered, long-acting opioid agonist, is the most common pharmacologic treatment for opioid addiction. Its use is associated with decreased heroin use, decreased needle sharing, and improved quality of life. Because of its opioid-induced effects on gastric emptying and the metabolism of cytochrome P (CYP) 450 isoenzymes 2B6, 3A4, and 2D6, pharmacologic effects and interactions with ARV agents may commonly occur *[13]*. These may diminish the effectiveness of either or both therapies by causing opioid withdrawal or overdose, increased methadone toxicity, and/or decreased ARV efficacy. Efavirenz (EFV), nevirapine (NVP), and lopinavir/ritonavir (LPV/r) have been associated with significant decreases in methadone levels. It is necessary to inform patients and substance abuse treatment facilities of the likelihood of this interaction. 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.

**Buprenorphine and ART.** Buprenorphine, a partial μ-opioid agonist, is administrated sublingually and is often coformulated with naloxone. It is being increasingly used for opioid dependence treatment. The lower risk of respiratory depression and overdose compared with methadone allows it to be prescribed by physicians in primary care for the treatment of opioid dependency. This flexible treatment setting could be of significant value to opioid-addicted HIV-infected patients who require ART because 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 *[13-14]*. Findings from available studies show a more favorable drug interaction profile than that of methadone.

**Naltrexone and ART.** A once monthly extended-release intramuscular formulation of naltrexone was recently approved for prevention of relapse in patients who have undergone an opioid detoxification program. Naltrexone is also indicated for treatment of alcohol dependency. Naltrexone is not metabolized via the CYP 450 enzyme system and is not expected to interact with protease inhibitors (PIs) or nonnucleoside reverse transcriptase inhibitors (NNRTIs) *[15]*.

**Table 11** provides the currently available pharmacokinetic interaction data that clinicians can use as a guide for managing patients receiving ART and methadone or buprenorphine. Particular attention is needed concerning communication between HIV care providers and drug treatment programs regarding additive drug toxicities and drug interactions resulting in opiate withdrawal or excess.

Methylenedioxymethamphetamine (MDMA), GHB, ketamine, and methamphetamine all have the potential to interact with ARV agents because all are metabolized, at least in part, by the CYP 450 system. Overdoses secondary to interactions between the party drugs (i.e., MDMA or GHB) and PI-based ART have been reported *[16]*.

### *Summary*

It is usually possible over time to support most active drug users such that acceptable adherence levels with ARV agents can be achieved *[17-18]*. Providers must work to combine all available resources to stabilize an active drug user in preparation for ART. This should include identification of concurrent medical and psychiatric illnesses, drug treatment, needle and syringe exchange, reduction in high-risk sexual behavior, and harm reduction strategies. A

history of drug use alone is insufficient reason to withhold ART because individuals with a history of prior drug use have adherence rates similar to individuals who do not abuse drugs.

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 ARV agents, including the increased risk of side effects and toxicities. Simple regimens should be considered to enhance medication adherence. Preference should be given to ARV agents that have a lower risk of hepatic and neuropsychiatric side effects, simple dosing schedules, and minimal interaction with methadone.

## Table 11. Drug Interactions between Antiretroviral Agents and Drugs Used to Treat Opioid Addiction (January 10, 2011)



| Concomitant Drug | Antiretroviral Class/Drug | Pharmacokinetic Interactions Recommendations/Clinical Comments |
|---|---|---|
| **Buprenorphine** | EFV | buprenorphine AUC ↓ 50%; norbuprenorphine* AUC ↓ 71%<br><br>No withdrawal symptoms reported. No dosage adjustment recommended; however, monitor for withdrawal symptoms. |
| | ATV | buprenorphine AUC ↑ 93%; norbuprenorphine AUC ↑ 76%; ↓ ATV levels possible<br><br>Do not coadminister buprenorphine with unboosted ATV. |
| | ATV/r | buprenorphine AUC ↑ 66%; norbuprenorphine AUC ↑ 105%<br><br>Monitor for sedation. Buprenorphine dose reduction may be necessary. |
| | DRV/r | buprenorphine: no significant effect, norbuprenorphine AUC ↑ 46% and $C_{min}$ ↑ 71%<br><br>No dose adjustment necessary. |
| | TPV/r | buprenorphine: no significant effect; norbuprenorphine AUC, $C_{max}$, and $C_{min}$ ↓ 80%; TPV Cmin ↓ 19%–40%<br><br>Consider monitoring TPV level. |
| | 3TC, ddI, TDF, ZDV, NVP, LPV/r, NFV | No significant effect<br><br>No dosage adjustment necessary. |
| | ABC, d4T, FTC, ETR, FPV +/- RTV, IDV +/- RTV, SQV/r, RAL, MVC, T20 | No data |

**Table 11. Drug Interactions between Antiretroviral Agents and Drugs Used to Treat Opioid Addiction**


| Concomitant Drug | Antiretroviral Class/Drug | Pharmacokinetic Interactions Recommendations/Clinical Comments |
|---|---|---|
| **Methadone** | ABC | methadone clearance ↑ 22%<br><br>No dosage adjustment necessary. |
| | d4T | d4T AUC ↓ 23% and $C_{max}$ ↓ 44%<br><br>No dosage adjustment necessary. |
| | ZDV | ZDV AUC ↑ 29%–43%<br><br>Monitor for ZDV-related adverse effects. |
| | EFV | methadone AUC ↓ 52%<br><br>Opioid withdrawal common; increased methadone dose often necessary. |
| | NVP | methadone AUC ↓ 41%<br>NVP: no significant effect<br><br>Opioid withdrawal common; increased methadone dose often necessary. |
| | ATV/r, DRV/r, FPV/r, IDV/r, LPV/r, SQV/r, TPV/r | With ATV/r, DRV/r, FPV/r: R-methadone† AUC ↓ 16%–18%;<br>With LPV/r: methadone AUC ↓ 26%–53%;<br>With SQV/r 1,000/100mg BID: R-methadone AUC ↓ 19%;<br>With TPV/r: R-methadone AUC ↓ 48%<br><br>Opioid withdrawal unlikely but may occur. No adjustment in methadone usually required; however, monitor for opioid withdrawal and increase methadone dose as clinically indicated. |
| | FPV | No data with FPV (unboosted)<br>With APV: R-methadone $C_{min}$ ↓ 21%, AUC no significant change<br><br>Monitor and titrate methadone as clinically indicated.<br>The interaction with FPV is presumed to be similar. |
| | NFV | methadone AUC ↓ 40%<br><br>Opioid withdrawal rarely occurs. Monitor and titrate dose as clinically indicated. May require increased methadone dose. |
| | ddI (EC capsule), 3TC, TDF, ETR, RTV, ATV, IDV, RAL | No significant effect<br><br>No dosage adjustment necessary. |
| | FTC, MVC, T20 | No data |

*Norbuprenorphine is an active metabolite of buprenorphine.
† R-methadone is the active form of methadone.

**Acronyms:** 3TC = lamivudine, d4T = stavudine, T20 = enfuvirtide, ABC = abacavir, APV = amprenavir, ATV = atazanavir, ATV/r = atazanavir/ritonavair, ddI = didanosine, DRV/r = darunavir/ritonavir, EFV = efavirenz, ETR = etravirine, FPV = fosamprenavir, FPV/r = fosamprenavir/ritonavir, FTC = emtricitabine, IDV = indinavir, IDV/r = indinavir/ritonavir, LPV/r = lopinavir/ritonavir, MVC = maraviroc, NFV = nelfinavir, NVP = nevirapine, RAL = raltegravir, RTV = ritonavir, SQV/r = sacquinavir/ritonavir, TDF = tenofovir, TPV = tipranavir, TPV/r = tipranavir/ritonavir, ZDV = zidovudine

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## HIV-INFECTED WOMEN (Updated January 10, 2011)

***Panel's Recommendations:***

- ***The indications for initiation of antiretroviral therapy (ART) and the goals of treatment are the same for HIV-infected women as for other HIV-infected adults and adolescents (AI).***
- ***Women taking antiretroviral (ARV) drugs that have significant pharmacokinetic interactions with oral contraceptives should use an additional or alternative contraceptive method for prevention of unintended 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 persons, including pregnant women, prior to initiation of ART (AIII) and for women entering pregnancy with detectable HIV RNA levels while on therapy (AI).***
- ***When selecting an ARV combination regimen for a pregnant woman, clinicians should consider the known safety, efficacy, and pharmacokinetic data of each agent during pregnancy (AIII).***
- ***Efavirenz (EFV) 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 Health and Human Services (HHS) Perinatal Guidelines when designing a regimen for a pregnant woman (AIII).***

***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***

This section provides discussion of some basic principles and unique considerations 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 current ***Perinatal Guidelines*** *[1]* for in-depth discussion and management assistance.

### *Gender Considerations in Antiretroviral Therapy*

In general, studies to date have not shown differences in virologic efficacy of ART by gender *[2-4]*, although a number of studies have suggested that gender or sex may influence the frequency, presentation, and severity of selected ARV-related adverse events *[5]*. Although data are limited, there is also evidence that women may metabolize and respond to specific medications, including ARV drugs, differently than men *[6-8]*.

**Adverse Effects**:

- ***Nevirapine (NVP)-associated hepatotoxicity***: NVP has been associated with an increased risk of symptomatic, potentially fatal, and often rash-associated liver toxicity among ARV-naïve individuals; women with higher CD4 counts (>250 cells/mm$^3$) appear to be at greatest risk *[9-12]*. It is generally recommended that NVP not be prescribed to ARV-naïve women who have CD4 counts >250 cells/mm$^3$ unless there is no other alternative and the benefit from NVP 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 reverse transcriptase inhibitors (NRTIs). Lactic acidosis is most common with stavudine (d4T), didanosine (ddI), and zidovudine (ZDV); however, it can occur with other NRTIs *[13]*.
- ***Metabolic complications***: A few studies have compared women to men in terms of metabolic complications associated with ARV use. HIV-infected women are more likely to experience increases in central fat with ART and are less likely to have triglyceride elevations on treatment *[14-15]*. Women have an increased risk of osteopenia/osteoporosis, particularly after menopause, and this risk may be exacerbated by HIV and ART *[16-17]*. At the present time, none of these differences requires a change in recommendations regarding treatment or monitoring.

### *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 ARV use when trying to conceive and during pregnancy. (See ***Perinatal Guidelines*** *[1]*). 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 women. As part of the evaluation for initiating ART, women should be counseled about the potential teratogenic risk of EFV-containing regimens, should pregnancy occur. EFV-containing regimens should be avoided in women who are trying to conceive or who are sexually active and not using effective and consistent contraception.

Effective contraception should be available for women who wish to prevent pregnancy. Several protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) have drug interactions with combined oral contraceptives (COCs). Interactions include either a decrease or an increase in blood levels of ethinyl estradiol, norethindrone, or norgestimate (see **Tables 15a and b**), which potentially decrease contraceptive efficacy or increase estrogen- or progestin-related adverse effects (e.g., thromboembolic risk). In general, women who are on any of these ARV drugs 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 ARVs and COCs. Data on drug interactions between ARVs and progestin-only contraceptive methods are limited; however, recent data have found no significant changes in ARV drug concentrations of nelfinavir (NFV), NVP, or EFV when used with depot medroxyprogesterone acetate (DMPA), and there is no evidence of reduced DMPA effectiveness *[18-20]*. Intrauterine devices have been shown to be safe and effective in HIV-infected women *[21-22]*. Counseling about reproductive issues should be provided on an ongoing basis.

### *Pregnant Women*

The use of combination ARV regimens is recommended for all HIV-infected pregnant women, regardless of virologic, immunologic, or clinical parameters, primarily for prevention of HIV transmission from mother to child and for treatment of maternal infection **(AI)**. Pregnant HIV-infected women should be counseled regarding the known benefits versus potential risks of ARV use during pregnancy to the mother, fetus, and newborn. A woman's decision regarding ARV use 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 maternal, fetal, and neonatal well-being.

**Prevention of Mother-to-Child Transmission (PMTCT).** Both reduction of HIV RNA levels and use of ARVs appear to have an independent effect on reduction of perinatal transmission of HIV *[23-25]*. The goal of ARV use is to achieve maximal and sustained suppression of HIV RNA levels during pregnancy, but most critically by late pregnancy and the time of delivery, when most transmission occurs.

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

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

**Regimen Considerations.** Pregnancy should not preclude the use of optimal drug regimens. However, recommendations regarding the choice of ARVs 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 ARV-associated adverse effects in pregnant women,
- effect on the risk of perinatal transmission of HIV, and
- potential short- and long-term effects of the ARV on the fetus and newborn, which are unknown for many drugs.

Clinicians should review the ***Perinatal Guidelines*** *[1]* for a detailed discussion of drug choices. Combination drug regimens are considered the standard of care in pregnancy, both for the treatment of HIV infection and for PMTCT. ZDV 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.

**NRTIs:**

- Although no longer considered a preferred NRTI for non-pregnant adults and adolescents, ZDV is still one of the preferred NRTI drugs when used in pregnancy based on long-term effectiveness in prevention of transmission and safety data in pregnancy (for more detailed discussion, see the ***Perinatal Guidelines*** *[1]*). However, ZDV should not be included in a regimen if there is severe toxicity, documented resistance, or if the woman is also receiving d4T. Women already on a fully suppressive regimen that does not include ZDV should continue on the regimen **(AIII)**.
- The syndrome of lactic acidosis and hepatic steatosis may present with similar signs and symptoms to certain pregnancy-specific disorders (i.e., acute fatty liver of pregnancy, HELLP [hemolysis, elevated liver enzymes, low platelet count] syndrome). Given this similarity, clinicians should have a low threshold for considering lactic acidosis in the differential diagnosis and for appropriate evaluation of pregnant HIV-infected women receiving NRTIs with a consistent clinical picture, particularly if they have accompanying hepatitis or pancreatitis.

**NNRTIs:**

- EFV-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 EFV *[26-27]*. EFV may be considered for use after the first trimester if indicated because of toxicity, resistance, drug interaction issues, or other clinical concerns (e.g., adherence, presentation after first trimester on EFV-containing regimen) *[28]*.
- Although there is no evidence that pregnancy additionally increases risk of NVP toxicity over that in nonpregnant women *[29]*, NVP should not be initiated as a component of a combination regimen in ARV-naïve pregnant women who have CD4 counts >250 cells/mm$^3$ unless the benefit clearly outweighs the risk **(AII)**.

**PIs:**

- Several small studies show that optimal levels of several PIs may not be achieved in pregnancy with standard dosing, especially in the third trimester, although the clinical relevance of this is unknown *[30-32]*. For more information regarding potential dosing alterations, please refer to the ***Perinatal Guidelines*** *[1]*. Once-daily lopinavir/ritonavir (LPV/r) dosing is not recommended in pregnancy, because there are no data to address adequacy of blood levels with this dosing regimen **(BII)**.

Minimal data exist on the use of newer agents, including entry inhibitors and integrase inhibitors, in pregnancy.

Clinicians who are treating HIV-infected pregnant women are strongly encouraged to report cases of prenatal exposure to ARVs (either administered alone or in combinations) to the Antiretroviral Pregnancy Registry (**http://www.apregistry.com**). The registry collects observational data regarding exposure to FDA-approved ARV drugs during pregnancy for the purpose of assessing potential teratogenicity. For more information regarding selection and use of ART during pregnancy, refer to the ***Perinatal Guidelines*** *[1]*. Lastly, women should be counseled regarding the avoidance of breastfeeding. Continued clinical, immunologic, and virologic follow-up should be done as recommended for non-pregnant adults and adolescents.

### *Discontinuation of Antiretroviral Therapy Postpartum*

Following delivery, considerations regarding continuation of ART for maternal therapeutic indications are the same as for other non-pregnant individuals. The decision of whether to continue therapy after delivery should take into account current recommendations for initiation of ART, current and nadir CD4 T-cell counts and trajectory, HIV RNA levels, adherence issues, and patient preference. A study from the Women and Infants Transmission Study (WITS) of women who were ARV naïve prior to pregnancy and had CD4 counts >350/mm$^3$ *[33]* found no significant differences in CD4 count, viral load, or disease progression among those who did or did not continue ART 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. In one study, NVP resistance was identified in 16% of women on an NVP-containing regimen despite continuation of the NRTI backbone for 5 days after stopping NVP *[34]*. For women whose antepartum regimen included an NNRTI and who plan to stop ARV prophylaxis after delivery, consideration should be given to stopping the NNRTI and continuing the other ARV or switching from an NNRTI to a PI prior to interruption and continuing the PI with the other ARV for a period of time before electively stopping ART. The optimal interval between stopping an NNRTI and the other ARV is not known; at least 7 days is recommended but some experts recommend continuing the other ARV or substituting a PI plus two other agents for up to 30 days. 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 and to assess the effect of limited-duration, fully suppressive ARV prophylaxis in pregnancy on future treatment efficacy. (See **Discontinuation or Interruption of Antiretroviral Therapy**.)

In HIV and hepatitis B virus (HBV) co-infected pregnant women who are receiving ART only for perinatal prophylaxis and who are stopping therapy after delivery, careful clinical and laboratory monitoring for HBV flare should be performed postpartum when ARVs 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**.)

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## HIV-2 INFECTION (Updated January 10, 2011)

HIV-2 infection is endemic in West Africa. Although HIV-2 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 (ART) may become necessary during the course of infection. Concomitant HIV-1 and HIV-2 infection may occur and should be considered in patients from an area with high prevalence of HIV-2. 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 counts despite apparent virologic suppression on ART.

The Multispot HIV-1/HIV-2 Rapid Test (Bio-Rad Laboratories) is Food and Drug Administration (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 no HIV-2 commercial viral load assays are 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, no validated HIV-2 genotypic or phenotypic antiretroviral (ARV) resistance assays are available.

To date, there have been no randomized trials addressing the question of when to start ART 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 non-nucleoside reverse transcriptase inhibitors (NNRTIs) *[7]* and to enfuvirtide *[8]*. *In vitro* data suggest HIV-2 is sensitive to the currently available nucleoside reverse transcriptase inhibitors (NRTIs), although with a lower barrier to resistance than HIV-1 *[9-10]*. Variable sensitivity among protease inhibitors (PIs) has been reported; lopinavir (LPV), saquinavir (SQV), and darunavir (DRV) are more active against HIV-2 than other approved PIs *[11-14]*. The integrase inhibitor, raltegravir (RAL) *[15]*, and the CCR5 antagonist, maraviroc (MVC), appear active against some HIV-2 isolates, although no approved assays to determine HIV-2 coreceptor tropism exist and HIV-2 is known to utilize multiple minor coreceptors in addition to CCR5 and CXCR4 *[16]*. Several small studies suggest poor responses among HIV-2 infected individuals treated with some ARV regimens, including dual-NRTI regimens, regimens containing two NRTIs + NNRTI, and some unboosted PI-based regimens including nelfinavir (NFV) or indinavir (IDV) plus zidovudine (ZDV) and lamivudine(3TC) *[6, 17-19]*. Clinical data on the utility of triple-NRTI regimens are conflicting *[20-21]*. In general, boosted PI-containing regimens have resulted in more favorable virologic and immunologic responses *[21]*. One small study suggested satisfactory responses to lopinavir/ritonavir (LPV/r)-containing regimens in 17 of 29 (59%) of ARV-naïve subjects *[22]*.

Resistance-associated mutations develop commonly in HIV-2 patients on therapy *[17, 21, 23]*. Genotypic algorithms used to predict drug resistance in HIV-1 may not be applicable to HIV-2, because pathways and mutational patterns leading to resistance may differ *[10, 21, 24]*. CD4 cell recovery on therapy may be poor *[25]*, suggesting that more reliable methods for monitoring disease progression and treatment efficacy in HIV-2 infection are needed.

Some groups have recommended specific preferred and alternative regimens for initial therapy of HIV-2 infection *[24]*, though as yet there are no controlled trial data to reliably predict their success. Until more definitive data are available in an ART-naïve patient with HIV-2 mono-infection or with HIV-1/HIV-2 dual infection who requires treatment, clinicians should initiate a regimen containing two NRTIs and a boosted PI. Monitoring of virologic 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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# Considerations for Antiretroviral Use in Patients with Coinfections

## HEPATITIS B (HBV)/HIV COINFECTION (January 10, 2011)

***Panel's Recommendations:***

- ***Prior to intiation of antiretroviral therapy (ART), all patients who test positive for hepatitis B surface antigen (HBsAg) should be tested for hepatitis B virus (HBV) DNA using a quantitative assay to determine the level of HBV replication (AIII).***
- ***Because emtricitabine (FTC), lamivudine (3TC), and tenofovir (TDF) have activity against both HIV and HBV, if HBV or HIV treatment is needed, ART should be initiated with the combination of TDF + FTC or TDF + 3TC as the nucleoside reverse transcriptase inhibitor (NRTI) backbone of a fully suppressive antiretroviral (ARV) regimen (AI).***
- ***If HBV treatment is needed and TDF cannot safely be used, the alternative recommended HBV therapy is entecavir in addition to a fully suppressive ARV regimen (BI). Other HBV treatment regimens include peginterferon alfa monotherapy or adefovir in combination with 3TC or FTC or telbivudine in addition to a fully suppressive ARV regimen (BII).***
- ***Entecavir has activity against HIV; its use for HBV treatment without ART in patients with dual infection may result in the selection of the M184V mutation that confers HIV resistance to 3TC and FTC. Therefore, entecavir must be used in addition to a fully suppressive ARV regimen when used in HIV/HBV-coinfected patients (AII).***
- ***Discontinuation of agents with anti-HBV activity may cause serious hepatocellular damage resulting from reactivation of HBV; patients should be advised against self-discontinuation and carefully monitored during interruptions in HBV treatment (AII).***
- ***If ART needs to be modified due to HIV virologic failure and the patient has adequate HBV suppression, the ARV drugs active against HBV should be continued for HBV treatment in combination with other suitable ARV agents to achieve HIV suppression (AIII).***

***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***

Approximately 5%–10% of HIV-infected persons also have chronic HBV infection, defined as testing positive for HBsAg for more than 6 months *[1]*. The progression of chronic HBV to cirrhosis, end-stage liver disease, and/or hepatocellular carcinoma is more rapid in HIV-infected persons than in persons with chronic HBV alone *[2]*. Conversely, chronic HBV does not substantially alter the progression of HIV infection and does not influence HIV suppression or CD4 cell responses following ART initiation *[3-4]*. However, several liver-associated complications that are ascribed to flares in HBV activity, discontinuation of dually active ARVs, or toxicity of ARVs can affect the treatment of HIV in patients with HBV coinfection *[5-7]*. These include the following:

- FTC, 3TC, and TDF are approved ARVs that also have antiviral activity against HBV. Discontinuation of these drugs may potentially cause serious hepatocellular damage resulting from reactivation of HBV *[8]*.
- Entecavir has activity against HIV; its use for HBV treatment without ART in patients with dual infection may result in the selection of the M184V mutation that confers HIV resistance to 3TC and FTC. Therefore, entecavir must be used in addition to a fully suppressive ARV regimen when used in HIV/HBV-coinfected patients **(AII)** *[9]*.
- 3TC-resistant HBV is observed in approximately 40% of patients after 2 years on 3TC for chronic HBV and in approximately 90% of patients after 4 years when 3TC is used as the only active drug for HBV in coinfected patients. Therefore, 3TC or FTC should be used in combination with other anti-HBV drugs **(AII)** *[10]*.
- Immune reconstitution after initiation of treatment for HIV and/or HBV can be associated with elevation in transaminases, possibly because HBV is primarily an immune-mediated disease *[11]*.
- Some ARV agents can cause increases in transaminase levels. The rate and magnitude of these increases are higher with HBV coinfection *[12-13]*. The etiology and consequences of these changes in liver function tests are unclear

because continuation of ART may be accompanied by resolution of the changes. Nevertheless, some experts suspend the implicated agent(s) when the serum alanine transferase (ALT) level is increased to 5–10 times the upper limit of normal. However, in HIV/HBV-coinfected persons, increases in transaminase levels can herald hepatitis B e antigen (HBeAg) seroconversion due to immune reconstitution, so the cause of the elevations should be investigated prior to the decision to discontinue medications. In persons with transaminase increases, HBeAg seroconversion should be evaluated by testing for HBeAg and anti-HBe as well as HBV DNA levels.

***Recommendations for HBV/HIV-Coinfected Patients***

- All patients with chronic HBV should be advised to abstain from alcohol, assessed for immunity to hepatitis A virus (HAV) infection (anti-HAV antibody total) and vaccinated if nonimmune, advised on methods to prevent HBV transmission (methods that do not differ from those to prevent HIV transmission), and evaluated for the severity of HBV infection as outlined in the ***Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents*** *[14]*.

- Prior to intiation of ART, all persons who test positive for HBsAg should be tested for HBV DNA using a quantitative assay to determine the level of HBV replication **(AIII)**. Persons with chronic HBV infection already receiving ART active against HBV should undergo quantitative HBV DNA testing every 6–12 months to determine the effectiveness of therapy in suppressing HBV replication. The goal of HBV therapy with NRTIs is to prevent liver disease complications by sustained suppression of HBV replication to the lowest achievable level.

- **If not yet on therapy and HBV or HIV treatment is needed:** In persons without HIV infection, the recommended anti-HBV drugs for the treatment of persons naïve to HBV therapy are TDF and entecavir *[15-16]*. In HIV-infected patients, however, only TDF can be considered part of the ARV regimen; entecavir has weak anti-HIV activity and must not be considered part of an ARV regimen. In addition, only TDF is fully active for the treatment of persons with known or suspected 3TC-resistant HBV infection. To avoid selection of HBV-resistant variants, when possible, these agents should not be used as the only agent with anti-HBV activity in an ARV regimen **(AIII)**.

  ***Preferred regimen***. The combination of TDF + FTC or TDF + 3TC should be used as the NRTI backbone of a fully suppressive ARV regimen and for the treatment of HBV infection *[17-19]* **(AII)**.

  ***Alternative regimens***. If TDF cannot safely be used**,** entecavir should be used in addition to a fully suppressive ARV regimen **(AII)**; importantly, entecavir should not be considered to be a part of the ARV regimen *[20]* **(BII)**. Due to a partially overlapping HBV-resistance pathway, it is not known if the combination of entectavir + 3TC or FTC will provide additional virologic or clinical benefit compared with entecavir alone. In persons with known or suspected 3TC-resistant HBV infection, the entecavir dose should be increased from 0.5 mg/day to 1 mg/day. However, entecavir resistance may emerge rapidly in patients with 3TC-resistant HBV infection. Therefore, entecavir should be used with caution in such patients with frequent monitoring (~ every 3 months) of the HBV DNA level to detect viral breakthrough. Other HBV treatment regimens include peginterferon alfa monotherapy or adefovir in combination with 3TC or FTC or telbivudine in addition to a fully suppressive ARV regimen *[17, 21-22]*; however, data on these regimens in persons with HIV/HBV coinfection are limited **(BII)**. Due to safety concerns, peginterferon alfa should not be used in HIV/HBV-coinfected persons with cirrhosis.

- **Need to discontinue medications active against HBV:** The patient's clinical course should be monitored with frequent liver function tests. The use of adefovir dipivoxil, entecavir, or telbivudine to prevent flares, especially in patients with marginal hepatic reserve such as persons with compensated or decompensated cirrhosis, can be considered *[8]*. These alternative HBV regimens should only be used in addition to a fully suppressive ARV regimen.

- **Need to change ART because of HIV resistance:** If the patient has adequate HBV suppression, the ARV drugs active against HBV should be continued for HBV treatment in combination with other suitable ARV agents to achieve HIV suppression **(AIII)**.

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## HEPATITIS C (HCV)/HIV COINFECTION (Updated December 1, 2009)

Long-term studies of patients with chronic hepatitis C virus (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 than 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 (ARV)-associated hepatotoxicity *[7-8]*. Multiple studies have shown poor prognosis for HCV/HIV coinfection in the era of combination antiretroviral therapy (ART). It is unclear if HCV infection accelerates the rate of HIV progression *[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 ART reduces the attributable morbidity/mortality from untreated HCV is unknown, the presence of chronic HCV infection influences the treatment of HIV with ARV as discussed below.

### *Assessment of HCV/HIV Coinfection Prior to Antiretroviral Therapy*

- Prior to initiation of ART, 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 receive hepatitis A (HAV) and hepatitis B (HBV) vaccines 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 cells/mm$^3$), it may be preferable to initiate ART 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 (ddI) should not be given with ribavirin because of the potential for drug-drug interactions leading to life-threatening ddI-associated mitochondrial toxicity including hepatomegaly/steatosis, pancreatitis, and lactic acidosis *[16]*.
    - Zidovudine (ZDV) 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 (ABC) 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; ZDV 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 ART is more common in HIV/HCV coinfection. The greatest risk of 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 ARV-associated DILI *[22]*.
    - Given the substantial heterogeneity in patient populations and drug regimens, comparison of DILI incidence rates for individual ARV 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 ARV drugs that are no longer commonly used in clinical practice and that include stavudine (d4T) (with or without ddI), nevirapine (NVP), full-dose ritonavir (RTV) (600 mg twice daily), or tipranavir (TPV) (boosted by low-dose RTV) *[23]*. Also, due to the potential for concurrent fatty liver disease (steatosis), the use of d4T or ddI should be limited *[24]*.
    - Patients should be monitored by following alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels at 1 month and then every 3 months after initiation of ART. Mild to moderate fluctuations in ALT and/or AST 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 ART. Significant ALT and/or AST elevation (>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 HAV or HBV infection, hepatobiliary disease, or alcoholic hepatitis); short-term interruption of ART may be required *[25]*.

- When to start ART: The rate of liver disease (fibrosis) progression is accelerated by HIV/HCV coinfection, particularly in persons with low CD4 counts (≤350 cells/$mm^3$). Data derived largely from retrospective cohort studies regarding the effect of ART on the natural history of HCV disease are inconsistent *[6, 26-27]*. However, ART 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 ART outweigh concerns regarding DILI.
    - ART should be started in HCV/HIV-coinfected persons in accordance with the Panel's recommendation for initiating ART in ART-naïve patients.

- What to start and what not to use: Initial combination regimens for the ARV-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 ART *[31]*. Special considerations for ART in persons with HCV/HIV coinfection include:
    - Patients receiving or considering therapy with ribavirin should avoid ddI, d4T, and ZDV.
    - ARV 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 ARV 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 WITH HIV COINFECTION

**(Updated January 10, 2011)**

***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).***
- ***All HIV-infected patients with diagnosed active TB should be started on TB treatment immediately (AI).***
- ***All HIV-infected patients with diagnosed active TB should be treated with antiretroviral therapy (ART) (AI).***
- ***For patients with CD4 count <200 cells/mm$^3$, ART should be initiated within 2–4 weeks of starting TB treatment (AI).***
- ***For patients with CD4 count 200–500 cells/mm$^3$, the Panel recommends initiation of ART within 2–4 weeks, or at least by 8 weeks after commencement of TB therapy (AIII).***
- ***For patients with CD4 count >500 cells/mm$^3$, most Panel members also recommend starting ART within 8 weeks of TB therapy (BIII).***
- ***Despite pharmacokinetic drug interactions, a rifamycin should be included in regimens for patients receiving ART, with dosage adjustment if necessary (AII).***
- ***If a protease inhibitor (PI)-based regimen is used, rifabutin is the preferred rifamycin in HIV-infected patients with active TB disease due to its lower risk of substantial interactions with PIs (AII). Coadministration of rifampin and PIs (with or without ritonavir [RTV] boosting) is not recommended (AII).***
- ***Immune reconstitution inflammatory syndrome (IRIS) may occur after initiation of ART. Both ART and TB treatment should be continued while managing IRIS (AIII).***
- ***Treatment support, including directly observed therapy (DOT) of TB treatment, is strongly recommended for HIV-infected patients with active TB disease (AII).***

***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***

**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. "HIV/TB coinfection" is not used because the term can refer to either active TB or latent TB infection (LTBI) in the presence of HIV infection and may cause confusion.

### *Treatment of Active TB in HIV Patients*

HIV infection significantly increases the risk of progression from latent to active TB disease. The CD4 cell count influences both the frequency and severity of active TB disease *[1-2]*. Active TB also negatively affects HIV disease. It may be associated with a higher HIV viral load and more rapid progression of HIV disease *[2-3]*.

Active pulmonary or extrapulmonary TB disease requires prompt initiation of TB treatment. The treatment of active TB disease in HIV-infected patients should follow the general principles for persons without HIV (**AI**). Treatment of drug-susceptible TB disease should include a standard regimen that consists of isoniazid (INH) + a rifamycin (rifampin or rifabutin) + pyrazinamide + ethambutol given for 2 months, followed by INH + a rifamycin for 4 to 7 months *[4]*. A more complete discussion of the diagnosis and treatment of TB disease and LTBI in HIV patients is available in the ***Guidelines for Preventing and Treating Opportunistic Infections in HIV-Infected Adults and Adolescents*** *[4]*.

All patients with HIV/TB disease should be treated with ART **(AI)**. Important issues related to the use of ART in patients with active TB disease include: (1) when to start ART, (2) significant pharmacokinetic drug interactions with rifamycins, (3) the additive toxicities associated with ARV and TB drugs, (4) the development of IRIS with TB after

ART initiation, and (5) the need for treatment support including DOT and the integration of HIV and TB care and treatment.

## When to Start Antiretroviral Therapy

### *Patients Diagnosed with TB While Receiving ART*

At the time TB treatment is initiated in patients receiving ART, the patient's ARV regimen should be assessed with particular attention to potential pharmacokinetic interactions with rifamycins (discussed below). The patient's regimen may need to be modified to permit use of the optimal TB treatment regimen.

### *Patients Receiving Treatment for Active TB but Not Yet on ART*

When to initiate ART in patients with active TB has been the subject of differing recommendations based upon observational studies and expert opinion *[4-6]*. Two randomized controlled trials now provide some additional evidence regarding this issue. In these studies, concomitant administration of therapy for both TB disease and HIV infection resulted in significant reduction in HIV/TB disease mortality *[7-8]*. The results of an ACTG trial will soon be available and may provide further guidance or support for recommendations concerning when to start ART in patients with active TB.

In the SAPIT study from South Africa, HIV-infected patients with smear-positive TB and CD4 counts <500 cells/$mm^3$ were randomized to one of three treatment arms: integrated therapy with ART initiated either during the first 4 weeks of TB therapy or after the second month (i.e., during the continuation phase of TB therapy) or sequential therapy with ART initiated after the conclusion of standard TB therapy. The sequential arm was stopped when an early analysis demonstrated a 55% reduction in mortality in the combined two integrated arms compared with the sequential therapy arm *[7]*. In the CAMELIA study from Cambodia *[8]*, patients with CD4 counts <200 cells/$mm^3$ were randomized to initiate ART at 2 weeks or at 8 weeks of TB treatment. A 34% reduction in mortality was seen with ART initiation at 2 weeks compared with initiation at 8 weeks ($p = 0.002$). The populations in these two studies differed: the median CD4 count among SAPIT participants was 140–150 cells/$mm^3$; in the CAMELIA trial, the median CD4 count at entry was 25 cells/$mm^3$. Low CD4 count at study baseline predicted poorer survival in both studies. Both studies demonstrated excellent ART response: 90% and >95% of participants achieved suppressed HIV RNA (<400 copies/mL) at 12 months in the SAPIT study and CAMELIA trial, respectively. Although in both studies IRIS was more common in patients initiating ART earlier, the syndrome was not associated with mortality.

Based on the available data and the potential benefits of ART in patients with active TB, the Panel recommends the following:

- ***For patients with CD4 count <200 cells/$mm^3$, ART should be initiated within 2–4 weeks of starting TB treatment (AI).***
- ***For patients with CD4 count 200–500 cells/$mm^3$, the Panel recommends initiation of ART within 2–4 weeks, or at least by 8 weeks after commencement of TB therapy (AIII).***
- ***For patients with CD4 count >500 cells/$mm^3$, most Panel members also recommend starting ART within 8 weeks of TB therapy (BIII).***

ART should be started as early as feasible for all HIV-infected pregnant women with active TB, both for maternal health and for prevention of mother-to-child transmission (PMTCT) of HIV **(AIII)**. An augmented immune or inflammatory response in patients with some manifestations of TB, such as meningitis, pericarditis, or respiratory failure, might be life threatening. In these circumstances, delaying initiation of ART briefly beyond recommended intervals may be appropriate **(CIII)**.

## Drug Interaction Considerations

A rifamycin is a crucial component for the treatment of drug-sensitive TB. However, both rifampin and rifabutin are inducers of the hepatic cytochrome P (CYP) 450 and uridine diphosphate gluconyltransferase (UGT) 1A1 enzymes and are associated with interactions with most ARV agents including all PIs, non-nucleoside reverse transcriptase

inhibitors (NNRTIs), maraviroc (MVC), and raltegravir (RAL). Rifampin is a strong enzyme inducer, leading to enhanced drug clearance and greater reduction in ARV drug exposure. Rifabutin, a weaker enzyme inducer, is an alternative to rifampin. Because rifabutin is a substrate of the CYP 450 enzyme system, its metabolism may be affected by the NNRTI or PI as discussed below. **Tables 15a and 15b** outline the magnitude of these interactions and provide dosing recommendations when rifamycins and selected ARV drugs are used concomitantly. After determining the drugs and doses to use, patients should be closely monitored to assure good control of both TB and HIV. Suboptimal HIV suppression or suboptimal response to TB treatment should prompt assessment of drug adherence, subtherapeutic drug levels (consider therapeutic drug monitoring [TDM]), and acquired drug resistance.

***Rifamycins and NNRTIs***

Rifampin induces metabolism of both nevirapine (NVP) *[9]* and efavirenz (EFV) *[10]* leading to reduced NNRTI drug exposure. The extent of induction is less pronounced with EFV than with NVP. Despite the interactions, some observational studies suggest that good virologic, immunologic, and clinical outcomes may be achieved with standard doses of either EFV *[11-12]* or NVP *[13-14]* when combined with rifampin.

Rifabutin does not significantly affect EFV and NVP drug exposure. Because both EFV and NVP can induce rifabutin metabolism, an increased rifabutin dose is recommended. Few data exist on the use of rifampin and etravirine (ETR); however, because rifampin is expected to induce ETR metabolism, concomitant use is not recommended. Rifabutin is recommended in this situation.

***Rifamycins and PIs***

Rifampin can significantly decrease PI drug exposure, despite ritonavir (RTV) boosting, with resultant risk of ART failure *[15-16]*. Some investigators had explored the use of an additional RTV dose or doubling PI doses in attempt to overcome rifampin's induction effect. However, a high rate of serious hepatotoxicity and significant gastrointestinal intolerance resulted in terminations of these studies *[15, 17-18]*. Therefore, coadministration of rifampin and PIs is **not recommended** (**AII**).

Because rifabutin has a less significant impact on the pharmacokinetics of RTV-boosted PIs, it is the preferred rifamycin to use with PI-based regimens **(AII)**. Both RTV-boosted and -unboosted PIs can inhibit rifabutin metabolism and the optimal dose of rifabutin is yet to be defined. Most PI manufacturers suggest rifabutin 150 mg every other day (instead of normal doses of 300 mg once daily). Lower than expected drug exposure *[19-20]* and acquired rifamycin resistance have been reported in HIV-infected patients who received PI-based regimens and intermittent doses of rifabutin *[19, 21]*. If available, TDM can be helpful in assessing the adequacy of rifabutin drug exposure.

***Rifamycins and MVC or RAL***

MVC is a substrate of CYP3A4 and rifampin can significantly reduce MVC concentration. If concomitant use is necessary, the MVC dose should be increased. Rifabutin may be an alternative rifamycin. (See **Table 15d** for recommended doses of MVC used with rifamycins.)

Rifampin, a strong UGT1A1 enzyme inducer, significantly accelerates the metabolism of RAL *[22]*. When used in combination with rifampin, the RAL dose should be increased to 800 mg twice daily. Rifabutin has minimal effect on RAL metabolism and may be more appropriate in this situation.

## Anti-TB/ARV Toxicities

ARV agents and TB drugs, particularly INH, rifamycin, and pyrazinamide, can cause drug-induced hepatitis. These first-line TB drugs should still be used for treatment of active TB disease, 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. Peripheral neuropathy can occur with INH, didanosine (ddI), or stavudine (d4T) or may be a manifestation of HIV. All patients receiving INH should also receive supplemental pyridoxine to reduce peripheral

neuropathy. Patients should be monitored closely for signs of drug-related toxicities and receive alternatives to ddI or d4T.

### IRIS with TB and ARV Agents

IRIS occurs in two forms, "unmasking" and "paradoxical." The mechanism is the same for both forms of IRIS: restoration of immune competence by administration of ARV agents, resulting in an exuberant host response to TB bacilli and/or antigens. Unmasking IRIS refers to the initial clinical expression of active TB occurring soon after ARV agents are started. Paradoxical IRIS refers to the worsening of TB clinical manifestations after ARV agents are started in patients who are receiving TB treatment. Severity of IRIS ranges from mild to severe to life threatening. IRIS has been reported in 8% to greater than 40% of patients starting ART after TB is diagnosed, although the incidence depends on the definition of IRIS and the intensity of monitoring *[23-24]*.

Predictors of IRIS include CD4 count <50 cells/mm$^3$, higher on-ART CD4 counts, high pre-ART and lower on-ART HIV viral loads, severity of TB disease, especially high pathogen burden, and less than 30-day interval between initiation of TB and HIV treatments. *[5, 25-29]*. Most IRIS in HIV/TB disease occurs within 3 months of the start of TB treatment. Delaying the start of ART for 2–8 weeks may reduce the incidence and severity of IRIS but must be weighed against the potential benefit of earlier ART in improving immune function and preventing progression of HIV disease and mortality.

Milder or moderately severe cases of IRIS can be managed symptomatically or treated with nonsteroidal inflammatory agents. More severe cases can be successfully treated with corticosteroids. A recent randomized, placebo-controlled trial demonstrated benefit of corticosteroid treatment as measured by decreasing days of hospitalization and Karnofsky performance score without adverse consequences *[30]*. In the presence of IRIS, neither TB therapy nor ART should be stopped because both therapies are necessary for the long-term health of the patient **(AIII)**.

### Immune Reconstitution with ART: Conversion to Positive Tuberculin Skin Test (TST) and Interferon-Gamma (IFN-γ) Release Assay (IGRA)

Immune reconstitution with ART may result in unmasking LTBI (i.e., conversion of a previously negative TST to a positive TST or a positive IGRA for *Mycobacterium tuberculosis*-specific proteins). A positive IGRA, similar to a positive TST, is indicative of LTBI in the absence of evidence of active TB disease *[31]*. Because treatment for LTBI is indicated in the absence of evidence of active TB disease, clinicians should be aware of this phenomenon. Patients with a negative TST or IGRA and advanced HIV disease (i.e., CD4 count <200 cells/mm$^3$) should have a repeat TST or IGRA after initiation of ART and CD4 count increase to >200 cells/mm$^3$ *[32]* **(BII)**.

## *Caring for Patients with HIV and TB*

Integration of diagnosis and treatment and/or close collaboration between TB and HIV clinicians, health care institutions, and public health programs are necessary in order to improve medication adherence and TB treatment completion rates, reduce toxicities, and maximize HIV outcomes in HIV-infected patients with active TB disease *[4]*. These patients should receive treatment support, including adherence counseling and DOT, corresponding to their needs **(AII)**. ART simplification or use of coformulated fixed-dose combinations may also be helpful to improve drug adherence.

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# Limitations to Treatment Safety and Efficacy

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

Adherence to antiretroviral therapy (ART) 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. This section of the guidelines provides clinicians with a basis to approach the challenging and complicated topic of adherence.

### *Predictors of Adherence*

Adherence is related to characteristics of the patient, the regimen, the clinical setting, and the relationship of the provider and the patient *[3]*. To assure adherence, it is critical that the patient receive and understand information about HIV disease and the specific regimen prescribed. 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, inadequate 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 taking medication (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 ART with unboosted protease inhibitors (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 non-nucleoside reverse transcriptase inhibitors (NNRTIs) suggest that boosted PIs and efavirenz (EFV) 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 (ARV) 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 also can 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 (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 individualized to each patient's schedule, competing psychosocial needs, learning needs, and literacy level should be identified to foster adherence.

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.

A growing menu of possible interventions has demonstrated efficacy in improving adherence toART. For example, a meta-analysis of 19 randomized controlled trials of ARV 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 as 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 ART-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 ART 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*

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

## Table 12. Strategies to Improve Adherence to Antiretroviral Therapy

| Strategies | Examples |
|---|---|
| Use a multidisciplinary team approach<br>Provide an accessible, trusting health care team | • Nurses, social workers, pharmacists, and medication managers |
| Establish a trusting relationship with the patient | |
| Establish readiness to start ART | |
| Identify potential barriers to adherence prior to starting ART | • Psychosocial issues<br>• Active substance abuse or at high risk of relapse<br>• Low literacy level<br>• Busy daily schedule and/or travel away from home<br>• Lack of disclosure of HIV diagnosis<br>• Skepticism about ART<br>• Lack of prescription drug coverage |
| Provide resources for the patient | • Referrals for mental health and/or substance abuse treatment<br>• Resources to obtain prescription drug coverage<br>• Pillboxes |
| Involve the patient in antiretroviral (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 | • Use a simple checklist the patient can complete in the waiting room<br>• Have other members of the health care team also assess adherance<br>• Ask the patient open-ended questions (e.g., *In the last 3 days, please tell me how you took your medicines.*) |
| Identify the type of nonadherence | • Failure to fill the prescription(s)<br>• Failure to take the right dose(s) at the right time(s)<br>• Nonadherence to food requirements |
| Identify reasons for nonadherence | • Adverse effects from medications<br>• Complexity of regimen (pill burden, dosing frequency, etc.)<br>• Difficulty swallowing large pills<br>• Forgetfulness<br>• Failure to understand dosing instructions<br>• Inadequate understanding of drug resistance and its relationship to adherence<br>• Pill fatigue<br>• Other potential barriers (see list above) |
| Assess and simplify regimen, if possible | |

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## ADVERSE EFFECTS OF ANTIRETROVIRAL AGENTS (Updated January 10, 2011)

Adverse effects have been reported with all antiretroviral (ARV) 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 antiretroviral therapy (ART)-naïve patients enrolled in randomized trials appear to be declining with newer ARV regimens and are generally now less than 10%. However, most clinical trials have a relatively short follow-up duration and can underestimate longer term complications of therapy. 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]*.

Several factors may predispose individuals to adverse effects of ARV medications. For example, women seem to have a higher propensity of developing Stevens-Johnson syndrome, rashes, and hepatotoxicity from nevirapine (NVP) (ART-naïve women with CD4 counts >250 cells/$mm^3$) *[3-5]* as well as higher rates of lactic acidosis from nucleoside reverse transcriptase inhibitors (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 [ddI], which may increase ddI-associated toxicities) *[13-15]*); or genetic factors predisposing patients to abacavir (ABC) hypersensitivity reaction *[16-17]*.

Although the therapeutic goals of ART include achieving and maintaining viral suppression and improving patient immune function, an overarching goal should be to select a regimen that not is only effective but also is safe. This requires consideration of not only the toxicity potential of an ARV regimen but also 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:

**Table 13** provides clinicians with a list of the most common and/or severe known ARV-associated adverse events listed by drug class. **Appendix B, Tables 1–6** summarize the most common adverse effects of individual ARV agents. Some approaches to the management of complications of ART have been published and will not be discussed in these tables *[18-21]*.

## Table 13. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (January 10, 2011)



**(See Appendix B for additional information listed by drug.)**

| Adverse Effects | NRTIs | NNRTIs | PIs | INSTI | EI |
|---|---|---|---|---|---|
| **Bleeding events** | | | **All PIs:** ↑ spontaneous bleeding, hematuria in hemophilia<br><br>**TPV:** Reports of intracranial hemorrhage. Risks include CNS lesions; trauma; surgery; hypertension; alcohol abuse; coagulopathy, anti-coagulant, or anti-platelet agents including vitamin E | | |
| **Bone marrow suppression** | **ZDV:** Anemia, neutropenia | | | | |
| **Cardiovascular disease (CVD)** | **ABC** and **ddI:** Associated with myocardial infarction (MI) in some but not all cohort studies. Risk greatest among those with traditional CVD risk factors. | | **PIs:** Associated with MI and stroke in some cohort studies. Risk greatest among those with traditional CVD risk factors. Limited data on newer PIs (ATV, DRV, TPV).<br><br>**SQV/r**, **ATV/r,** and **LPV/r:** PR interval prolongation. Risks include structural heart disease, conduction system abnormalities, cardiomyopathy, ischemic heart disease, and coadministration with drugs that prolong PR interval.<br><br>**SQV/r:** QT interval prolongation in a healthy volunteer study. Risks include underlying heart conditions, pre-existing prolonged QT or arrhythmia, or use with other QT-prolonging drugs. ECG prior to SQV initiation is recommended and should be considered during therapy. | | |
| **Central nervous system (CNS) effects** | **d4T:** Associated with rapidly progressive ascending neuromuscular weakness resembling Guillain-Barré syndrome (rare) | **EFV:** Somnolence, insomnia, abnormal dreams, dizziness, impaired concentration, depression, psychosis, suicidal ideation. Most symptoms subside or diminish after 2–4 weeks. Bedtime dosing may reduce symptoms. Risks include history of psychiatric illness, concomitant use of agents with neuropsychiatric effects, and ↑ plasma EFV concentrations due to genetic factors or absorption (i.e., with food). | | | |
| **Diabetes mellitus (DM)/insulin resistance** | **ZDV, d4T,** and **ddI** | | • Reported for some **PIs (IDV, LPV/r)**, but not all PIs studied<br>• **ATV** +/- **RTV** not found to alter insulin sensitivity | | |
| **Dyslipidemia** | **d4T > ZDV > ABC:**<br>•↑ LDL and TG | **EFV**<br>•↑TG<br>•↑LDL<br>•↑HDL | ↑LDL, ↑TG, ↑HDL: **all RTV-boosted PIs**<br><br>↑TG: **LPV/r** = **FPV/r** and **LPV/r** > **DRV/r** and **ATV/r** | | |
| **Gastrointestinal (GI)** | Nausea and vomiting: **ddI** and **ZDV** > other **NRTIs**<br><br>Pancreatitis: **ddI** | | GI intolerance (diarrhea, nausea, vomiting)<br><br>Diarrhea: common with **NFV**. **LPV/r** > **DRV/r** and **ATV/r** | | |

| Adverse Effects | NRTIs | NNRTIs | PIs | INSTI | EI |
|---|---|---|---|---|---|
| **Hepatic effects** | Reported for most **NRTIs**<br><br>**ddI:** prolonged exposure linked to noncirrhotic portal hypertension, some cases with esophageal varicees<br><br>Steatosis: most commonly seen with **ZDV**, **d4T**, or **ddI**<br><br>Flares: hepatitis B virus (HBV)-coinfected patients may develop severe hepatic flare when **TDF**, **3TC**, and **FTC** are withdrawn or when HBV resistance develops. | **NVP > other NNRTIs**<br>**NVP:**<br>• Severe hepatic toxicity with **NVP** is often associated with skin rash or symptoms of hypersensitivity.<br>• For ARV-naïve patients, risk is greater for women with pre-**NVP** CD4 count >250 cells/mm$^3$ and men with pre-**NVP** CD4 count >400 cells/mm$^3$. Risk is higher for women.<br>• 2-week dose escalation of **NVP** reduces risk of rash and possibly hepatotoxicity if related to hypersensitivity.<br>• Given high risk in those with competent immune systems, **NVP** should never be used for post-exposure prophylaxis in HIV-uninfected individuals.<br>• **NVP** is contraindicated in patients with Child-Pugh classification B or C. | **All PIs:** Drug-induced hepatitis and hepatic decompensation (and rare cases of fatalities) have been reported with all PIs to varying degrees. **TPV/r** has a higher frequency of hepatic events than other PIs.<br><br>**IDV, ATV**: jaundice due to indirect hyperbilirubinemia<br><br>**TPV/r:** Contraindicated in patients with moderate to severe hepatic insufficiency (Child-Pugh classification B or C) | | |
| **Hypersensitivity reaction (HSR) (excluding rash alone or Stevens Johnson syndrome[SJS])** | **ABC**:<br>• HLA-B*5701 screening prior to initiation of **ABC**. Should not be started if HLA-B*5701 is positive.<br>• Symptoms of HSR include (in descending frequency): fever, skin rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, respiratory symptoms<br>• Worsen with continuation of **ABC**<br>• Median onset 9 days; ~ 90% of reactions within first 6 weeks<br>• Onset of rechallenge reactions is within hours of rechallenge dose | **NVP**:<br>• Hypersensitivity syndrome of hepatic toxicity and rash that may be accompanied by fever, general malaise, fatigue, myalgias, arthralgias, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, granulocytopenia, lymphadenopathy, or renal dysfunction.<br>• For ARV-naïve patients, risk is greater for women with pre-**NVP** CD4 count >250 cells/mm$^3$ and men with pre-**NVP** CD4 count >400 cells/mm$^3$. Risk is higher for women.<br>• 2-week dose escalation of **NVP** reduces risk. | | | |
| **Lactic acidosis** | **NRTIs,** especially **d4T, ZDV,** and **ddI**<br>• Insidious onset with GI prodrome, weight loss, and fatigue. May be rapidly progressive, with tachycardia, tachypnea, jaundice, muscular weakness, mental status changes, respiratory distress, pancreatitis, and organ failure.<br>• Mortality up to 50% in some case series, especially in patients with serum lactate >10 mmol/L<br>• Increased risk: female sex, obesity<br><br>Laboratory findings:<br>• ↑ lactate (often >5 mmol/L), anion gap, AST, ALT, PT, bilirubin<br>• ↑ amylase and lipase in patients with pancreatitis<br>• ↓ arterial pH, serum bicarbonate, serum albumin | | | | |

| Adverse Effects | NRTIs | NNRTIs | PIs | INSTI | EI |
|---|---|---|---|---|---|
| **Lipodystrophy** | Lipoatrophy: **Thymidine analogs (d4T > ZDV).** May be more likely when combined with **EFV** vs. **boosted PI**. | Lipohypertophy: Trunk fat increase observed with **EFV**-, **PI**-, and **RAL**-containing regimens; however, causal relationship has not been established. | | | |
| **Myopathy/elevated CPK** | **ZDV:** myopathy | | | **RAL:** ↑ CPK. muscle weakness and rhabdomyolysis | |
| **Nephrotoxicity/ urolithiasis** | **TDF:** ↑ serum creatinine, proteinuria, hypophosphatemia, urinary phosphate wasting, glycosuria, hypokalemia, non-anion gap metabolic acidosis<br><br>Concurrent use of **PI** may increase risk. | | **IDV**: ↑ serum creatinine, pyuria; hydronephrosis or renal atrophy<br>**IDV, ATV**: Stone, crystal formation; adequate hydration may reduce risk. | | |
| **Osteopenia/ osteoporosis** | **TDF:** Associated with greater loss of bone mineral density (BMD) compared with **ZDV, d4T,** and **ABC.** | Decreases in BMD observed in studies of regimens containing different **NRTIs** combined with either **NNRTIs** or **PIs**. | | | |
| **Peripheral neuropathy** | Peripheral neuropathy (pain and/or paresthesias, lower extremities > upper extremities): **d4T > ddI** and **ddC** (can be irreversible)<br><br>**d4T:** Associated with rapidly progressive ascending neuromuscular weakness resembling Guillain-Barré syndrome (rare) | | | | |
| **Rash** | | **All NNRTIs** | **ATV, DRV, FPV** | | **MVC** |
| **Stevens-Johnson syndrome (SJS/toxic epidermal necrosis (TEN)** | **ddI, ZDV:** Reported cases | **NVP > DLV, EFV, ETR**<br>For **NVP** risks include:<br>•Female sex<br>•Black, Asian, Hispanic race/ethnicity | **FPV, DRV, IDV, LPV/r, ATV:** Reported cases | | |

**Acronyms:**
*Drug Classes*: EI = entry inhibitor; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PIs = protease inhibitor
*Antiretroviral Drugs*: 3TC = lamivudine; ABC = abacavir; ATV = atazanavir; ATV/r = atazanavir + ritonavir; d4T = stavudine; ddC = zalcitabine; ddI = didanosine; DLV = delaviridine; DRV = darunavir; DRV/r = darunavir + ritonavir; EFV = efavirenz; ETR = etravirine; FPV = fosamprenavir; FPV/r = fosamprenavir + ritonavir; FTC = emtricitabine; IDV = indinavir; LPV/r = lopinavir + ritonavir; MVC = maraviroc; NFV = nelfinavir; NVP = nevirapine; RAL = raltegravir; RTV = ritonavir; SQV/r = saquinavir + ritonavir; TDF = tenofovir; TPV = tipranavir; ZDV = zidovudine
*Other*: ALT = alanine aminotransferase; ARV = antiretroviral; AST = aspartate aminotransferase; BMD = bone mineral density; CNS = central nervous system; CPK = creatine phosphokinase; CVD = cardiovascular disease; DM = diabetes mellitus; ECG = electrocardiogram; GI = gastrointestinal; HBV = hepatitis B virus; HDL = high-density lipoprotein; HSR = hypersensitivity reaction; LDL = low-density lipoprotein; MI = myocardial infarction; PT = prothrombin time; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrosis; TG = triglyceride

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## DRUG INTERACTIONS (Updated January 10, 2011)

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

### *Protease Inhibitors (PIs) and Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)*

Most drug interactions with ARV drugs are mediated through inhibition or induction of hepatic drug metabolism *[1]*. All PIs and NNRTIs are metabolized in the liver by the cytochrome P (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-infected 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 interactions that risk adverse clinical effects.

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 in the gut and elsewhere. Tipranavir (TPV), for example, is a potent inducer of CYP3A4 and P-glycoprotein. The net effect of tipranavir/ritonavir (TPV/r) 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 TPV/r. The net effect of TPV/r on a drug that is a substrate for both CYP3A and P-glycoprotein cannot be confidently predicted; significant decreases in saquinavir (SQV), amprenavir (APV), and lopinavir (LPV) concentrations have been observed *in vivo* when given with TPV/r.

The NNRTIs are also substrates of CYP3A4 and can act as an inducer (nevirapine [NVP]), an inhibitor (delavirdine [DLV]), or a mixed inducer and inhibitor (efavirenz [EFV]). Etravirine (ETR) is a substrate of CYPs 3A4, 2C9, and 2C19. It is also an inducer of CYP3A4 and an inhibitor of CYPs 2C9 and 2C19. Thus, these ARV 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 (RTV), however, can be beneficial when added to a PI, such as atazanavir (ATV), fosamprenavir (FPV), or indinavir (IDV) *[2]*. The PIs darunavir (DRV), LPV, SQV, and TPV require coadministration with RTV. Lower than therapeutic doses of RTV (100 to 400 mg per day) 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 $C_{min}$: inhibitory concentration ($IC_{50}$) 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 ARV 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 ARV 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]*. Because rifabutin is a less potent inducer, it is generally considered a reasonable alternative to rifampin for the treatment of tuberculosis (TB) when it is used with a PI-based regimen, despite wider experience with rifampin use *[6]*. **Tables 15a and 15b** list dosage recommendations for concomitant use of rifamycins and other CYP3A4 inducers with PIs and NNRTIs.

### *Nucleoside Reverse Transcriptase Inhibitors (NRTIs)*

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 (ddI) is used in combination with hydroxyurea *[7-8]* or ribavirin *[9]*, additive bone marrow suppressive effects of zidovudine (ZDV) and ganciclovir *[10]*, and antagonism of intracellular phosphorylation with the combination of ZDV and stavudine (d4T) *[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 ddI concentration in the presence of tenofovir (TDF) *[12]* and decreases in ATV concentration when ATV is coadministered with TDF *[13]*. **Table 15c** lists significant interactions with NRTIs.

### *CCR5 Antagonist*

Maraviroc (MVC), the first Food and Drug Administration (FDA)-approved CCR5 antagonist, is a substrate of CYP3A enzymes and P-glycoprotein. As a consequence, the concentrations of MVC can be significantly increased in the presence of strong CYP3A inhibitors (such as RTV and other PIs, except for TPV/r) and are reduced when used with CYP3A inducers (such as EFV or rifampin). Dose adjustment is necessary when MVC is used in combination with these agents. (See **Table 16b** or **Appendix B, Table 6** for dosage recommendations.) MVC is neither an inducer nor an inhibitor of the CYP3A system and does not alter the pharmacokinetics of the drugs evaluated in interaction studies to date.

### *Integrase Inhibitor*

Raltegravir (RAL), an HIV integrase strand transfer inhibitor, is primarily eliminated by glucuronidation that is mediated by the uridine diphosphate (UDP)-glucuronosyltransferase (UGT) 1A1 enzymes. Strong inducers of UGT1A1 enzymes (e.g., rifampin) can significantly reduce the concentration of RAL *[14]*. (See **Table 15e** for dosage recommendations.) Other inducers of UGT1A1, such as EFV and TPV/r, can also reduce RAL concentration. A pharmacokinetic interaction should be considered if optimal virologic response is not achieved when these drugs are used in combination.

### *Fusion Inhibitor*

The fusion inhibitor enfuvirtide (T-20) 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 T-20 to date.

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# Table 14. Drugs That Should Not Be Used With PI, NNRTI, or CCR5 Antagonist
**(Updated January 10, 2011)**

This table lists only drugs that should not be coadministered at any dose and regardless of RTV boosting. See **Tables 15 and 16** for more detailed pharmacokinetic interaction data and dosage adjustments.

| Drug Categories | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Antiretroviral Agents**[1, 2] | **Cardiac Agents** | **Lipid-lowering Agents** | **Antimyco-bacterials** | **Gastro-intestinal Drugs** | **Neuro-leptics** | **Psycho-tropics** | **Ergot Derivatives (vasoconstrictors)** | **Herbs** | **Antiretroviral Agents** | **Others** |
| **ATV +/– RTV** | none | lovastatin<br>pitavastatin<br>simvastatin | rifampin<br>rifapentine[3] | cisapride[5] | pimozide | midazolam[6]<br>triazolam | dihydroergotamine<br>ergonovine<br>ergotamine<br>methylergonovine | St. John's wort | ETR<br>NVP | alfuzosin<br>irinotecan<br>salmeterol<br>sildenafil for PAH |
| **DRV/r** | none | lovastatin<br>pitavastatin<br>simvastatin | rifampin<br>rifapentine[3] | cisapride[5] | pimozide | midazolam[6]<br>triazolam | dihydroergotamine<br>ergonovine<br>ergotamine<br>methylergonovine | St. John's wort | none | alfuzosin<br>salmeterol<br>sildenafil for PAH |
| **FPV +/– RTV** | flecainide<br>propafenone | lovastatin<br>pitavastatin<br>simvastatin | rifampin<br>rifapentine[3] | cisapride[5] | pimozide | midazolam[6]<br>triazolam | dihydroergotamine<br>ergonovine<br>ergotamine<br>methylergonovine | St. John's wort | ETR | alfuzosin<br>salmeterol<br>sildenafil for PAH |
| **LPV/r** | none | lovastatin<br>pitavastatin<br>simvastatin | rifampin[4]<br>rifapentine[3] | cisapride[5] | pimozide | midazolam[6]<br>triazolam | dihydroergotamine<br>ergonovine<br>ergotamine<br>methylergonovine | St. John's wort | none | alfuzosin<br>salmeterol<br>sildenafil for PAH |
| **RTV** | amiodarone<br>flecainide<br>propafenone<br>quinidine | lovastatin<br>pitavastatin<br>simvastatin | rifapentine[3] | cisapride[5] | pimozide | midazolam[6]<br>triazolam | dihydroergotamine<br>ergonovine<br>ergotamine<br>methylergonovine | St. John's wort | none | alfuzosin<br>sildenafil for PAH |
| **SQV/r** | amiodarone<br>dofetilide<br>flecainide<br>lidocaine<br>propafenone<br>quinidine | lovastatin<br>pitavastatin<br>simvastatin | rifampin[4]<br>rifapentine | cisapride[5] | pimozide | midazolam[6]<br>triazolam<br>trazodone | dihydroergotamine<br>ergonovine<br>ergotamine<br>methylergonovine | St. John's wort<br>garlic supplements | none | alfuzosin<br>salmeterol<br>sildenafil for PAH |
| **TPV/r** | amiodarone<br>flecainide<br>propafenone<br>quinidine | lovastatin<br>pitavastatin<br>simvastatin | rifampin<br>rifapentine[3] | cisapride[5] | pimozide | midazolam[6]<br>triazolam | dihydroergotamine<br>ergonovine<br>ergotamine<br>methylergonovine | St. John's wort | ETR | alfuzosin<br>salmeterol<br>sildenafil for PAH |
| **EFV** | none | none | rifapentine[3] | cisapride[5] | pimozide | midazolam[6]<br>triazolam | dihydroergotamine<br>ergonovine<br>ergotamine<br>methylergonovine | St. John's wort | other NNRTIs | none |
| **ETR** | none | none | rifampin<br>rifapentine[3] | none | none | none | none | St John's wort | unboosted PIs<br>ATV/r, FPV/r, or TPV/r<br>other NNRTIs | carbamazepine<br>phenobarbital<br>phenytoin<br>clopidogrel |
| **NVP** | none | none | rifapentine[3] | none | none | none | none | St. John's wort | ATV +/– RTV<br>other NNRTIs | ketoconazole |
| **MVC** | none | none | rifapentine[3] | none | none | none | none | St. John's wort | none | none |

1 DLV, IDV, and NFV are not included in this table. Refer to the FDA package insert for information regarding DLV-, IDV-, and NFV-related 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-infected 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 RTV was added to LPV/r or SQV or when double-dose LPV/r was used with rifampin to compensate for rifampin's induction effect, 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 Use of oral midazolam is contraindicated. Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation.

**Suggested alternatives to**:
**Lovastatin, simvastatin**: Pravastatin and fluvastatin have the least potential for drug-drug interactions (except for pravastatin with DRV/r, see **Table 15a**). Use atorvastatin and rosuvastatin with caution; start with the lowest possible dose and titrate based on tolerance and lipid-lowering efficacy.
**Rifampin**: Rifabutin (with dosage adjustment – see **Tables 15a and 15b**)
**Midazolam, triazolam**: temazepam, lorazepam, oxazepam

**Acronyms**: ATV +/- RTV = atazanavir +/- ritonavir, DLV = delavirdine, DRV/r = darunavir/ritonavir, EFV = efavirenz, ETV = etravirine, FDA = Food and Drug Administration, FPV +/- RTV = fosamprenavir +/- ritonavir, HIV = human immunodeficiency virus, IDV = indinavir, LPV/r = lopinavir/ritonavir, MVC = maraviroc, NFV = nelfinavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PAH = pulmonary arterial hypertension, PI = protease inhibitor, RTV = ritonavir, SQV/r = saquinavir/ritonavir, TPV/r = tipranavir/ritonavir

# Table 15a. Drug Interactions between PIs* and Other Drugs (Updated January 10, 2011)



*NFV and IDV are not included in this table. Please refer to the FDA package insert for information regarding NFV and IDV drug interactions.

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

| Concomitant Drug | 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 hours before or 1 hour after antacids or buffered medications. |
| | FPV | APV AUC ↓ 18%; no significant change in APV $C_{min}$ | Give FPV simultaneously with or at least 2 hours before or 1 hour after antacids. |
| | TPV/r | TPV AUC ↓ 27% | Give TPV at least 2 hours before or 1 hour 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 40 mg BID in ART-naïve patients or 20 mg BID in ART-experienced patients.<br><br>Give ATV 300 mg + RTV 100 mg simultaneously with and/or ≥10 hours after the $H_2$ receptor antagonist.<br><br>If using TDF and $H_2$ receptor antagonist in ART-experienced patients, use ATV 400 mg + RTV 100 mg. |
| | 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 20 mg or total daily dose equivalent of famotidine 20 mg BID in ART-naïve patients.<br><br>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 $C_{min}$ | Give FPV at least 2 hours before $H_2$ receptor antagonist if concomitant use 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, RTV boosting, or alternative PIs. |
| | ATV/r | ↓ ATV | PPIs should not exceed a dose equivalent to omeprazole 20 mg daily in PI-naïve patients. PPIs should be administered at least 12 hours prior to ATV/r.<br><br>**PPIs are not recommended in PI-experienced patients**. |
| | DRV/r, TPV/r | ↓ omeprazole<br>PI: no significant effect | May need to increase omeprazole dose with TPV/r. |
| | FPV +/– RTV, LPV/r | No significant effect | |
| | SQV/r | SQV AUC ↑ 82% | Monitor for SQV toxicities. |
| **Anticoagulants** | | | |
| **Warfarin** | ATV +/- RTV, DRV/r, FPV +/- RTV, LPV/r, SQV/r, TPV/r | ↑ or ↓ warfarin possible<br>DRV/r ↓ S-warfarin AUC 21% | Monitor INR closely when stopping or starting PI and adjust warfarin dose accordingly. |

**Table 15a. Drug Interactions between PIs and Other Drugs**


| Concomitant Drug | PI | Effect on PI or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Anticonvulsants** | | | |
| **Carbamazepine** | **RTV-boosted PIs** | | |
| | ATV/r, FPV/r, LPV/r, SQV/r, TPV/r | ↑ carbamazepine possible<br>TPV/r ↑ carbamazepine AUC 26%<br>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%<br>DRV: no significant change | Monitor anticonvulsant level and adjust dose accordingly. |
| | **PIs without RTV** | | |
| | ATV, FPV | May ↓ PI levels substantially | Monitor anticonvulsant level and virologic response. Consider alternative anticonvulsant; RTV boosting for ATV and FPV; and/or monitoring PI level. |
| **Lamotrigine** | LPV/r | lamotrigine AUC ↓ 50%<br>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, SQV/r, TPV/r | ↓ phenytoin possible<br>↓ PI possible | Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. |
| | FPV/r | phenytoin AUC ↓ 22%<br>APV AUC ↑ 20% | Monitor phenytoin level and adjust dose accordingly. No change in FPV/r dose recommended. |
| | LPV/r | phenytoin AUC ↓ 31%<br>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 | May ↓ PI levels substantially | Consider alternative anticonvulsant; RTV boosting for ATV and FPV; and/or monitoring PI level.<br>Monitor anticonvulsant level and virologic response. |
| **Valproic acid (VPA)** | LPV/r | ↓VPA possible<br>LPV AUC ↑ 75% | Monitor VPA levels and response. Monitor for LPV-related toxicities. |
| **Antidepressants** | | | |
| **Bupropion** | LPV/r | bupropion AUC ↓ 57% | Titrate bupropion dose based on clinical response. |
| | TPV/r | bupropion AUC ↓ 46% | |
| **Paroxetine** | DRV/r | paroxetine AUC ↓ 39% | Titrate paroxetine dose based on clinical response. |
| | FPV/r | paroxetine AUC ↓ 58% | |
| **Sertraline** | DRV/r | sertraline AUC ↓ 49% | Titrate sertraline dose based on clinical response. |
| **Trazodone** | ATV +/- RTV, DRV/r, FPV +/- RTV, LPV/r, TPV/r | RTV 200 mg BID (for 2 days)<br>↑ trazodone AUC 240% | Use lowest dose of trazodone and monitor for CNS and cardiovascular adverse effects. |
| | SQV/r | ↑ trazodone expected | **Contraindicated. Do not coadminister.** |
| **Tricyclic antidepressants (TCAs) (amitriptyline, desipramine, imipramine, nortriptyline)** | All RTV-boosted PIs | ↑ TCA expected | Use lowest possible TCA dose and titrate based on clinical assessment and/or drug levels. |

| Concomitant Drug | PI | Effect on PI or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Antifungals** | | | |
| **Fluconazole** | **RTV-boosted PIs** | | |
| | ATV/r | No significant effect | |
| | SQV/r | No data with RTV boosting<br>SQV (1,200mg TID) AUC ↑ 50% | |
| | TPV/r | TPV AUC ↑ 50% | Fluconazole >200 mg daily is not recommended. If high-dose fluconazole is indicated, consider alternative PI or another class of ARV drug. |
| **Itraconazole** | **RTV-boosted PIs** | | |
| | ATV/r, DRV/r, FPV/r, TPV/r | ↑ itraconazole possible<br>↑ 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 200 mg 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. |
| | **PIs without RTV** | | |
| | ATV, FPV | ↑ itraconazole possible<br>↑ PI possible | Consider monitoring itraconazole level to guide dosage adjustments. |
| **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, LPV/r, SQV/r, TPV/r | RTV 400 mg BID ↓ voriconazole AUC 82%<br><br>RTV 100 mg BID ↓ voriconazole AUC 39% | **Do not coadminister** voriconazole and RTV unless benefit outweighs risk. If administered, consider monitoring voriconazole level. |
| | **PIs without RTV** | | |
| | ATV, FPV | ↑ voriconazole possible<br>↑ PI possible | Monitor for toxicities. |
| **Anti-mycobacterials** | | | |
| **Clarithromycin** | ATV +/− RTV | clarithromycin AUC ↑ 94% | May cause QTc prolongation. Reduce clarithromycin dose by 50%. Consider alternative therapy. |
| | DRV/r, FPV/r, LPV/r, SQV/r, TPV/r | DRV/r ↑ clarithromycin AUC 57%<br>FPV/r ↑ clarithromycin possible<br>LPV/r ↑ clarithromycin expected<br>RTV 500 mg BID ↑ clarithromycin 77%<br>SQV unboosted ↑ clarithromycin 45%<br>TPV/r ↑ clarithromycin 19% and ↓ active metabolite 97%<br>clarithromycin ↑ unboosted SQV 177%<br>clarithromycin ↑ TPV 66% | Monitor for clarithromycin-related toxicities.<br><br>Reduce clarithromycin dose by 50% in patients with CrCl 30–60 mL/min.<br><br>Reduce clarithromycin dose by 75% in patients with CrCl <30 mL/min. |
| | FPV | APV AUC ↑ 18% | No dose adjustment |

| Concomitant Drug | PI | Effect on PI or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Rifabutin** | **RTV-boosted PIs** | | |
| | ATV +/– RTV | rifabutin (150 mg once daily) AUC ↑ 110% and metabolite AUC ↑ 2,101% compared with rifabutin 300 mg daily alone | Rifabutin 150 mg every other day or three times a week. Some experts recommend rifabutin 150 mg daily or 300 mg three times a week. Monitor for antimycobacterial activity.<br><br>Therapeutic drug monitoring for rifabutin is recommended. Rifabutin 150 mg three times a week in combination with LPV/r has resulted in inadequate rifabutin levels and has led to acquired rifamycin resistance in patients with HIV-associated TB.<br><br>Pharmacokinetic data reported in this table are results from healthy volunteer studies. |
| | DRV/r | rifabutin (150 mg every other day) and metabolite AUC ↑ 55% compared with rifabutin 300 mg once daily alone | |
| | FPV/r | rifabutin (150 mg every other day) and metabolite AUC ↑ 64% compared with rifabutin 300 mg once daily alone | |
| | LPV/r | rifabutin (150mg once daily) and metabolite AUC ↑ 473% compared with rifabutin 300 mg daily alone | |
| | SQV/r | ↑ rifabutin with unboosted SQV | |
| | TPV/r | rifabutin (150 mg x 1 dose) and metabolite AUC ↑ 333% | |
| | **PIs without RTV** | | |
| | FPV | ↑ rifabutin AUC expected | Rifabutin 150 mg daily or 300 mg three times a week |
| **Rifampin** | All PIs | ↓ PI >75% approximately | **Do not coadminister rifampin and PIs.** Additional RTV does not overcome this interaction and increases hepatotoxicity. |
| **Benzodiazepines** | | | |
| **Alprazolam**<br>**Diazepam** | All PIs | ↑ benzodiazepine possible<br>RTV 200 mg BID for two days<br>↑ alprazolam half-life 222% and AUC 248% | Consider alternative benzodiazepines such as lorazepam, oxazepam, or temazepam. |
| **Lorazepam**<br>**Oxazepam**<br>**Temazepam** | All PIs | No data | Metabolism of these benzodiazepines via non-CYP450 pathways decreases interaction potential compared with other benzodiazepines. |
| **Midazolam** | All PIs | ↑ midazolam expected<br>SQV/r ↑ midazolam (oral) AUC 1,144% and $C_{max}$ 327% | **Do not coadminister oral midazolam and PIs.**<br><br>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<br>RTV 200 mg BID ↑ triazolam half-life 1,200% and AUC 2,000% | **Do not coadminister triazolam and PIs.** |
| **Cardiac Medications** | | | |
| **Bosentan** | All PIs | LPV/r ↑ bosentan 48-fold (Day 4) and 5-fold (Day 10)<br>↓ ATV expected | **Do not coadminister bosentan and ATV without RTV.**<br><br>In patients on a PI (other than unboosted ATV) >10 days: start bosentan at 62.5 mg once daily or every other day.<br><br>In patients on bosentan who require a PI (other than unboosted ATV): stop bosentan ≥36 hours prior to PI initiation and restart 10 days after PI initiation at 62.5 mg once daily or every other day. |

| Concomitant Drug | PI | Effect on PI or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Digoxin** | RTV, SQV/r | RTV 200 mg BID ↑ digoxin AUC 29% and half-life 43%<br>SQV/r ↑ digoxin AUC 49% | Use with caution. Monitor digoxin levels. Digoxin dose may need to be decreased. |
| **Dihydropyridine calcium channel blockers (CCBs)** | All PIs | ↑ dihydropyridine possible | 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, LPV/r, SQV/r, TPV/r | ↑ diltiazem possible | Use with caution. Adjust diltiazem according to clinical response and toxicities. |
| **Corticosteroids** | | | |
| **Dexamethasone** | All PIs | ↓ PI levels possible | Use systemic dexamethasone with caution or consider alternative corticosteroid for long-term use. |
| **Fluticasone (inhaled or intranasal)** | All RTV-boosted PIs | RTV 100 mg BID ↑ fluticasone AUC 350-fold and ↑ $C_{max}$ 25-fold | Coadministration can result in adrenal insufficiency, including Cushing's syndrome. **Do not coadminister unless potential benefit outweighs risk of systemic corticosteroid adverse effects.** |
| **Prednisone** | LPV/r | ↑ prednisolone AUC 31% | No dosage adjustment necessary. |
| **Herbal Products** | | | |
| **St. John's wort** | All PIs | ↓ PI expected | **Do not coadminister.** |
| **Hormonal Contraceptives** | | | |
| **Hormonal contraceptives** | **RTV-boosted PIs** | | |
| | ATV/r | ↓ ethinyl estradiol<br>↑ norgestimate | Oral contraceptive should contain at least 35 mcg of ethinyl estradiol. Oral contraceptives containing progestins other than norethindrone or norgestimate have not been studied. |
| | DRV/r | ethinyl estradiol AUC ↓ 44%<br>norethindrone AUC ↓ 14% | Use alternative or additional method. |
| | FPV/r | ethinyl estradiol AUC ↓ 37%<br>norethindrone AUC ↓ 34% | Use alternative or additional method. |
| | LPV/r | ethinyl estradiol AUC↓ 42%<br>norethindrone AUC ↓ 17% | Use alternative or additional method. |
| | SQV/r | ↓ ethinyl estradiol | Use alternative or additional method. |
| | TPV/r | ethinyl estradiol AUC ↓ 48%<br>norethindrone: no significant change | Use alternative or additional method. |
| | **PIs without RTV** | | |
| | ATV | ethinyl estradiol AUC ↑ 48%<br>norethindrone AUC ↑ 110% | Oral contraceptive should contain no more than 30 mcg of ethinyl estradiol or use alternate method. Oral contraceptives containing less than 25 mcg of ethinyl estradiol or progestins other than norethindrone or norgestimate have not been studied. |
| | FPV | With APV: ↑ ethinyl estradiol and ↑ norethindrone; ↓ APV 20% | Use alternative method. |

| Concomitant Drug | PI | Effect on PI or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **HMG-CoA Reductase Inhibitors** | | | |
| **Atorvastatin** | All PIs | DRV/r + atorvastatin 10 mg similar to atorvastatin 40 mg alone;<br>FPV +/– RTV ↑ atorvastatin AUC 130%–153%;<br>LPV/r ↑ atorvastatin AUC 488%;<br>SQV/r ↑ atorvastatin AUC 79%;<br>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.** |
| **Pitavastatin** | ATV | pitavastatin AUC ↑ 31%;<br>$C_{max}$ ↑ 60%<br>ATV: no significant effect | No dosage adjustment needed for ATV without RTV. |
| | All RTV-boosted PIs | ↑ pitavastatin possible | **Do not coadminister** due to possible increase in pitavastatin concentration and increased risk of rhabdomyolitis. |
| **Pravastatin** | DRV/r | pravastatin AUC ↑ 81% | Use lowest possible starting dose with careful monitoring. |
| | LPV/r | pravastatin AUC ↑ 33% | No dose adjustment necessary |
| | SQV/r | pravastatin AUC ↓ 47%–50% | No dose adjustment necessary |
| **Rosuvastatin** | ATV/r | rosuvastatin AUC ↑ 213% and $C_{max}$ ↑ 600% | Use lowest possible starting dose with careful monitoring or consider other HMG-CoA reductase inhibitors with less potential for interaction. |
| | DRV/r, FPV +/- RTV, SQV/r | ↑ rosuvastatin possible | |
| | LPV/r | rosuvastatin AUC ↑ 108% and $C_{max}$ ↑ 366% | |
| | TPV/r | rosuvastatin AUC ↑ 26% and $C_{max}$ ↑ 123% | |
| **Simvastatin** | All PIs | Significant ↑ simvastatin level;<br>SQV/r 400 mg/400 mg BID<br>↑ simvastatin AUC 3,059% | **Contraindicated. Do not coadminister**. |
| **Narcotics/Treatment for Opioid Dependence** | | | |
| **Buprenorphine** | ATV | buprenorphine AUC ↑ 93%<br>norbuprenorphine AUC ↑ 76%<br>↓ ATV possible | **Do not coadminister buprenorphine with unboosted ATV.**<br>Norbuprenorphine is an active metabolite of buprenorphine. |
| | ATV/r | buprenorphine AUC ↑ 66%<br>norbuprenorphine AUC ↑ 105% | Monitor for sedation. Buprenorphine dose reduction may be necessary.<br>Norbuprenorphine is an active metabolite of buprenorphine. |
| | DRV/r | buprenorphine: no significant effect<br>norbuprenorphine AUC ↑ 46% and $C_{min}$ ↑ 71% | No dose adjustment necessary. Clinical monitoring is recommended.<br>Norbuprenorphine is an active metabolite of buprenorphine. |
| | LPV/r | No significant effect | No dose adjustment necessary |
| | TPV/r | buprenorphine: no significant effect<br>norbuprenorphine AUC, $C_{max}$, and $C_{min}$ ↓ 80%<br>TPV $C_{min}$ ↓ 19–40% | Consider monitoring TPV level.<br>Norbuprenorphine is an active metabolite of buprenorphine. |
| **Methadone** | **RTV-boosted PIs** | | |
| | ATV/r, DRV/r, FPV/r, LPV/r, SQV/r, TPV/r | ATV/r, DRV/r, FPV/r<br>↓ R-methadone AUC 16%–18%;<br>LPV/r ↓ methadone AUC 26%–53%;<br>SQV/r 1,000/100mg BID<br>↓ R-methadone AUC 19%;<br>TPV/r ↓ R-methadone AUC 48% | Opioid withdrawal unlikely but may occur. No adjustment in methadone usually required but monitor for opioid withdrawal and increase methadone dose as clinically indicated.<br><br>(R-methadone is the active form of methadone.) |

**Table 15a. Drug Interactions between PIs and Other Drugs**


| Concomitant Drug | PI | Effect on PI or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Methadone (continued)** | **PIs without RTV** | | |
| | ATV | No significant effect | No dosage adjustment necessary. |
| | FPV | No data with unboosted FPV<br>APV ↓ R-methadone $C_{min}$ 21%, AUC no significant change | Monitor and titrate methadone as clinically indicated. The interaction with FPV is presumed to be similar.<br><br>(R-methadone is the active form of methadone.) |
| **Phosphodiesterase Type 5 (PDE5) Inhibitors** | | | |
| **Sildenafil** | All PIs | DRV/r + sildenafil 25mg similar to sildenafil 100mg alone;<br>RTV 500 mg BID ↑ sildenafil AUC 1,000%;<br>SQV unboosted ↑ sildenafil AUC 210% | For treatment of erectile dysfunction<br>Start with sildenafil 25 mg every 48 hours and monitor for adverse effects of sildenafil.<br><br>For treatment of pulmonary arterial hypertension<br>**Contraindicated** |
| **Tadalafil** | All PIs | RTV 200 mg BID ↑ tadalafil AUC 124%;<br>TPV/r (1st dose) ↑ tadalafil AUC 133%;<br>TPV/r steady state: no significant effect | For treatment of erectile dysfunction<br>Start with tadalafil 5 mg dose and do not exceed a single dose of 10 mg every 72 hours. Monitor for adverse effects of tadalafil.<br><br>For treatment of pulmonary arterial hypertension<br>*In patients on a PI >7 days*:<br>Start with tadalafil 20 mg once daily and increase to 40 mg once daily based on tolerability.<br>*In patients on tadalafil who require a PI*:<br>Stop tadalafil ≥24 hours prior to PI initiation, restart 7 days after PI initiation at 20 mg once daily, and increase to 40 mg once daily based on tolerability. |
| **Vardenafil** | All PIs | RTV 600 mg BID ↑ vardenafil AUC 49-fold | Start with vardenafil 2.5 mg every 72 hours and monitor for adverse effects of vardenafil. |
| **Miscellaneous Interactions** | | | |
| All PIs | Colchicine | All PIs | For treatment of gout flares<br>Colchicine 0.6 mg x 1 dose, followed by 0.3 mg 1 hour later. Do not repeat dose for at least 3 days.<br>*With FPV without RTV*: 1.2 mg x 1 dose and no repeat dose for at least 3 days<br><br>For prophylaxis of gout flares<br>Colchicine 0.3 mg once daily or every other day<br>*With FPV without RTV*: colchicine 0.3 mg BID or 0.6 mg once daily or 0.3 mg once daily<br><br>For treatment of familial Mediterranean fever<br>Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID.<br>*With FPV without RTV*: Do not exceed 1.2 mg once daily or 0.6 mg BID.<br><br>**Do not coadminister in patients with hepatic or renal impairment.** |
| | Salmeterol | ↑ salmeterol possible | **Do not coadminister** because of potential increased risk of salmeterol-associated cardiovascular events, including QT prolongation, palpitations, and sinus tachycardia. |
| ATV/r<br>LPV/r | Atovaquone/proguanil | ATV/r ↓ atovaquone AUC 46% and ↓ proguanil AUC 41%<br>LPV/r ↓ atovaquone AUC 74% and ↓ proguanil AUC 38% | No dosage recommendation. Consider alternative drug for malaria prophylaxis, if possible. |

**Acronyms**: APV = amprenavir, ARV = antiretroviral, ATV = atazanavir, ATV/r = atazanavir + ritonavir, AUC = area under the curve, BID = twice daily, CCB = calcium channel blocker, $C_{max}$ = maximum plasma concentration, $C_{min}$ = minimum plasma concentration, CNS = central nervous system, CrCl = creatinine clearance, CYP = cytochrome P, DRV/r = darunavir + ritonavir, ECG = electrocardiogram, FDA = Food and Drug Administration, FPV = fosamprenavir (FPV is a prodrug of APV), FPV/r = fosamprenavir + ritonavir, IDV = indinavir, IDV/r = indinavir + ritonavir, INR = international normalized ratio, LPV = lopinavir, LPV/r = lopinavir + ritonavir, NFV = nelfinavir, PDE5 = phosphodiesterase type 5, PI = protease inhibitor, PPI = proton pump inhibitor, RTV = ritonavir, SQV = saquinavir, SQV/r = saquinavir + ritonavir, TB = tuberculosis, TCA = tricyclic antidepressant, TID = three times a day, TPV = tipranavir, TPV/r = tipranavir + ritonavir, VPA = valproic acid.

# Table 15b. Drug Interactions between NNRTIs* and Other Drugs (Updated January 10, 2011)



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

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

| Concomitant Drug Class/Name | NNRTI | Effect on NNRTI or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Anticoagulants/Antiplatelets** | | | |
| **Warfarin** | EFV, NVP | ↑ or ↓ warfarin possible | Monitor INR and adjust warfarin dose accordingly. |
| | ETR | ↑ warfarin possible | Monitor INR and adjust warfarin dose accordingly. |
| **Clopidogrel** | ETR | ↓ activation of clopidogrel possible | ETR may prevent metabolism of clopidogrel (inactive) to its active metabolite. Avoid coadministration, if possible. |
| **Anticonvulsants** | | | |
| **Carbamazepine**<br>**Phenobarbital**<br>**Phenytoin** | EFV | carbamazepine + EFV: carbamazepine AUC ↓ 27% and EFV AUC ↓ 36%<br>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. |
| **Antidepressants** | | | |
| **Bupropion** | EFV | bupropion AUC ↓ 55% | Titrate bupropion dose based on clinical response. |
| **Paroxetine** | ETR | No significant effect | No dosage adjustment necessary. |
| **Sertraline** | EFV | sertraline AUC ↓ 39% | Titrate sertraline dose based on clinical response. |
| **Antifungals** | | | |
| **Fluconazole** | EFV | No significant effect | |
| | ETR | ETR AUC ↑ 86% | No dosage adjustment. Use with caution. |
| | NVP | NVP AUC ↑ 110% | Increased risk of hepatotoxicity possible with this combination<br>Monitor NVP toxicity or use alternative antiretroviral agent. |
| **Itraconazole** | EFV | itraconazole and OH-itraconazole AUC, $C_{max}$, and $C_{min}$ ↓ 35%–44% | Dose adjustments for itraconazole may be necessary. Monitor itraconazole level and antifungal response. |
| | ETR | ↓ itraconazole possible<br>↑ ETR possible | Dose adjustments for itraconazole may be necessary. Monitor itraconazole level and antifungal response. |
| | NVP | ↓ itraconazole possible<br>↑ NVP possible | Consider monitoring NNRTI and itraconazole levels and antifungal response. |
| **Posaconazole** | EFV | posaconazole AUC ↓ 50%<br>↔ EFV | Consider alternative antifungal if possible or consider monitoring posaconazole level if available. |
| | ETR | ↑ ETR possible | No dosage adjustment necessary |
| **Voriconazole** | EFV | voriconazole AUC ↓ 77%<br>EFV AUC ↑ 44% | **Contraindicated at standard doses**.<br>Dose: voriconazole 400 mg BID, EFV 300 mg daily |
| | ETR | voriconazole AUC ↑ 14%<br>ETR AUC ↑ 36% | No dosage adjustment; use with caution. Consider monitoring voriconazole level. |
| | NVP | ↓ voriconazole possible<br>↑ NVP possible | Monitor for toxicity and antifungal response and/or voriconazole level. |
| **Antimycobacterials** | | | |
| **Clarithromycin** | EFV | clarithromycin AUC ↓ 39% | Monitor for efficacy or consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment. |
| | ETR | clarithromycin AUC ↓ 39%<br>OH-clarithromycin AUC ↑ 21%<br>ETR AUC ↑ 42% | Consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment. |
| | NVP | clarithromycin AUC ↓ 31%<br>OH-clarithromycin AUC ↑ 42% | Monitor for efficacy or use alternative agent, such as azithromycin, for MAC prophylaxis and treatment. |

**Table 15b. Drug Interactions between NNRTIs* and Other Drugs**
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| Concomitant Drug Class/Name | NNRTI | Effect on NNRTI or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Antimycobacterials (continued)** | | | |
| **Rifabutin** | EFV | rifabutin ↓ 38% | Dose: rifabutin 450–600 mg once daily or 600 mg three times a week if EFV is not coadministered with a PI. |
| | ETR | rifabutin and metabolite AUC ↓ 17%<br>ETR AUC ↓ 37% | **If ETR is used with an RTV-boosted PI, rifabutin should not be coadministered.**<br><br>Dose: rifabutin 300 mg once daily **if** ETR is not coadministered with an RTV-boosted PI. |
| | NVP | rifabutin AUC ↑ 17% and metabolite AUC ↑ 24%<br>NVP $C_{min}$ ↓ 16% | No dosage adjustment necessary. Use with caution. |
| **Rifampin** | EFV | EFV AUC ↓ 26% | Maintain EFV dose at 600 mg once daily and monitor for virologic response.<br>Some clinicians suggest EFV 800 mg dose in patients >60kg. |
| | ETR | Significant ↓ ETR possible | **Do not coadminister.** |
| | NVP | NVP ↓ 20%–58% | **Do not coadminister.** |
| **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 $C_{max}$ ↑ 16%, AUC no significant effect | No dosage adjustment necessary |
| **Midazolam** | EFV | Significant↑ midazolam expected | **Do not coadminister with oral midazolam.**<br>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 | |
| **Corticosteroids** | | | |
| **Dexamethasone** | ETR* | ↓ ETR possible | Use systemic dexamethasone with caution or consider alternative corticosteroid for long-term use. |
| **Herbal Products** | | | |
| **St. John's wort** | EFV, ETR, NVP | ↓ NNRTI | **Do not coadminister.** |
| **Hormonal Contraceptives** | | | |
| **Hormonal contraceptives** | EFV | ethinyl estradiol ↔<br>levonorgestrel AUC ↓ 83%<br>norelgestromin AUC ↓ 64% | Use alternative or additional methods. Norelgestromin and levonorgestrel are active metabolites of norgestimate. |
| | ETR | ethinyl estradiol AUC ↑ 22%<br>norethindrone: no significant effect | No dosage adjustment necessary. |
| | NVP | ethinyl estradiol AUC ↓ 20%<br>norethindrone AUC ↓ 19% | Use alternative or additional methods. |
| | | depomedroxyprogesterone acetate: no significant change | No dosage adjustment necessary |
| Levonorgestrel | EFV | levonorgestrel AUC ↓ 58% | Effectiveness of emergency postcoital contraception may be diminished. |
| **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. |

** Error corrected January 18, 2011*

**Table 15b. Drug Interactions between NNRTIs* and Other Drugs**
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| Concomitant Drug Class/Name | NNRTI | Effect on NNRTI or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **HMG-CoA Reductase Inhibitors (continued)** | | | |
| **Lovastatin**<br>**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, NVP | ↓ lovastatin possible<br>↓ 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. |
| **Pitavastatin** | EFV, ETR, NVP | No data | No dosage recommendation |
| **Pravastatin**<br>**Rosuvastatin** | EFV | pravastatin AUC ↓ 44%<br>rosuvatatin: no data | Adjust statin dose according to lipid responses, not to exceed the maximum recommended dose. |
| | ETR | No significant effect expected with either pravastatin or rosuvastatin | No dosage adjustment necessary |
| **Narcotics/Treatment for Opioid Dependence** | | | |
| **Buprenorphine** | EFV | buprenorphine AUC ↓ 50%<br>norbuprenorphine AUC ↓ 71% | No withdrawal symptoms reported. No dosage adjustment recommended, but monitor for withdrawal symptoms. |
| | NVP | No significant effect | No dosage adjustment necessary |
| **Methadone** | EFV | methadone AUC ↓ 52% | Opioid withdrawal common; increased methadone dose often necessary. |
| | ETR | No significant effect | No dosage adjustment necessary |
| | NVP | methadone AUC ↓ 41%<br>NVP: no significant effect | Opioid withdrawal common; increased methadone dose often necessary. |
| **Phosphodiesterase Type 5 (PDE5) Inhibitors** | | | |
| **Sildenafil** | ETR | sildenafil AUC ↓ 57% | May need to increase sildenafil dose based on clinical effect. |
| **Tadalafil** | ETR | ↓ tadalafil possible | May need to increase tadalafil dose based on clinical effect. |
| **Vardenafil** | ETR | ↓ vardenafil possible | May need to increase vardenafil dose based on clinical effect. |
| **Miscellaneous Interactions** | | | |
| **Atovaquone/proguanil** | EFV | ↓ atovaquone AUC 75%<br>↓ progaunil AUC 43% | No dosage recommendation. Consider alternative drug for malaria prophylaxis, if possible. |

**Acronyms**: ARV = antiretroviral, AUC = area under the curve, CCB = calcium channel blocker, $C_{max}$ = maximum plasma concentration, $C_{min}$ = minimum plasma concentration, DLV = delavirdine, EFV = efavirenz, ETR = etravirine, FDA = Food and Drug Administration, INR = international normalized ratio, MAC = *Mycobacterium avium* complex, NNRTI = non-nucleoside reverse transcriptase inhibitor, NVP = nevirapine, OH-clarithromycin = active metabolite of clarithromycin, PDE5 = phosphodiesterase type 5, PI = protease inhibitor

# Table 15c. Drug Interactions between NRTIs and Other Drugs (Including ARV Agents)
**(Updated January 10, 2011)**

| Concomitant Drug Class/Name | NRTI | Effect on NRTI or Concomitant Drug Concentrations | Dosage Recommendations and Clinical Comments |
|---|---|---|---|
| **Antivirals** | | | |
| **Ganciclovir Valganciclovir** | 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** | | | |
| **RAL** | TDF | RAL AUC ↑ 49%, $C_{max}$ ↑ 64% | No dosage adjustment necessary |
| **Narcotics/Treatment for Opioid Dependence** | | | |
| **Buprenorphine** | 3TC, ddI, TDF, ZDV | No significant effect | No dosage adjustment necessary |
| **Methadone** | ABC | methadone clearance ↑ 22% | No dosage adjustment necessary |
| | d4T | d4T AUC ↓ 23% and $C_{max}$ ↓ 44% | No dosage adjustment necessary |
| | ZDV | ZDV AUC ↑ 29%–43% | Monitor for ZDV-related adverse effects. |
| **NRTIs** | | | |
| **ddI** | d4T | No significant PK interaction | **Avoid coadministration**. Additive toxicities of peripheral neuropathy, lactic acidosis, and pancreatitis seen with this combination. |
| | TDF | ddI-EC AUC and $C_{max}$ ↑ 48%–60% | **Avoid coadministration**. |
| **Other** | | | |
| **Allopurinol** | ddI | ddI AUC ↑ 113%<br>ddI AUC ↑ 312% with renal impairment | **Contraindicated. Do not coadminister.** Potential for increased ddI-associated toxicities. |
| **PIs** | | | |
| **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 $C_{min}$ ↓ 23%–40% (higher $C_{min}$ with RTV than without)<br>TDF AUC ↑ 24%–37% | Dose: ATV/r 300/100 mg daily coadministered with TDF 300 mg daily. Avoid concomitant use without RTV. If using TDF and $H_2$ receptor antagonist in ART-experienced patients, use ATV/r 400 mg/100 mg daily.<br><br>Monitor for TDF-associated toxicity. |
| | ZDV | ZDV $C_{min}$ ↓ 30%, no change in AUC | Clinical significance unknown. |
| **DRV/r** | TDF | TDF AUC↑ 22%, $C_{max}$ ↑ 24% and $C_{min}$ ↑ 37% | Clinical significance unknown. Monitor for TDF toxicity. |
| **LPV/r** | TDF | LPV/r AUC ↓ 15%<br>TDF AUC ↑ 34% | Clinical significance unknown. Monitor for TDF toxicity. |
| **TPV/r** | ABC | ABC ↓ 35%–44% with TPV/r 1,250/100 mg BID | Appropriate doses for this combination have not been established. |
| | ddI | ddI-EC ↓ 10% and TPV $C_{min}$ ↓34% with TPV/r 1,250/100 mg BID | Separate doses by at least 2 hours. |
| | ZDV | ZDV AUC ↓ 31%–43% and $C_{max}$ ↓ 46%–51% with TPV/r 1,250/100 mg BID | Appropriate doses for this combination have not been established. |

**Acronyms:** 3TC = lamivudine, ABC = abacavir, ARV = antiretroviral, ATV = atazanavir, AUC = area under the curve, BID = twice daily, $C_{max}$ = maximum plasma concentration, $C_{min}$ = minimum plasma concentration, d4T = stavudine, ddI = didanosine, DRV/r = darunavir/ritonavir, EC = enteric coated, LPV/r = lopinavir/ritonavir, NRTI = nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, PK = pharmacokinetic, RAL = raltegravir, TDF = tenofovir, TPV/r = tipranavir/ritonavir, ZDV = zidovudine.

## Table 15d. Drug Interactions between CCR5 Antagonist and Other Drugs (Updated January 10, 2011)

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

| Concomitant Drug Class/Name | CCR5 Antagonist | Effect on CCR5 Antagonist or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Anticonvulsants** | | | |
| **Carbamazepine<br>Phenobarbital<br>Phenytoin** | MVC | ↓ MVC possible | If used without a strong CYP3A inhibitor, use MVC 600 mg BID or an alternative antiepileptic agent. |
| **Antifungal** | | | |
| **Itraconazole** | MVC | ↑ MVC possible | Dose: MVC 150 mg BID |
| **Ketoconazole** | MVC | MVC AUC ↑ 400% | Dose: MVC 150 mg BID |
| **Voriconazole** | MVC | ↑ MVC possible | Consider dose reduction to MVC 150 mg BID |
| **Antimycobacterials** | | | |
| **Clarithromycin** | MVC | ↑ MVC possible | Dose: MVC 150 mg BID |
| **Rifabutin** | MVC | ↓ MVC possible | If used without a strong CYP3A inducer or inhibitor, use MVC 300 mg BID.<br><br>If used with a strong CYP3A inhibitor, use MVC 150 mg BID. |
| **Rifampin** | MVC | MVC AUC ↓ 64% | Coadministration is not recommended.<br>If coadministration is necessary use MVC 600 mg BID.<br>If coadministered with a strong CYP3A inhibitor, use MVC 300 mg 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 |
| **Narcotics/Treatment for Opioid Dependence** | | | |
| **Methadone** | MVC | No data | |

**Acronyms**: ARV = antiretroviral, AUC = area under the curve, BID = twice daily, CYP = cytochrome P, MVC = maraviroc

## Table 15e. Drug Interactions between Integrase Inhibitor and Other Drugs (Updated January 10, 2011)

| Concomitant Drug Class/Name | Integrase Inhibitor | Effect on Integrase Inhibitor or Concomitant Drug Concentrations | Dosing Recommendations and Clinical Comments |
|---|---|---|---|
| **Acid Reducers** | | | |
| **Omeprazole** | RAL | RAL AUC ↑ 212%, $C_{max}$ ↑ 315%, and $C_{min}$ ↑ 46% | No dosage adjustment recommended |
| **Antimycobacterials** | | | |
| **Rifabutin** | RAL | RAL AUC ↑ 19%, $C_{max}$ ↑ 39%, and $C_{min}$ ↓ 20% | No dosage adjustment recommended |
| **Rifampin** | RAL | RAL AUC ↓ 40% and $C_{min}$ ↓ 61% with RAL 400 mg<br><br>Rifampin with RAL 800 mg BID compared with RAL 400 mg BID alone: RAL AUC ↑ 27% and $C_{min}$ ↓ 53% | Dose: RAL 800 mg BID<br>Monitor closely for virologic response. |
| **Hormonal Contraceptives** | | | |
| **Hormonal contraceptives** | RAL | No clinically significant effect | Safe to use in combination |
| **Narcotics/Treatment for Opioid Dependence** | | | |
| **Methadone** | RAL | No significant effect | No dosage adjustment necessary |

**Acronyms:** AUC = area under the curve, BID = twice daily, $C_{max}$ = maximum plasma concentration, $C_{min}$ = minimum plasma concentration, RAL = raltegravir

## Table 16a. Interactions Among PIs* (Updated January 10, 2011)

*NFV and IDV are not included in this table. Please refer to the FDA package insert for information regarding NFV and IDV drug interactions.

| Drug Affected | ATV | FPV | LPV/r | RTV | SQV | TPV |
|---|---|---|---|---|---|---|
| **DRV** | Dose: ATV 300 mg once daily + DRV 600 mg BID + RTV 100 mg BID | No data | **Should not be coadministered because doses are not established** | Dose: (DRV 600 mg + RTV 100 mg) BID or (DRV 800 mg + RTV 100 mg) once daily | **Should not be coadministered because doses are not established** | No data |
| **FPV** | Dose: Insufficient data | • | **Should not be coadministered because doses are not established** | Dose: (FPV 1,400 mg + RTV 100 mg or 200 mg) once daily; or (FPV 700 mg + RTV 100 mg) BID | Dose: Insufficient data | **Should not be coadministered because doses are not established** |
| **LPV/r** | Dose: ATV 300 mg once daily + LPV/r 400/100 mg BID | See LPV/r + FPV cell | • | LPV is coformulated with RTV as Kaletra. | See LPV/r + SQV cell | **Should not be coadministered because doses are not established** |
| **RTV** | Dose: (ATV 300mg + RTV 100mg) once daily | See RTV + FPV cell | LPV is coformulated with RTV as Kaletra. | • | Dose: (SQV 1,000 mg + RTV 100 mg) BID | Dose: (TPV 500 mg + RTV 200 mg) BID |
| **SQV** | Dose: Insufficient data | Dose: Insufficient data | Dose: SQV 1,000 mg BID + LPV/r 400/100 mg BID | See SQV + RTV cell | • | **Should not be coadministered because doses are not established** |

**Acronyms**: ATV = atazanavir, BID = twice daily, DRV = darunavir, FDA = Food and Drug Administration, FPV = fosamprenavir, IDV = indinavir, LPV/r = lopinavir/ritonavir, NFV = nelfinavir, PI = protease inhibitor, RTV = ritonavir, SQV = saquinavir, TPV = tipranavir

# Table 16b. Interactions between NNRTIs*, MVC, RAL, and PIs* (Updated January 10, 2011)



*DLV, IDV, and NFV are not included in this table. Refer to the FDA package insert for information regarding DLV, IDV, and NFV drug interactions.

| | | EFV | ETR | NVP | MVC | RAL |
|---|---|---|---|---|---|---|
| **ATV** | **PK data** | With unboosted ATV<br>ATV: AUC ↓ 74%<br>EFV: no significant change<br><br>With (ATV 300 mg + RTV 100 mg) once daily with food<br>ATV concentrations similar to unboosted ATV without EFV | With unboosted ATV<br>ETR: AUC ↑ 50%, $C_{max}$ ↑ 47%, and $C_{min}$ ↑ 58%<br>ATV: AUC ↓ 17% and $C_{min}$ ↓ 47%<br><br>With (ATV 300 mg + RTV 100 mg) once daily<br>ETR: AUC, $C_{max}$, and $C_{min}$ ↑ approximately 30%<br>ATV: AUC ↓ 14% and $C_{min}$ ↓ 38% | With (ATV 300 mg + RTV 100 mg) once daily<br>ATV: AUC ↓ 42% and $C_{min}$ ↓ 72%<br>NVP: AUC ↑ 25% | With unboosted ATV<br>MVC: AUC ↑ 257%<br><br>With (ATV 300 mg + RTV 100 mg) once daily<br>MVC: AUC ↑ 388% | With unboosted ATV<br>RAL: AUC ↑ 72%<br><br>With (ATV 300 mg + RTV 100 mg) once daily<br>RAL: AUC ↑ 41% |
| | **Dose** | **Do not coadminister with unboosted ATV.**<br><br>In ART-naïve patients<br>(ATV 400 mg + RTV 100 mg) once daily<br><br>**Do not coadminister in ART-experienced patients.** | **Do not coadminister with ATV +/− RTV.** | **Do not coadminister with ATV +/− RTV.** | MVC 150 mg BID with ATV +/− RTV | Standard |
| **DRV –** always use with RTV | **PK data** | With (DRV 300 mg + RTV 100 mg) BID<br>DRV: AUC ↓ 13%, $C_{min}$ ↓ 31%<br>EFV: AUC ↑ 21% | ETR 100 mg BID with (DRV 600 mg + RTV 100 mg) BID<br>DRV: no significant change<br>ETR: AUC ↓ 37%, $C_{min}$ ↓ 49% | With (DRV 400 mg + RTV 100 mg BID)<br>DRV: AUC ↑ 24%†<br>NVP: AUC ↑ 27% and $C_{min}$ ↑ 47% | With (DRV 600 mg + RTV 100 mg) BID<br>MVC: AUC ↑ 305%<br><br>With (DRV 600 mg + RTV 100 mg) BID + ETR<br>MVC: AUC ↑ 210% | With (DRV 600 mg + RTV 100 mg) BID<br>RAL: AUC ↓ 29% and $C_{min}$ ↑ 38% |
| | **Dose** | Clinical significance unknown. Use standard doses and monitor closely. Consider monitoring levels. | Standard (ETR 200 mg BID)<br>Despite decreased ETR, safety and efficacy established with this combination in a clinical trial | Standard | MVC 150 mg BID | Standard |
| **EFV** | **PK data** | • | ↓ ETR possible | NVP: no significant change<br>EFV: AUC ↓ 22% | MVC: AUC ↓ 45% | EFV: AUC ↓ 36% |
| | **Dose** | | **Do not coadminister.** | **Do not coadminister.** | MVC: 600 mg BID | Standard |
| **ETR** | **PK data** | ↓ ETR possible | • | ↓ ETR possible | MVC: AUC ↓ 53%, $C_{max}$ ↓ 60% | ETR: $C_{min}$ ↓ 17%<br>RAL: $C_{min}$ ↓ 34% |
| | **Dose** | **Do not coadminister.** | | **Do not coadminister**. | MVC 600 mg BID | Standard |
| **FPV** | **PK data** | With (FPV 1,400 mg + RTV 200 mg) once daily<br>APV: $C_{min}$ ↓ 36% | With (FPV 700 mg + RTV 100 mg) BID<br>APV: AUC ↑ 69%, $C_{min}$ ↑ 77% | With unboosted FPV 1,400 mg BID<br>APV: AUC ↓ 33%<br>NVP: AUC ↑ 29%<br><br>With (FPV 1,400 mg + RTV 100 mg) BID<br>NVP: $C_{min}$ ↑ 19% | Unknown; ↑ MVC possible | No data |
| | **Dose** | (FPV 1,400 mg + RTV 300 mg) once daily; or (FPV 700 mg + RTV 100 mg) BID<br>EFV standard | **Do not coadminister with FPV +/− RTV.** | (FPV 700 mg + RTV 100 mg) BID<br>NVP standard | MVC 150 mg BID | Standard |
| **LPV/r** | **PK data** | With LPV/r tablets 500/125 mg BID‡ + EFV 600 mg<br>LPV levels similar to LPV/r 400/100 mg BID without EFV | With LPV/r tablets<br>ETR: levels ↓ 30%–45% (comparable to the decrease with DRV/r)<br>LPV: levels ↓ 13%–20%. | With LPV/r capsules<br>LPV: AUC ↓ 27% and $C_{min}$ ↓51% | MVC: AUC ↑ 295%<br><br>With LPV/r + EFV<br>MVC: AUC ↑153% | ↓ RAL<br>↔ LPV/r |
| | **Dose** | LPV/r tablets 500/125 mg‡ BID; LPV/r oral solution 533/133 mg BID<br><br>EFV standard | Standard | LPV/r tablets 500/125 mg‡ BID; LPV/r oral solution 533/133 mg BID<br><br>NVP standard | MVC 150 mg BID | Standard |

| | | EFV | ETR | NVP | MVC | RAL |
|---|---|---|---|---|---|---|
| **NVP** | **PK data** | NVP: no significant change<br>EFV: AUC ↓ 22% | ↓ ETR possible | • | No significant change | No data |
| | **Dose** | **Do not coadminister.** | **Do not coadminister.** | | Without PI<br>MVC 300 mg BID<br><br>With PI (except TPV/r)<br>MVC 150 mg BID | Standard |
| **RAL** | **PK data** | RAL: AUC ↓ 36% | ETR: $C_{min}$ ↑ 17%<br>RAL: $C_{min}$ ↓ 34% | No data | RAL: AUC ↓ 37%<br>MVC: AUC ↓ 21% | • |
| | **Dose** | Standard | Standard | No data | Standard | |
| **RTV** | **PK data** | Refer to information for boosted PI | Refer to information for boosted PI | Refer to information for boosted PI | With RTV 100 mg BID<br>MVC: AUC ↑ 161% | With RTV 100 mg BID<br>RAL: AUC ↓ 16% |
| | **Dose** | | | | MVC 150 mg BID | Standard |
| **SQV -** always use with RTV | **PK data** | With SQV 1,200 mg TID<br>SQV: AUC ↓ 62%<br>EFV: AUC ↓ 12% | With (SQV 1,000 mg + RTV 100 mg) BID<br>SQV: AUC unchanged<br>ETR: AUC ↓ 33%, $C_{min}$ ↓ 29%<br>Reduced ETR levels similar to reduction with DRV/r | With SQV 600 mg TID<br>SQV: AUC ↓ 38%<br>NVP: no significant change | With (SQV 1,000 mg + RTV 100 mg) BID<br>MVC: AUC ↑ 877%<br><br>With (SQV 1,000 mg + RTV 100 mg) BID + EFV<br>MVC: AUC ↑ 400% | No data |
| | **Dose** | (SQV 1,000 mg + RTV 100 mg) BID | (SQV 1,000 mg + RTV 100 mg) BID | (SQV 1,000 mg + RTV 100mg) BID | MVC 150 mg BID | Standard |
| **TPV –** always use with RTV | **PK data** | With (TPV 500 mg + RTV 100 mg) BID<br>TPV: AUC ↓ 31%, $C_{min}$ ↓ 42%<br>EFV: no significant change<br><br>With (TPV 750 mg + RTV 200 mg) BID<br>TPV: no significant change<br>EFV: no significant change | With (TPV 500 mg + RTV 200 mg) BID<br>ETR: AUC ↓ 76%, $C_{min}$ ↓ 82%<br>TPV: AUC ↑ 18%, $C_{min}$ ↑ 24% | With (TPV 250 mg + RTV 200 mg) BID and with (TPV 750 mg + RTV 100 mg) BID<br>NVP: no significant change<br>TPV: no data | With (TPV 500 mg + RTV 200 mg) BID<br>MVC: no significant change in AUC<br>TPV: no data | With (TPV 500 mg + RTV 200 mg) BID<br>RAL: AUC ↓ 24% |
| | **Dose** | Standard | **Do not coadminister.** | Standard | MVC 300 mg BID | Standard |

† Based on between-study comparison.

‡Use a combination of two LPV/r 200 mg/50 mg tablets + one LPV/r 100 mg/25 mg tablet to make a total dose of LPV/r 500 mg/125* mg. *(* Error corrected January 18, 2011)*

**Acronyms**: AUC = area under the curve, ATV = atazanavir, BID = twice daily, $C_{max}$ = maximum plasma concentration, $C_{min}$ = minimum plasma concentration, DLV = delavirdine, DRV = darunavir, EFV = efavirenz, ETR = etravirine, FDA = Food and Drug Administration, FPV = fosamprenavir, IDV = indinavir, LPV/r = lopinavir/ritonavir, MVC = maraviroc, NFV = nelfinavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, PK = pharmacokinetic, RAL = raltegravir, RTV = ritonavir, SQV = saquinavir, TID = three times a day, TPV = tipranavir

# 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 the Centers for Disease Control and Prevention (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 *[8]* 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 *[9-11]* and opiate substitution treatment with methadone *[12-13]*.

There is evidence of increases in HIV risk behaviors among infected persons coinciding with the availability of potent combination antiretroviral therapy (ART). 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 increased in those who believed that receiving ART or having a suppressed viral load protects against transmitting HIV *[14]*. Attitudinal shifts away from safer sexual practices since the availability of potent ART 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 *[14-15]*.

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

ART 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 *[16-17]*. Observational studies have demonstrated a decreased rate of HIV transmission among serodiscordant heterosexual couples following antiretroviral (ARV)-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 *[18-19]*. 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 ARV regimen; and (3) the absence of a concomitant STI. Detection of HIV RNA in the genital secretions has been documented in individuals with controlled plasma HIV RNA *[20-21]*. 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 ART 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: Key to Acronyms

| | |
|---|---|
| 3TC | lamivudine |
| 3TC/ZDV | lamivudine + zidovudine |
| ABC | abacavir |
| ABC/3TC | abacavir + lamivudine |
| ABC/3TC/ZDV | abacavir + lamivudine + zidovudine |
| ACTG | AIDS Clinical Trials Group |
| AIDS | acquired immune deficiency syndrome |
| ALT | alanine aminotransferase |
| APV | amprenavir |
| ART | antiretroviral therapy |
| ART-CC | ART Cohort Collaboration |
| ARV | antiretroviral |
| AST | aspartate aminotransferase |
| ATV | atazanavir |
| ATV/r | atazanavir/ritonavir or ritonavir-boosted atazanavir |
| AUC | area under the curve |
| AV | atrioventricular |
| bDNA | branched DNA |
| BID | twice a day |
| BMD | bone mineral density |
| BUN | blood urea nitrogen |
| CAPD | chronic ambulatory peritoneal dialysis |
| CBC | complete blood count |
| CCB | calcium channel blocker |
| CDC | Centers for Disease Control and Prevention |
| CI | confidence interval |
| $C_{max}$ | maximum concentration or peak concentration |
| CME | continuing medical education |
| $C_{min}$ | minimum concentration or trough concentration |
| CMV | cytomegalovirus |
| CNS | central nervous system |
| CPK | creatine phosphokinase |
| CrCl | creatinine clearance |
| CVD | cardiovascular disease |
| CYP | cytochrome P |
| d4T | stavudine |
| D:A:D | Data Collection on Adverse Events of Anti-HIV Drugs Study |
| ddC | zalcitabine |
| ddI | didanosine |
| DHHS | Department of Health and Human Services |
| DILI | drug-induced liver injury |
| DLV | delavirdine |
| DM | diabetes mellitus |
| D/M | dual or mixed (tropic) |
| DMPA | depot medroxyprogesterone |
| DOT | directly observed therapy |
| DRV | darunavir |
| DRV/r | darunavir/ritonavir or ritonavir-boosted darunavir |

| | |
|---|---|
| DXA | dual-energy x-ray absorptiometry |
| EBV | Epstein-Barr virus |
| EC | enteric coated |
| ECG | electrocardiogram |
| EFV | efavirenz |
| EFV/FTC/TDF | efavirenz + emtricitabine + tenofovir disoproxil fumarate |
| EIA | enzyme immunoassay |
| ETR | etravirine |
| FDA | Food and Drug Administration |
| FI | fusion inhibitor |
| FPV | fosamprenavir |
| FPV/r | fosamprenavir/ritonavir or ritonavir-boosted fosamprenavir |
| FTC | emtricitabine |
| FTC/TDF | emtricitabine + tenofovir disoproxil fumarate |
| GAZT | AZT glucuronide |
| GHB | gamma hydroxybutyrate |
| GI | gastrointestinal |
| HAV | hepatitis A virus |
| HBeAg | hepatitis B e antigen |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HD | hemodialysis |
| HDL | high-density lipoprotein |
| HELLP | hemolysis, elevated liver enzymes, low platelet count (syndrome) |
| HHS | Health and Human Services |
| HHV | human herpes virus |
| HHV-8 | human herpes virus 8 |
| HIV | human immunodeficiency virus |
| HIV-1 | human immunodeficiency virus type 1 |
| HIV-2 | human immunodeficiency virus type 2 |
| HIVAN | HIV-associated nephropathy |
| HPV | human papilloma virus |
| HR | hazard ratio |
| HRSA | Health Resource Services Administration |
| hsCRP | high sensitivity C-reactive protein |
| HSR | hypersensitivity reaction |
| HTLV | human T-cell leukemia virus |
| HTLV-1 | human T-cell leukemia virus type 1 |
| HTLV-2 | human T-cell leukemia virus type 2 |
| IAS-USA | International AIDS Society-USA |
| IC | inhibitory concentration |
| IDU | illicit drug user |
| IDV | indinavir |
| IDV/r | indinavir/ritonavir or ritonavir-boosted indinavir |
| IFN-γ | interferon-gamma |
| IGRA | interferon-gamma release assay |
| IL-2 | interleukin-2 |
| IL-6 | interleukin-6 |
| IL-7 | interleukin-7 |
| IND | investigational new drug |

| | |
|---|---|
| INH | isoniazid |
| INR | international normalized ratio |
| INSTI | integrase strand transfer inhibitor |
| IQ | inhibitory quotient |
| IRB | Institutional Review Board |
| IRIS | immune reconstitution inflammatory syndrome |
| LDL | low-density lipoprotein |
| LPV | lopinavir |
| LPV/r | lopinavir/ritonavir or ritonavir-boosted lopinavir |
| LTBI | latent tuberculosis infection |
| MAC | *Mycobacterium avium* complex |
| MDMA | methylenedioxymethamphetamine |
| MDRD | modification of diet in renal disease (equation) |
| MHC | major histocompatability complex |
| MI | myocardial infarction |
| msec | milliseconds |
| MSM | men who have sex with men |
| MTB | *Mycobacterium tuberculosis* |
| MTCT | mother-to-child transmission |
| MVC | maraviroc |
| NA-ACCORD | The North American AIDS Cohort Collaboration on Research and Design |
| NFV | nelfinavir |
| NIH | National Institutes of Health |
| NNRTI | non-nucleoside reverse transcriptase inhibitor |
| NRTI | nucleoside reverse transcriptase inhibitor |
| NVP | nevirapine |
| OAR | Office of AIDS Research |
| OARAC | Office of AIDS Research Advisory Council |
| PAH | pulmonary arterial hypertension |
| PCP | *Pneumocystis jirocevi* pneumonia |
| PDE5 | phosphodiesterase type 5 |
| PI | protease inhibitor |
| PK | pharmacokinetic |
| PMTCT | prevention of mother-to-child transmission |
| PO | by mouth |
| PPI | proton pump inhibitor |
| PR | protease (gene) |
| PT | prothrombin time |
| RAL | raltegravir |
| RT | reverse transcriptase (gene) |
| RT-PCR | reverse transcriptase-polymerase chain reaction |
| RTV | ritonavir |
| SJS | Stevens-Johnson syndrome |
| SPT | skin patch test |
| SQV | saquinavir |
| SQV/r | saquinavir/ritonavir or ritonavir-boosted saquinavir |
| STI | sexually transmitted infection |
| $t_{½}$ | half-life |

| | |
|---|---|
| T-20 | enfuvirtide |
| TAM | thymidine analogue mutation |
| TB | tuberculosis |
| TCA | tricyclic antidepressant |
| TDF | tenofovir disoproxil fumarate or tenofovir |
| TDM | therapeutic drug monitoring |
| TEN | toxic epidermal necrosis |
| TG | triglyceride |
| TID | three times a day |
| TPV | tipranavir |
| TPV/r | tipranavir/ritonavir or ritonavir-boosted tipranavir |
| TST | tuberculin skin test |
| UDP | uridine diphosphate |
| UGT1A1 | uridine diphosphate glucuronosyltransferase 1A1 |
| VPA | valproic acid |
| WBC | white blood cell |
| WHO | World Health Organization |
| WITS | Women and Infants Transmission Study |
| ZDV | zidovudine |

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



**(Updated January 10, 2011)**

| Generic Name (abbreviation)/ Trade Name | Formulations | Dosing Recommendations (For dosage adjustment in renal or hepatic insufficiency, see Appendix B, Table 7.) | Elimination | Serum/ Intracellular Half-lives | Adverse Events (Also see Table 13) |
|---|---|---|---|---|---|
| **Abacavir** (ABC)/ Ziagen<br><br>**Also available as**: | Ziagen<br>- 300-mg tablets<br>- 20-mg/mL oral solution | Ziagen<br>300 mg BID or<br>600 mg once daily<br><br>Take without regard to meals | Metabolized by alcohol dehydrogenase and glucuronyl transferase<br><br>Renal excretion of metabolites 82%<br><br>Dosage adjustment for ABC recommended in patients with hepatic insufficiency (See **Appendix B, Table 7**.) | 1.5 hrs/<br>12–26 hrs | • *Hypersensitivity reactions (HSR)*: Patients positive for HLA-B*5701 are at highest risk. HLA screening should be done prior to initiation of ABC. Rechallenge is not recommended.<br>• Symptoms of HSR may include fever, rash, nausea, vomiting, diarrhea, abdominal pain, malaise, or fatigue or respiratory symptoms such as sore throat, cough, or shortness of breath.<br>• Some cohort studies suggest increased risk of myocardial infarction (MI) with recent or current use of ABC, but this risk is not substantiated in other studies. |
| Trizivir<br>ABC<br>with ZDV+3TC | Trizivir<br>ABC 300 mg +<br>ZDV 300 mg +<br>3TC 150 mg | Trizivir<br>1 tablet BID | | | |
| Epzicom<br>ABC with 3TC | Epzicom<br>ABC 600 mg +<br>3TC 300 mg | Epzicom<br>1 tablet once daily | | | |
| **Didanosine** (ddI)/ Videx EC (generic available; dose same as Videx EC) | Videx EC<br>125-, 200-, 250-, 400-mg capsules<br><br>Buffered tablets (non-EC) no longer available<br><br>Videx<br>10-mg/mL oral solution | **Body weight ≥60kg**:<br>400 mg once daily*<br>*With TDF*: 250 mg once daily<br><br>**Body weight <60kg**:<br>250 mg once daily*<br>*With TDF*: 200 mg once daily<br><br>Take 1/2 hour before or 2 hours after a meal<br><br>*Preferred dosing with oral solution is BID (total daily dose divided into 2 doses) | Renal excretion 50%<br><br>Dosage adjustment in renal insufficiency recommended (See **Appendix B, Table 7**.) | 1.5 hrs/<br>>20 hrs | • Pancreatitis<br>• Peripheral neuropathy<br>• Retinal changes, optic neuritis<br>• Lactic acidosis with hepatic steatosis +/- pancreatitis (rare but potentially life-threatening toxicity)<br>• Nausea, vomiting<br>• Potential association with noncirrhotic portal hypertension, some cases presented with esophageal varices<br>• One cohort study suggested increased risk of MI with recent or current use of ddI, but this risk is not substantiated in other studies.<br>• Insulin resistance/diabetes mellitus |
| **Emtricitabine** (FTC)/ Emtriva<br><br>**Also available as:** | Emtriva<br>- 200-mg hard gelatin capsule<br>- 10-mg/mL oral solution | Emtriva<br>*Capsule*: 200 mg once daily<br>*Oral solution*: 240 mg (24 mL) once daily<br><br>Take without regard to meals | Renal excretion 86%<br><br>Dosage adjustment in renal insufficiency recommended (See **Appendix B, Table 7**.) | 10 hrs/<br>>20 hrs | • Minimal toxicity<br>• Hyperpigmentation/skin discoloration<br>• Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue FTC. |
| Atripla<br>FTC<br>with EFV+TDF | Atripla<br>FTC 200 mg +<br>EFV 600 mg +<br>TDF 300 mg | Atripla<br>1 tablet at or before bedtime<br><br>Take on an empty stomach to reduce side effects | | | |
| Truvada<br>FTC with TDF | Truvada<br>FTC 200 mg +<br>TDF 300 mg | Truvada<br>1 tablet once daily | | | |

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


| Generic Name (abbreviation)/ Trade Name | Formulations | Dosing Recommendations (For dosage adjustment in renal or hepatic insufficiency, see Appendix B, Table 7.) | Elimination | Serum/ Intracellular Half-lives | Adverse Events (Also see Table 13) |
|---|---|---|---|---|---|
| **Lamivudine** (3TC)/ Epivir<br><br>**Also available as:** | Epivir<br>• 150-, 300-mg tablets<br>• 10-mg/mL oral solution | Epivir<br>150 mg BID or<br>300 mg once daily<br><br>Take without regard to meals | Renal excretion 70%<br><br>Dosage adjustment in renal insufficiency recommended (See Appendix B, Table 7.) | 5–7 hrs/<br>18–22 hrs | • Minimal toxicity<br>• Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue 3TC. |
| Combivir<br>3TC with ZDV | Combivir<br>3TC 150 mg + ZDV 300 mg | Combivir<br>1 tablet BID | | | |
| Epzicom<br>3TC with ABC | Epzicom<br>3TC 300 mg + ABC 600 mg | Epzicom<br>1 tablet once daily | | | |
| Trizivir<br>3TC with ZDV+ABC | Trizivir<br>3TC 150 mg + ZDV 300 mg + ABC 300 mg | Trizivir<br>1 tablet BID | | | |
| **Stavudine** (d4T)/ Zerit | Zerit<br>• 15-, 20-, 30-, 40-mg capsules<br>• 1-mg/mL oral solution | **Body weight ≥60 kg**:<br>40 mg BID<br>**Body weight <60 kg**:<br>30 mg BID*<br><br>Take without regard to meals<br><br>*WHO recommends 30 mg BID dosing regardless of body weight. | Renal excretion 50%<br><br>Dosage adjustment in renal insufficiency recommended (See Appendix B, Table 7.) | 1 hr/<br>7.5 hrs | • Peripheral neuropathy<br>• Lipoatrophy<br>• Pancreatitis<br>• Lactic acidosis/severe hepatomegaly with hepatic steatosis (rare but potentially life-threatening toxicity)<br>• Hyperlipidemia<br>• Insulin resistance/diabetes mellitus<br>• Rapidly progressive ascending neuromuscular weakness (rare) |
| **Tenofovir Disoproxil Fumarate** (TDF)/ Viread<br><br>**Also available as:** | Viread<br>300-mg tablet | Viread<br>1 tablet once daily<br><br>Take without regard to meals | Renal excretion<br><br>Dosage adjustment in renal insufficiency recommended (See Appendix B, Table 7.) | 17 hrs/<br>>60 hrs | • Renal insufficiency, Fanconi syndrome<br>• Osteomalacia<br>• Potential decrease in bone mineral density<br>• Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue TDF.<br>• Asthenia, headache, diarrhea, nausea, vomiting, and flatulence |
| Atripla<br>TDF with EFV+FTC | Atripla<br>TDF 300 mg + EFV 600 mg + FTC 200 mg | Atripla<br>1 tablet at or before bedtime<br><br>Take on an empty stomach to reduce side effects | | | |
| Truvada<br>TDF with FTC | Truvada<br>TDF 300 mg + FTC 200 mg | Truvada<br>1 tablet once daily<br><br>Take without regard to meals | | | |
| **Zidovudine** (ZDV)/ Retrovir (generic available; dose same as retrovir)<br><br>**Also available as:** | Retrovir<br>• 100-mg capsules<br>• 300-mg tablets<br>• 10-mg/mL intravenous solution<br>• 10-mg/mL oral solution | Retrovir<br>300 mg BID or<br>200 mg TID<br><br>Take without regard to meals | Metabolized to GAZT<br>Renal excretion of GAZT<br><br>Dosage adjustment in renal insufficiency recommended (See Appendix B, Table 7.) | 1.1 hrs/<br>7 hrs | • Bone marrow suppression: macrocytic anemia or neutropenia<br>• Nausea, vomiting, headache, insomnia, asthenia<br>• Nail pigmentation<br>• Lactic acidosis/severe hepatomegaly with hepatic steatosis (rare but potentially life-threatening toxicity)<br>• Hyperlipidemia<br>• Insulin resistance/diabetes mellitus<br>• Lipoatrophy<br>• Myopathy |
| Combivir<br>ZDV with 3TC | Combivir<br>ZDV 300 mg + 3TC 150 mg | Combivir<br>1 tablet BID | | | |
| Trizivir<br>ZDV with 3TC+ABC | Trizivir<br>ZDV 300 mg + 3TC 150 mg + ABC 300 mg | Trizivir<br>1 tablet BID | | | |

# Appendix B, Table 2. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) (Updated January 10, 2011)

| Generic Name (abbreviation)/ Trade Name | Formulations | Dosing Recommendations (For dosage adjustment in renal or hepatic insufficiency, see Appendix B, Table 7.) | Elimination | Serum Half-life | Adverse Events (Also see Table 13) |
|---|---|---|---|---|---|
| **Delavirdine** (DLV)/ Rescriptor | 100-, 200-mg tablets | 400 mg TID (Four 100-mg tablets can be dispersed in >3 oz. of water to produce a slurry; 200-mg tablets should be taken as intact tablets.)<br>Take without regard to meals<br>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*<br>• Increased transaminase levels<br>• Nausea, headache |
| **Efavirenz** (EFV)/ Sustiva<br><br>**Also available as**:<br><br>Atripla<br>EFV with FTC + TDF | • 50-, 200-mg capsules<br>• 600-mg tablets<br><br>Atripla<br>EFV 600 mg + FTC 200 mg + TDF 300 mg | 600 mg once daily at or before bedtime<br>Take on an empty stomach to reduce side effects<br><br>Atripla<br>1 tablet once daily at or before bedtime | Metabolized by CYPs 2B6 and 3A4<br>CYP3A4 mixed inducer/ inhibitor (more an inducer than an inhibitor) | 40–55 hrs | • Rash*<br>• Neuropsychiatric symptoms†<br>• Increased transaminase levels<br>• Hyperlipidemia<br>• False-positive results reported with some cannabinoid and benzodiazepine screening assays<br>• Teratogenic in nonhuman primates and potentially teratogenic in humans |
| **Etravirine** (ETR)/ Intelence | • 100-, 200-mg tablets | 200 mg BID<br>Take following a meal | CYP3A4, 2C9, and 2C19 substrate<br>3A4 inducer; 2C9 and 2C19 inhibitor | 41 +/– 20 hrs | • Rash, including Stevens-Johnson syndrome*<br>• Hypersensitivity reactions (HSRs) have been reported, characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure<br>• Nausea |
| **Nevirapine** (NVP)/ Viramune | • 200-mg tablets<br>• 50-mg/5-mL oral suspension | 200 mg once daily for 14 days (lead-in period); thereafter, 200 mg BID<br>Take without regard to meals<br>Repeat lead-in period if therapy is discontinued for >7 days<br>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, inducer of 3A4 and 2B6; 80% excreted in urine (glucuronidated metabolites, <5% unchanged); 10% in feces | 25–30 hrs | • Rash, including Stevens-Johnson syndrome*<br>• 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. Approximately 50% of patients receiving EFV may experience any of these symptoms. Symptoms usually subside spontaneously after 2–4 weeks, but may necessitate discontinuation of EFV in a small percentage of patients.

‡ Symptomatic, sometimes serious, and even fatal hepatic events (accompanied by rash in approximately 50% of cases) occur at significantly higher frequency in ARV-naïve female patients with pre-NVP CD4 counts >250 cells/$mm^3$ or in ARV-naïve male patients with pre-NVP CD4 counts >400 cells/$mm^3$. 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 January 10, 2011)



| Generic Name (abbreviation)/ Trade Name | Formulations | Dosing Recommendations (For dosage adjustment in hepatic insufficiency, see Appendix B, Table 7) | Elimination | Serum Half-life | Storage | Adverse Events (Also see Table 13) |
|---|---|---|---|---|---|---|
| **Atazanavir** (ATV)/ Reyataz | 100-, 150-, 200-, 300-mg capsules | ARV-naïve patients: 400 mg once daily or (ATV 300 mg + RTV 100 mg) once daily<br>With TDF or for ARV-experienced patients: (ATV 300 mg + RTV 100 mg) once daily<br>With EFV in ARV-naïve patients: (ATV 400 mg + RTV 100 mg) once daily<br><br>(For dosing recommendations with $H_2$ antagonists and proton pump inhibitor (PPIs), refer to Table 16a)<br><br>Take with food | CYP3A4 inhibitor and substrate<br><br>Dosage adjustment in hepatic insufficiency recommended (See Appendix B, Table 7.) | 7 hrs | Room temperature (up to 25ºC or 77ºF) | • Indirect hyperbilirubinemia<br>• PR interval prolongation: First degree symptomatic atrioventricular (AV) block reported. Use with caution in patients with underlying conduction defects or on concomitant medications that can cause PR prolongation.<br>• Hyperglycemia<br>• Fat maldistribution<br>• Possible increased bleeding episodes in patients with hemophilia<br>• Nephrolithiasis<br>• Skin rash (20%)<br>• Serum transaminase elevations<br>• Hyperlipidemia (especially with RTV boosting) |
| **Darunavir** (DRV)/ Prezista | 75-, 150-, 300-, 400-, 600-mg tablets | ARV-naïve patients or ARV-experienced patients with no DRV mutations: (DRV 800 mg + RTV 100 mg) once daily<br>ARV-experienced patients with at least one DRV mutation: (DRV 600 mg + RTV 100 mg) BID<br><br>Unboosted DRV is **not** recommended<br><br>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.<br>• Hepatotoxicity<br>• Diarrhea, nausea<br>• Headache<br>• Hyperlipidemia<br>• Serum transaminase elevation<br>• Hyperglycemia<br>• Fat maldistribution<br>• Possible increased bleeding episodes in patients with hemophilia |
| **Fosamprenavir** (FPV)/ Lexiva (a prodrug of amprenavir [APV]) | • 700-mg tablet<br>• 50-mg/mL oral suspension | ARV-naïve patients:<br>• FPV 1,400 mg BID or<br>• (FPV 1,400 mg + RTV 100–200 mg) once daily or<br>• (FPV 700 mg + RTV 100 mg) BID<br>PI-experienced patients (once-daily dosing **not** recommended):<br>• (FPV 700 mg + RTV 100 mg) BID<br>With EFV:<br>• (FPV 700 mg + RTV 100 mg) BID or<br>• (FPV 1,400 mg + RTV 300 mg) once daily<br><br>*Tablet*: Take without regard to meals (if not boosted with RTV tablet)<br><br>*Suspension*: Take without food<br><br>*FPV w/RTV tablet*: Take with meals | APV is a CYP3A4 substrate, inhibitor, and inducer<br><br>Dosage adjustment in hepatic insufficiency recommended (See Appendix B, Table 7.) | 7.7 hrs (APV) | Room temperature (up to 25ºC or 77ºF) | • Skin rash (12%–19%) – FPV has a sulfonamide moiety<br>• Diarrhea, nausea, vomiting<br>• Headache<br>• Hyperlipidemia<br>• Serum transaminase elevation<br>• Hyperglycemia<br>• Fat maldistribution<br>• Possible increased bleeding episodes in patients with hemophilia<br>• Nephrolithiasis |

**Appendix B, Table 3. Characteristics of Protease Inhibitors (PIs)**
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| Generic Name (abbreviation)/ Trade Name | Formulations | Dosing Recommendations (For dosage adjustment in hepatic insufficiency, see Appendix B, Table 7) | Elimination | Serum Half-life | Storage | Adverse Events (Also see Table 13) |
|---|---|---|---|---|---|---|
| **Indinavir** (IDV)/ Crixivan | 100-, 200-, 400-mg capsules | 800 mg every 8 hrs<br>Take 1 hour before or 2 hours after meals; may take with skim milk or low-fat meal<br><br>With RTV:<br>(IDV 800 mg + RTV 100–200 mg) BID<br>Take without regard to meals | CYP3A4 inhibitor and substrate<br>Dosage adjustment in hepatic insufficiency recommended (See Appendix B, Table 7.) | 1.5–2 hrs | Room temperature (15º–30ºC/ 59º–86ºF)<br>Protect from moisture | • Nephrolithiasis<br>• GI intolerance, nausea<br>• Hepatitis<br>• Indirect hyperbilirubinemia<br>• Hyperlipidemia<br>• Headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, alopecia, and hemolytic anemia<br>• Hyperglycemia<br>• Fat maldistribution<br>• Possible increased bleeding episodes in patients with hemophilia |
| **Lopinavir + Ritonavir** (LPV/r)/ Kaletra | Tablets:<br>(LPV 200 mg + RTV 50 mg) or (LPV 100 mg + RTV 25 mg)<br>Oral solution:<br>Each 5 mL contains (LPV 400 mg + RTV 100 mg)<br>Oral solution contains 42% alcohol | LPV/r 400-mg/100-mg BID<br>or<br>LPV/r 800-mg/200-mg once daily<br><br>Once-daily dosing is not recommended for patients with ≥3 LPV-associated mutations, pregnant women, or patients receiving EFV, NVP, FPV, NFV, carbamazepine, phenytoin, or phenobarbital.<br><br>With EFV or NVP (PI-naïve or PI-experienced patients):<br>LPV/r 500-mg/125-mg tablets BID (Use a combination of two LPV/r 200-mg/50-mg tablets + one LPV/r 100-mg/25-mg tablet to make a total dose of LPV/r 500 mg/125 mg.)<br>or<br>LPV/r 533-mg/133-mg oral solution BID<br><br>*Tablet*: Take without regard to meals<br>*Oral solution*: Take with food | CYP3A4 inhibitor and substrate | 5–6 hrs | Oral tablet is stable at room temperature.<br><br>Oral solution is stable at 2°–8°C (36°–46°F) 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<br>• Pancreatitis<br>• Asthenia<br>• Hyperlipidemia (especially hypertriglyceridemia)<br>• Serum transaminase elevation<br>• Hyperglycemia<br>• Insulin resistance/diabetes mellitus<br>• Fat maldistribution<br>• Possible increased bleeding episodes in patients with hemophilia<br>• PR interval prolongation<br>• QT interval prolongation and torsades de pointes have been reported; however, causality could not be established. |
| **Nelfinavir** (NFV)/ Viracept | • 250-, 625-mg tablets<br>• 50-mg/g oral powder | 1,250 mg BID or 750 mg TID<br><br>May dissolve tablets in a small amount of water; once dissolved, patients should mix the cloudy liquid well and consume it immediately.<br><br>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<br>• Hyperlipidemia<br>• Hyperglycemia<br>• Fat maldistribution<br>• Possible increased bleeding episodes in patients with hemophilia<br>• Serum transaminase elevation |

**Appendix B, Table 3. Characteristics of Protease Inhibitors (PIs)**
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| Generic Name (abbreviation)/ Trade Name | Formulations | Dosing Recommendations (For dosage adjustment in hepatic insufficiency, see Appendix B, Table 7) | Elimination | Serum Half-life | Storage | Adverse Events (Also see Table 13) |
|---|---|---|---|---|---|---|
| **Ritonavir** (RTV)/ Norvir | • 100-mg soft gel capsules<br>• 100-mg tablets<br>• 80-mg/mL oral solution<br><br>Oral solution contains 43% alcohol | As pharmacokinetic booster for other PIs: 100–400 mg per day in 1–2 divided doses (refer to other PIs for specific dosing recommendations)<br><br>*Tablet*: Take with food<br>*Capsule and oral solution*: Take with food, if possible, to improve tolerability. | CYP3A4 >2D6 substrate; potent 3A4, 2D6 inhibitor | 3–5 hrs | Refrigerate capsules<br>Capsules can be left at room temperature (up to 25ºC or 77ºF) for up to 30 days.<br>Tablets do not require refrigeration.<br>Oral solution should **not** be refrigerated; store at room temperature 20º–25ºC (68º–77ºF). | • GI intolerance, nausea, vomiting, diarrhea<br>• Paresthesias—circumoral and extremities<br>• Hyperlipidemia (especially hypertriglyceridemia)<br>• Hepatitis<br>• Asthenia<br>• Taste perversion<br>• Hyperglycemia<br>• Fat maldistribution<br>• Possible increased bleeding episodes in patients with hemophilia |
| **Saquinavir tablets and hard gel capsules** (SQV)/ Invirase | • 500-mg tablets<br>• 200-mg hard gel capsules | (SQV 1,000 mg + RTV 100 mg) BID<br><br>Unboosted SQV is **not** recommended.<br><br>Take with meals or within 2 hours after a meal | CYP3A4 inhibitor and substrate | 1–2 hrs | Room temperature (15º–30ºC/ 59º–86ºF) | • GI intolerance, nausea, and diarrhea<br>• Headache<br>• Serum transaminase elevation<br>• Hyperlipidemia<br>• Hyperglycemia<br>• Fat maldistribution<br>• Possible increased bleeding episodes in patients with hemophilia<br>• PR interval prolongation<br>• QT interval prolongation, torsades de pointes have been reported. Patients with pre-SQV QT interval >450 msec should not receive SQV (See Table 5b.). |
| **Tipranavir** (TPV)/ Aptivus | • 250-mg capsules<br>• 100-mg/mL oral solution | (TPV 500 mg + RTV 200 mg) BID<br><br>Unboosted TPV is **not** recommended.<br><br>*TPV taken with RTV **tablets**:* Take with meals<br><br>*TPV taken with RTV **capsules** or **solution**:* Take without regard to meals | Cytochrome P450 3A4 inducer and substrate<br><br>Net effect when combined with RTV (CYP 3A4, 2D6 inhibitor) | 6 hrs after single dose of TPV/r | Refrigerate capsules.<br>Capsules can be stored at room temperature (25ºC or 77ºF) for up to 60 days.<br><br>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 patients with underlying liver diseases.<br>• Skin rash (3%–21%): TPV has a sulfonamide moiety; use with caution in patients with known sulfonamide allergy.<br>• Rare cases of fatal and nonfatal intracranial hemorrhages have been reported. Risks include brain lesion, head trauma, recent neurosurgery, coagulopathy, hypertension, alcoholism,, use of anti-coagulant or anti-platelet agents including vitamin E.<br>• Hyperlipidemia<br>• Hyperglycemia<br>• Fat maldistribution<br>• Possible increased bleeding episodes in patients with hemophilia |

## Appendix B, Table 4. Characteristics of Integrase Inhibitor (Updated January 10, 2011)

| Generic Name (abbreviation)/ Trade Name | Formulations | Dosing Recommendations (For dosage adjustment in hepatic insufficiency, see Appendix B, Table 7.) | Serum half-life | Route of Metabolism | Adverse Events (Also see Table 13) |
|---|---|---|---|---|---|
| **Raltegravir** (RAL)/ Isentress | 400 mg tablets | 400 mg BID<br><br>With rifampin:<br>800 mg BID<br><br>Take without regard to meals | ~9 hrs | UGT1A1-mediated glucuronidation | • Nausea<br>• Headache<br>• Diarrhea<br>• Pyrexia<br>• CPK elevation, muscle weakness and rhabdomyolysis |

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

| Generic Name (abbreviation)/ Trade Name | Formulations | Dosing Recommendation | Serum half-life | Elimination | Storage | Adverse Events (Also see Table 13) |
|---|---|---|---|---|---|---|
| **Enfuvirtide** (T20)/ Fuzeon | • Injectable—supplied as lyophilized powder<br>• Each vial contains 108 mg of T20; reconstitute with 1.1mL of sterile water for injection for delivery of approximately 90mg/1mL. | 90 mg (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).<br>Reconsti-tuted solution should be refrigerated 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)<br>• Increased bacterial pneumonia<br>• 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 Antagonist (Updated January 29, 2008)

| Generic Name (abbreviation)/ Trade Name | Formulation | Dosing Recommendations (For dosage adjustment in hepatic insufficiency, see Appendix B, Table 7.) | Serum Half-life | Elimination | Adverse Events (Also see Table 13) |
|---|---|---|---|---|---|
| **Maraviroc** (MVC)/ Selzentry | 150-, 300-mg tablets | • **150 mg BID** when given with strong CYP3A inhibitors (with or without CYP3A inducers) including PIs (except TPV/r)<br>• **300 mg BID** when given with NRTIs, T-20, TPV/r, NVP, RAL, and other drugs that are not strong CYP3A inhibitors or inducers<br>• **600 mg BID** when given with CYP3A inducers, including EFV, ETR, etc. (without a CYP3A inhibitor)<br><br>Take without regard to meals | 14–18 hrs | CYP3A4 substrate | • Abdominal pain<br>• Cough<br>• Dizziness<br>• Musculoskeletal symptoms<br>• Pyrexia<br>• Rash<br>• Upper respiratory tract infections<br>• Hepatotoxicity<br>• Orthostatic hypotension |

# Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Updated January 10, 2011)



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

| Antiretrovirals<br>Generic Name (abbreviation)/Trade Name | Usual Daily Dose<br>(Refer to Appendix B Tables 1-6 for additional dosing information) | Dosing in Renal Insufficiency<br>(Including with chronic ambulatory peritoneal dialysis [CAPD] and hemodialysis [HD]) | Dosing in Hepatic Impairment |
|---|---|---|---|
| **Nucleoside Reverse Transcriptase Inhibitors**<br>**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**<br>(ABC)/<br>Ziagen | 300 mg PO BID | No dosage adjustment necessary | **Child-Pugh Score** — **Dose**<br>5–6 — 200 mg BID (use oral solution)<br>> 6 — Contraindicated |
| **Didanosine enteric coated**<br>(ddI)/<br>Videx EC | **Body weight ≥60 kg**:<br>400 mg PO once daily<br>**Body weight <60 kg**:<br>250 mg PO once daily | **Dose (once daily)**<br>**CrCl (mL/min)** — **≥60 kg** — **<60 kg**<br>30–59 — 200 mg — 125 mg<br>10–29 — 125 mg — 125 mg<br><10, HD, CAPD — 125 mg — use oral solution | No dosage adjustment necessary |
| **Didanosine oral solution**<br>(ddI)/<br>Videx | **Body weight ≥60 kg**:<br>200 mg PO BID or 400 mg PO once daily<br>**Body weight <60 kg**:<br>250 mg PO once daily or 125 mg PO BID | **Dose (once daily)**<br>**CrCl (mL/min)** — **≥60 kg** — **<60 kg**<br>30–59 — 200 mg — 150 mg<br>10–29 — 150 mg — 100 mg<br><10, HD, CAPD — 100 mg — 75 mg | No dosage adjustment necessary |
| **Emtricitabine**<br>(FTC)/<br>Emtriva | 200mg oral capsule PO once daily; or<br>240 mg (24 mL) oral solution PO once daily | **Dose**<br>**CrCl (mL/min)** — **Capsule** — **Solution**<br>30–49 — 200 mg q48h — 120 mg q24h<br>15–29 — 200 mg q72h — 80 mg q24h<br><15 or HD — 200 mg q96h — 60 mg q24h<br>Take dose after HD session on dialysis days | No dosage recommendation |
| **Lamivudine**<br>(3TC)/<br>Epivir | 300 mg PO once daily; or<br>150 mg PO BID | **CrCl (mL/min)** — **Dose**<br>30–49 — 150 mg q24h<br>15–29 — 1 x 150 mg, then 100 mg q24h<br>5–14 — 1 x 150 mg, then 50 mg q24h<br><5 or HD — 1 x 50 mg, then 25 mg q24h<br>Take dose after HD session on dialysis days | No dosage adjustment necessary |
| **Stavudine**<br>(D4T)/<br>Zerit | **Body weight ≥60 kg**:<br>40 mg PO BID<br>**Body weight <60 kg**:<br>30 mg PO BID | **Dose**<br>**CrCl (mL/min)** — **≥60 kg** — **<60 kg**<br>26–50 — 20 mg q12h — 15 mg q12h<br>10–25 or HD — 20 mg q24h — 15 mg q24h<br>Take dose after HD session on dialysis days | No dosage recommendation |
| **Tenofovir**<br>(TDF)/<br>Viread | 300 mg PO once daily | **CrCl (mL/min)** — **Dose**<br>30–49 — 300 mg q48h<br>10–29 — 300 mg twice weekly<br><10 not on HD — no recommendation<br>HD — 300 mg q7d<br>Take dose after HD session on dialysis days | No dosage adjustment necessary |
| **Emtricitabine** (FTC) + **Tenofovir** (TDF)/<br>Truvada | 1 tablet PO once daily | **CrCl (mL/min)** — **Dose**<br>30–49 — 1 tablet q48h<br><30 or HD — not recommended | No dosage recommendation |
| **Zidovudine**<br>(AZT, ZDV)/<br>Retrovir | 300 mg PO BID | **CrCl (mL/min)** — **Dose**<br>< 15 or HD — 100 mg TID or 300 mg once daily | No dosage recommendation |

**Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency**


| Antiretrovirals<br>Generic Name (abbreviation)/ Trade Name | Daily Dose | Dosing in Renal Insufficiency<br>(Including with chronic ambulatory peritoneal dialysis [CAPD] and hemodialysis [HD]) | Dosing in Hepatic Impairment |
|---|---|---|---|
| **Non-Nucleoside Reverse Transcriptase Inhibitors** | | | |
| **Delavirdine** (DLV)/ Rescriptor | 400 mg PO TID | No dosage adjustment necessary | No dosage recommendation; use with caution in patients with hepatic impairment |
| **Efavirenz** (EFV)/ Sustiva | 600 mg PO 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 | 200 mg PO BID | No dosage adjustment necessary | Child-Pugh Class A or B: no dosage adjustment<br>Child-Pugh Class C: no dosage recommendation |
| **Nevirapine** (NVP)/ Viramune | 200 mg PO BID | HD patients: limited data; no dosage recommendation | Child-Pugh Class B or C: contraindicated |
| **Protease Inhibitors** | | | |
| **Atazanavir** (ATV)/ Reyataz | 400 mg PO once daily or<br>(ATV 300 mg + RTV 100 mg) PO once daily | No dosage adjustment for patients with renal dysfunction not requiring HD<br><br>ARV-naïve patients on HD:<br>(ATV 300 mg + RTV 100 mg) once daily<br><br>ARV-experienced patients on HD: ATV or RTV-boosted ATV not recommended | **Child-Pugh Score** **Dose**<br>7–9 300 mg once daily<br>>9 not recommended<br>RTV boosting is **not** recommended in patients with hepatic impairment (Child-Pugh Score ≥7). |
| **Darunavir** (DRV)/ Prezista | (DRV 800 mg + RTV 100 mg) PO once daily (ARV-naïve patients) or<br>(DRV 600 mg + RTV 100 mg) PO BID | No dosage adjustment necessary | Mild to moderate hepatic impairment: no dosage adjustment<br>Severe hepatic impairment: not recommended |
| **Fosamprenavir** (FPV)/ Lexiva | 1,400 mg PO BID or<br>(FPV 1,400 mg + RTV 100–200 mg) PO once daily or<br>(FPV 700 mg + RTV 100 mg) PO BID | No dosage adjustment necessary | **Child-Pugh Score** **Dose**<br>PI-naïve patients only:<br>5–9 700 mg BID<br>10–15 350 mg BID<br><br>PI-naïve or PI-experienced patients:<br>5–6 700 mg BID + RTV 100 mg once daily<br>7–9 450 mg BID + RTV 100 mg once daily<br>10–15 300 mg BID + RTV 100 mg once daily |
| **Indinavir** (IDV)/ Crixivan | 800 mg PO q8h | No dosage adjustment necessary | Mild to moderate hepatic insufficiency because of cirrhosis: 600 mg q8h |
| **Lopinavir/ritonavir** (LPV/r) Kaletra | 400/100 mg PO BID or 800/200 mg PO once daily | Avoid once daily dosing in patients on HD | No dosage recommendation; use with caution in patients with hepatic impairment |
| **Nelfinavir** (NFV)/ Viracept | 1,250 mg PO BID | No dosage adjustment necessary | Mild hepatic impairment: no dosage adjustment<br>Moderate to severe hepatic impairment: do not use |
| **Ritonavir** (RTV)/ Norvir | As a PI-boosting agent:<br>100–400 mg per day | No dosage adjustment necessary | Refer to recommendations for the primary PI |
| **Saquinavir** (SQV)/ Invirase | (SQV 1,000 mg + RTV 100 mg) PO BID | No dosage adjustment necessary | Mild to moderate hepatic impairment: use with caution<br>Severe hepatic impairment: contraindicated |
| **Tipranavir** (TPV)/ Aptivus | (TPV 500 mg + RTV 200 mg) PO BID | No dosage adjustment necessary | Child-Pugh Class A: use with caution<br>Child-Pugh Class B or C: contraindicated |

**Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency**
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| Antiretrovirals Generic Name (abbreviation)/ Trade Name | Daily Dose | Dosing in Renal Insufficiency | Dosing in Hepatic Impairment |
|---|---|---|---|
| **Fusion Inhibitor** | | | |
| **Enfuvirtide** (T20)/ Fuzeon | 90 mg subcutaneous BID | No dosage adjustment necessary | No dosage adjustment necessary |
| **CCR5 Antagonist** | | | |
| **Maraviroc** (MVC)/ Selzentry | The recommended dose differs based on concomitant medications because of drug interactions. See **Appendix B, Table 6** for detailed dosing information. | **CrCl <30 mL/min or HD**<br>Without potent CYP3A inhibitors or inducers: 300 mg BID; reduce to 150 mg BID if postural hypotension occurs<br>With potent CYP3A inducers or inhibitors: not recommended | No dosage recommendations. Concentrations will likely be increased in patients with hepatic impairment. |
| **Integrase Inhibitor** | | | |
| **Raltegravir** (RAL)/ Isentress | 400 mg BID | No dosage adjustment necessary | Mild to moderate hepatic insufficiency: no dosage adjustment necessary<br>Severe hepatic insufficiency: no recommendation |

| Creatinine Clearance Calculation | |
|---|---|
| Male: $\frac{(140 - \text{age in years}) \times \text{weight (kg)}}{72 \times \text{Serum Creatinine}}$ | Female: $\frac{(140 - \text{age in years}) \times \text{weight (kg)} \times 0.85}{72 \times \text{Serum Creatinine}}$ |

| 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