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

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

Developed by the HHS 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* website (http://aidsinfo.nih.gov).

access AIDS*info* mobile site

What's New in the Guidelines? (Last updated March 27, 2012; last reviewed March 27, 2012)

Revisions to the October 14, 2011, version of the guidelines include both new sections and key updates to existing sections. The additions and updates, which are highlighted throughout the guidelines, are summarized below.

New Sections

The following two new sections have been added to the guidelines.

HIV and the Older Patient

Effective antiretroviral therapy (ART) has led to greater longevity in HIV-infected individuals resulting in an increasing number of older individuals living with HIV infection. Compared with younger HIV-infected patients, older patients may have more comorbidities, which can complicate treatments of HIV and other diseases. This section focuses on HIV diagnosis and treatment considerations in the older HIV-infected patient.

Antiretroviral Drug Cost Table (Appendix C)

This new table lists the monthly average wholesale price (AWP) for U.S. Food and Drug Administration (FDA)-approved brand and generic antiretroviral (ARV) drugs, including fixed-dose combination products. (The AWP listed for an ARV may not represent the pharmacy acquisition price or the price paid by consumers for that drug.)

Key Updates to Existing Sections

Following are key updates to existing sections of the guidelines.

Initiating Antiretroviral Therapy in Treatment-Naive Patients

The Panel updated its recommendations on initiation of ART in treatment-naive patients. The changes are primarily based on increasing evidence showing the harmful impact of ongoing HIV replication on AIDS and non-AIDS disease progression. In addition, the updated recommendations reflect emerging data showing the benefit of effective ART in preventing secondary transmission of HIV. The updated section includes more in-depth discussion on the rationale for these recommendations and on the risks and benefits of long-term ART.

The Panel's recommendations are listed below.

- ART is recommended for all HIV-infected individuals. The strength of this recommendation[a] varies on the basis of pretreatment CD4 cell count:
  - CD4 count <350 cells/mm^3 **(AI)**
  - CD4 count 350 to 500 cells/mm^3 **(AII)**
  - CD4 count >500 cells/mm^3 **(BIII)**
- Regardless of CD4 count, initiation of ART is strongly recommended for individuals with the following conditions:
  - Pregnancy **(AI)** (see perinatal guidelines for more detailed discussion)
  - History of an AIDS-defining illness **(AI)**
  - HIV-associated nephropathy (HIVAN) **(AII)**
  - HIV/hepatitis B virus (HBV) coinfection **(AII)**

- Effective ART also has been shown to prevent transmission of HIV from an infected individual to a sexual partner. Therefore, ART should be offered to patients who are at risk of transmitting HIV to sexual partners (**AI** [heterosexuals] or **AIII** [other transmission risk groups]).
- Patients starting ART should be willing and able to commit to 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 on the basis of clinical and/or psychosocial factors.

HIV-Infected Women

This revised section includes an expanded discussion on the use of hormonal contraception in HIV-infected women. The discussion focuses on drug-drug interactions between combined oral contraceptives and ARV drugs as well as on recent data showing a possible association between hormonal contraceptive use and acquisition or transmission of HIV.

HIV/Hepatitis C Coinfection

Updates to this section focus on the newly approved HCV NS3/4A protease inhibitors (PIs) boceprevir and telaprevir, the known interactions between these drugs and ART, and interim results from current ongoing research in HIV/HCV coinfected patients. The updated section includes preliminary recommendations on coadministration of the HCV NS3/4A drugs and ART.

Mycobacterium tuberculosis Disease with HIV Coinfection

This update provides recommendations for timing of initiation of ART in HIV-infected patients who have been diagnosed with tuberculosis (TB) and are not receiving ART. The recommendations are based on results from randomized controlled trials showing survival benefits (1) when ART was initiated during rather than after TB treatment and (2) when ART was started within 2 weeks of TB treatment in patients with pretreatment CD4 count <50 cells/mm^3. The updated section provides more in-depth discussions on the evidence and rationale supporting the recommendations.

The Panel's recommendations are as follows:

- For patients with CD4 counts <50 cells/mm^3, ART should be initiated within 2 weeks of starting TB treatment **(AI)**.
- For patients with CD4 counts ≥50 cells/mm^3 with clinical disease of major severity as indicated by clinical evaluation (including low Karnofsky score, low body mass index [BMI], low hemoglobin, low albumin, organ system dysfunction, or extent of disease), the Panel recommends initiation of ART within 2 to 4 weeks of starting TB treatment (**BI** for CD4 count 50–200 cells/mm^3 and **BIII** for CD4 count >200 cells/mm^3).
- For other patients with CD4 counts ≥50 cells/mm^3, ART can be delayed beyond 2 to 4 weeks but should be initiated by 8 to 12 weeks of TB therapy (**AI** for CD4 count 50–500 cells/mm^3; **BIII** for CD4 count >500 cells/mm^3).

Drug Interaction Tables (Tables 14-16b)

These tables are updated with recent data on pharmacokinetic (PK) interactions between ARV drugs and other drugs commonly prescribed for HIV-infected patients and the Panel's recommendations on coadministration of these drugs. The key updates include:

- Change in recommendation on dosing of rifabutin with HIV PIs

- New recommendation to not use HIV PIs and non-nucleoside reverse transcriptase inhibitors (NNRTIs) with rifapentine
- Addition of information on interactions of boceprevir and telaprevir with different ARV drugs and related recommendations
- Update of interactions between different ritonavir-boosted PI and HMG-CoA reductase inhibitors.

Prevention of Secondary HIV Transmission

This section is updated to discuss the role of effective ART in preventing HIV transmission. The updated section also indicates evidence-based interventions available to assist providers with HIV risk behavior identification and counseling.

Additional Updates
Minor revisions have also been made to the following sections:

- Treatment Goals
- What to Start: Initial Combination Regimens for the Antiretroviral-Naive Patient (new information regarding adverse effects of raltegravir)
- HIV and Illicit Drug Users (new drug interaction added to Table 11 included in the section)
- Adherence to Antiretroviral Therapy
- Adverse Effects of Antiretroviral Agents (and accompanying Table 13)
- Drug Characteristics Tables (Appendix B)

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[a] ***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*

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HHS Panel on Antiretroviral Guidelines for Adults and Adolescents
Panel Roster (Last updated March 27, 2012; last reviewed March 27, 2012)

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Acknowledgement

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Introduction (Last updated January 10, 2011; last reviewed 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-naive 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. Outline of the Guidelines Development Process

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.
Financial disclosures	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.
Users of the guidelines	HIV treatment providers
Developer	Panel on Antiretroviral Guidelines for Adults and Adolescents—a working group of 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

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

HIV Expertise in Clinical Care

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

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.
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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.
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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 (Last updated January 10, 2011; last reviewed 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 of 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 adequancy 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

Laboratory Testing for Initial Assessment and Monitoring While on Antiretroviral Therapy
(Last updated January 10, 2011; last reviewed 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-naive 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

	Entry into care	Follow-up before ART	ART initiation or modification[a]	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	√	√[b]	√[c]			√	√
Resistance testing	√		√[d]					√	√
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[e]	√		√ may repeat if HBsAg (-) and HBsAb (-) at baseline						√
Basic chemistry[f]	√	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[g]	√		√			√ if on TDF[h]	√		√
Pregnancy test			√ if starting EFV						√

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

[a] ARV modification may be done for treatment failure, adverse effects, or simplification.

[b] 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.

[c] 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.

[d] For ART-naive 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.

[e] 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.

[f] 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.

[g] 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]

[h] 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

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CD4 T-Cell Count (Last updated January 10, 2011; last reviewed 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-Naive 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.

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Plasma HIV RNA Testing (Last updated January 10, 2011; last reviewed 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 (Last updated January 10, 2011; last reviewed 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)-naive patients **(AIII)**. • Standard genotypic drug-resistance testing in ARV-naive 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[1] (see also http://www.iasusa.org/resistance_mutations). 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 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-naive 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 INSTI **(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 detecting resistance to CCR5 antagonists 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
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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. 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-naive 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). 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-naive 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.
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.

Table 4. Recommendations for Using Drug-Resistance Assays
Page 2 of 2

Clinical Setting/Recommendation	Rationale
Drug-resistance assay recommended	
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 (Last updated December 1, 2007; last reviewed January 10, 2011)

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 (Last updated January 10, 2011; last reviewed 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 (Last updated March 27, 2012; last reviewed March 27, 2012)

Eradication of HIV infection cannot be achieved with available antiretroviral (ARV) regimens even when new, potent drugs are added to a regimen that is already suppressing plasma viral load below the limits of detection of 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.

ART has reduced HIV-related morbidity and mortality[8-11] and has reduced perinatal[12] and behavior-associated transmission of HIV.[13-17] 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.[18-19]

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 design of the specific regimen. (See What to Start: Initial Combination Regimens for the Antiretroviral-Naive 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.

Viral load reduction to below limits of assay detection in an ART-naive 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,[20]
- low baseline viremia,[21]
- higher baseline CD4 count (>200 cells/mm^3),[22] and
- rapid reduction of viremia in response to treatment.[21,23]

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.[24]

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. Regimens should be tailored for the individual 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-naive patients,[25-29] and some studies suggest that the presence of transmitted drug-resistant viruses may lead to suboptimal virologic responses.[30] 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 patient access to medication and inadequate treatment education and support. Conditions that promote adherence should be maximized before and after initiation of ART. (See Adherence to Antiretroviral Therapy.)

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Initiating Antiretroviral Therapy in Treatment-Naive Patients

(Last updated March 29, 2012; last reviewed March 27, 2012)

Panel's Recommendations

• Antiretroviral therapy (ART) is recommended for all HIV-infected individuals. The strength of this recommendation varies on the basis of pretreatment CD4 cell count:
  • CD4 count <350 cells/mm^3 **(AI)**
  • CD4 count 350 to 500 cells/mm^3 **(AII)**
  • CD4 count >500 cells/mm^3 **(BIII)**

• Regardless of CD4 count, initiation of ART is strongly recommended for individuals with the following conditions:
  • Pregnancy **(AI)** (see perinatal guidelines for more detailed discussion)
  • History of an AIDS-defining illness **(AI)**
  • HIV-associated nephropathy (HIVAN) **(AII)**
  • HIV/hepatitis B virus (HBV) coinfection **(AII)**

• Effective ART also has been shown to prevent transmission of HIV from an infected individual to a sexual partner; therefore, ART should be offered to patients who are at risk of transmitting HIV to sexual partners (**AI** [heterosexuals] or **AIII** [other transmission risk groups]; see text for discussion).
• Patients starting ART should be willing and able to commit to 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 on the basis of 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*

Introduction

The primary goal of antiretroviral therapy (ART) is to reduce HIV-associated morbidity and mortality. This goal is best accomplished by using effective ART to maximally inhibit HIV replication, as defined by achieving and maintaining plasma HIV RNA (viral load) below levels detectable by commercially available assays. Durable viral suppression improves immune function and quality of life, lowers the risk of both AIDS-defining and non-AIDS-defining complications, and prolongs life. Based on emerging evidence, additional benefits of ART include a reduction in HIV-associated inflammation and possibly its associated complications.

The results of a randomized controlled trial and several observational cohort studies demonstrated that ART can reduce transmission of HIV. Therefore, a secondary goal of ART is to reduce an HIV-infected individual's risk of transmitting the virus to others. Although the Panel concurs that this public health benefit of ART is significant, Panel recommendations on when to initiate ART are based primarily on the benefit of treatment to the HIV-infected individual.

The strength of Panel recommendations depends on disease stage. Randomized controlled trials provide definitive evidence supporting the benefit of ART in patients with CD4 counts <350 cells/mm^3. Results from multiple observational cohort studies demonstrate benefits of ART in reducing AIDS- and non-AIDS-associated morbidity and mortality in patients with CD4 counts ranging from 350 to 500 cells/mm^3. The Panel therefore recommends ART for patients with CD4 counts ≤500 cells/mm^3 (**AI** for CD4 count <350

cells/mm^3 and **AII** for CD4 count 350 to 500 cells/mm^3).

The recommendation to initiate therapy at CD4 count >500 cells/mm^3 **(BIII)** is based on growing awareness that untreated HIV infection or uncontrolled viremia may be associated with development of many non-AIDS-defining diseases, including cardiovascular disease (CVD), kidney disease, liver disease, neurologic complications, and malignancy; availability of ART regimens that are more effective, more convenient, and better tolerated than earlier ART combinations no longer widely used; and evidence from one observational cohort study that showed survival benefit in patients who started ART when their CD4 counts were >500 cells/mm^3.

Tempering the enthusiasm to treat all patients regardless of CD4 count is the absence of randomized data that definitively demonstrate a clear benefit of ART in patients with CD4 count >500 cells/mm^3 and mixed results on the benefits of early ART from observational cohort studies. In addition, potential risks of short- or long-term drug-related complications and nonadherence to long-term therapy in asymptomatic patients may offset possible benefits of earlier initiation of therapy. When resources are not available to initiate ART in all patients, treatment should be prioritized for patients with the lowest CD4 counts and those with the following clinical conditions: pregnancy, history of an AIDS-defining illness, HIV-associated nephropathy (HIVAN), or HIV/hepatitis B virus (HBV) coinfection.

The decision to initiate ART should always include consideration of other conditions and considerations listed in the Panel's boxed recommendations, the willingness and readiness of the patient to initiate therapy, and the availability of resources. The known benefits and limitations of ART are discussed below.

Benefits of Antiretroviral Therapy

Reduction in Mortality and/or AIDS-Related Morbidity According to Pretreatment CD4 Cell Count

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 than HIV-infected patients with higher CD4 counts. 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 comparing earlier ART (initiated at CD4 count >200 cells/mm^3) with later treatment (initiated at CD4 count <200 cells/mm^3) also have provided strong support for these findings.[4-9]

Few large, randomized controlled trials address when to start therapy in patients with CD4 counts >200 cells/mm^3. CIPRA HT-001, a randomized clinical trial conducted in Haiti, enrolled 816 participants without AIDS. Participants were randomized to start ART at CD4 counts of 200 to 350 cells/mm^3 or to defer treatment until their CD4 counts dropped to <200 cells/mm^3 or they developed an AIDS-defining condition. An interim analysis of the study showed that, compared with participants who began ART with CD4 counts of 200 to 350 cells/mm^3, patients who deferred therapy had a higher mortality rate (23 vs. 6 deaths, hazard ratio [HR] = 4.0, 95% confidence interval [CI]: 1.6–9.8) and greater incident tuberculosis (TB) (HR = 2.0, 95% CI: 1.2–3.6).[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 CD4 counts between 350 and 500 cells/mm^3

Data supporting initiation of ART in patients with CD4 counts ranging from 350 to 500 cells/mm^3 are derived from large observational studies and secondary analysis of randomized controlled trials. Analysis of the findings from the observational studies involved use of advanced statistical methods that minimize the bias and confounding that arise when observational data are used to address the question of when to start

ART. However, unmeasured confounders for which adjustment was not possible may have influenced the analysis.

The ART Cohort Collaboration (ART-CC) included 45,691 patients from 18 cohort studies conducted primarily in North America and Europe. Data from ART-CC showed that the rate of progression to AIDS and/or death was higher when therapy was deferred until CD4 count fell to the 251 to 350 cells/mm^3 range than when ART was initiated at the 351 to 450 cells/mm^3 range (risk ratio: 1.28, 95% CI: 1.04–1.57).[6] When analysis of the data was restricted to mortality alone, the difference between the 2 strategies was weaker and not statistically significant (risk ratio: 1.13, 95% CI: 0.80–1.60).

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 their CD4 counts were <350 cells/mm^3 had greater risk of death than the 2,084 patients who initiated therapy with CD4 counts between 351 and 500 cells/mm^3 (risk ratio: 1.69, 95% CI: 1.26–2.26) after adjustment for other factors that differed between these 2 groups.[11]

Another collaboration of cohort studies from Europe and the United States (the HIV-CAUSAL Collaboration) included 8,392 ART-naive patients with initial CD4 counts >500 cells/mm^3 who experienced declines in CD4 count to <500 cells/mm^3.[9] The study estimated that delaying initiation of ART until a patient had a CD4 count <350 cells/mm^3 was associated with a greater risk of AIDS-defining illness or death than initating ART with a CD4 count between 350 and 500 cells/mm^3 (HR: 1.38, 95% CI: 1.23–1.56). There was, however, no evidence of a difference in mortality (HR: 1.01, 95% CI: 0.84–1.22).

A collaboration of cohort studies from Europe, Australia, and Canada (the CASCADE Collaboration) included 5,527 ART-naive patients with CD4 counts in the 350 to 499 cells/mm^3 range. Compared with patients who deferred therapy until their CD4 counts fell to <350 cells/mm^3, patients who started ART immediately had a marginally lower risk of AIDS-defining illness or death (HR: 0.75, 95% CI: 0.49–1.14) and a lower risk of death (HR: 0.51, 95% CI: 0.33–0.80).[12]

Randomized data showing clinical evidence favoring ART in patients with higher CD4 cell counts comes from a small subgroup analysis of the SMART trial, undertaken primarily in North and South America, Europe, and Australia, which randomized participants with CD4 counts >350 cells/mm^3 to continuous ART or to treatment interruption until CD4 count dropped to <250 cells/mm^3. In the subgroup of 249 participants who were ART naive at enrollment (median CD4 count: 437 cells/mm^3), participants who deferred therapy until CD4 count dropped to <250 cells/mm^3 had a greater risk of serious AIDS- and non-AIDS-related events than those who initiated therapy immediately (7 vs. 2 events, HR: 4.6, 95% CI: 1.0–22.2).[13]

HPTN 052 was a large multinational, multicontinental (Africa, Asia, South America, and North America) randomized trial that examined whether treatment of HIV-infected individuals reduces transmission to their uninfected sexual partners.[14] An additional objective of the study was to determine whether ART reduces clinical events in the HIV-infected participants. This trial enrolled 1,763 HIV-infected participants with CD4 counts between 350 and 550 cells/mm^3 and their HIV-uninfected partners. The infected participants were randomized to initiate ART immediately or to delay initiation until they had 2 consecutive CD4 counts less than 250 cells/mm^3. At a median follow-up of 1.7 years, there were 40 events/deaths in the immediate therapy arm versus 65 events/deaths in the delayed arm (HR: 0.59, 95% CI: 0.40–0.88). The observed difference was driven mainly by the incidence of extrapulmonary TB (3 events in the immediate therapy arm vs. 17 events in the delayed therapy arm). The difference in mortality rates observed between the immediate and deferred therapy arms (10 vs. 13 deaths, respectively; HR: 0.77, 95% CI: 0.34–1.76) was not significant.

Collectively, these studies suggest that initiating ART in patients with CD4 counts between 350 and 500 cells/mm^3 reduces HIV-related disease progression; whether there is a corresponding reduction in mortality is

unclear. This benefit supports the Panel's recommendation that ART should be initiated in patients with CD4 counts of 350 to 500 cells/mm^3 **(AII)**. Recent evidence demonstrating the public health benefit of earlier intervention further supports the strength of this recommendation (see Prevention of Sexual Transmission).

Patients with CD4 counts >500 cells/mm^3

The NA-ACCORD study also observed patients who started ART at CD4 counts >500 cells/mm^3 or after CD4 counts dropped below this threshold. The adjusted mortality rates were significantly higher in the 6,935 patients who deferred therapy until their CD4 counts fell to <500 cells/mm^3 than in the 2,200 patients who started therapy at CD4 count >500 cells/mm^3 (risk ratio: 1.94, 95% CI: 1.37–2.79).[11] Although large and generally representative of the HIV-infected patients in 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, results from 2 cohort studies did not identify a benefit of earlier initiation of therapy in reducing AIDS progression or death. In an analysis of the ART-CC cohort,[6] the rate of progression to AIDS/death associated with deferral of therapy until CD4 count in the the 351 to 450 cells/mm^3 range was similar to the rate with initiation of therapy with CD4 count in the 451 to 550 cells/mm^3 range (HR: 0.99, 95% CI: 0.76–1.29). There was no significant difference in rate of death identified (HR: 0.93, 95% CI: 0.60–1.44). 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%–2.1%). In the CASCADE Collaboration,[12] among the 5,162 patients with CD4 counts in the 500 to 799 cells/mm^3 range, compared with patients who deferred therapy, those who started ART immediately did not experience a significant reduction in the composite outcome of progression to AIDS/death (HR: 1.10, 95% CI: 0.67–1.79) or death (HR: 1.02, 95% CI: 0.49–2.12).

With a better understanding of the pathogenesis of HIV infection, the growing awareness that untreated HIV infection increases the risk of many non-AIDS-defining diseases (as discussed below), and the benefit of ART in reducing transmission of HIV, the Panel also recommends initiation of ART in patients with CD4 counts >500 cells/mm^3 **(BIII)**. However, in making this recommendation the Panel notes that the amount of data supporting earlier initiation of therapy decreases as the CD4 count increases to >500 cells/mm^3 and that concerns remain over the unknown overall benefit, long-term risks, and cumulative additional costs associated with earlier treatment.

When discussing starting ART at high CD4 cell counts (>500 cells/mm^3), clinicians should inform patients that data on the clinical benefit of starting treatment at such levels are not conclusive, especially for patients with very high CD4 counts. The same is true for individuals with low viral load set points at presentation and for "elite controllers". Further ongoing research (both 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 is needed. Findings from such research will provide the Panel with guidance to make future recommendations.

Effects of Viral Replication on HIV-Related Morbidity

Since the mid-1990s, measures of viral replication have been known to predict HIV disease progression. Among untreated HIV-infected individuals, time to clinical progression and mortality is fastest in those with greater viral loads.[15] This finding is confirmed across the wide spectrum of HIV-infected patient populations such as injection drug users (IDUs),[16] women,[17] and individuals with hemophilia.[18] Several studies have shown the prognostic value of pretherapy viral load for predicting post-therapy response.[19-20] Once therapy has been initiated, failure to achieve viral suppression[21-23] and viral load at the time of treatment failure[24] are predictive of clinical disease progression.

More recent studies have examined the impact of ongoing viral replication for both longer durations and at

higher CD4 cell counts. Using viremia copy-years, a novel metric for summarizing viral load over time, the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort found that total cumulative exposure to replicating virus over time is independently associated with mortality. Using viremia copy-years, the HR for mortality was 1.81 per $\log_{10}$ copy-year/mL (95% CI: 1.51–2.18), which was the only viral load-related variable that retained statistical significance in the multivariable model (HR 1.44 per $\log_{10}$ copy-year/mL; 95% CI: 1.07–1.94). These findings support the concept that unchecked viral replication, which occurs in the absence of effective ART, is a factor in disease progression and death, but the precise mechanism remains ill defined.[25]

The EuroSIDA collaboration evaluated HIV-infected individuals with CD4 counts >350 cells/ mm^3 segregated by three viral load strata (<500 copies/mL, 500–9,999 copies/mL, and ≥10,000 copies/mL) to determine the impact of viral load on fatal and nonfatal AIDS-related and non-AIDS-related events. The lower viral load stratum included more subjects on ART (92%) than the middle (62%) and high (31%) viral load strata. After adjustment for age, region, and ART, the rates of non-AIDS events were 61% ($P = 0.001$) and 66% ($P = 0.004$) higher in participants with viral loads 500 to 9,999 copies/mL and ≥10,000 copies/mL, respectively, than in individuals with viral loads <500 copies/mL. These data further confirm that unchecked viral replication is associated with adverse clinical outcomes in individuals with CD4 counts >350 cells/mm^3.[26]

Collectively, these data show that the harm of ongoing viral replication affects both untreated patients and those who are on ART but continue to be viremic. The harm of ongoing viral replication in patients on ART is compounded by the risk of emergence of drug-resistant virus. Therefore, all patients on ART should be carefully monitored and counseled on the importance of adherence to therapy.

Effects of ART on HIV-Related Morbidity

HIV-associated immune deficiency, the direct effects of HIV on end organs, and the indirect effects of HIV-associated inflammation on these organs all contribute to HIV-related morbidity and mortality. In general, the available data demonstrate that:

- Untreated HIV infection may have detrimental effects at all stages of infection.
- Earlier treatment may prevent the damage associated with HIV replication during early stages of infection.
- ART is beneficial even when initiated later in infection; however, later therapy may not repair damage associated with viral replication during early stages of infection.
- Sustaining viral suppression and maintaining higher CD4 count, mostly as a result of effective combination ART, may delay, prevent, or reverse some non-AIDS-defining complications, such as HIV-associated kidney disease, liver disease, CVD, neurologic complications, and malignancies, as discussed below.

HIV-associated nephropathy

HIVAN is the most common cause of chronic kidney disease in HIV-infected individuals that may lead to end-stage kidney disease.[27] HIVAN is almost exclusively seen in black patients and can occur at any CD4 count. Ongoing viral replication appears to be directly involved in renal injury[28] and HIVAN is extremely uncommon in virologically suppressed patients.[29] ART in patients with HIVAN has been associated with both preserved renal function and prolonged survival.[30-32] Therefore, ART should be started in patients with HIVAN, regardless of CD4 count, at the earliest sign of renal dysfunction **(AII)**.

Coinfection with hepatitis B virus and/or hepatitis C virus

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.[33-34] The pathogenesis of accelerated liver disease in HIV-infected patients has not been fully elucidated but HIV-related immunodeficiency and a direct interaction between HIV and hepatic stellate and Kupffer cells have been

implicated.[35-38] In individuals coinfected with HBV and/or hepatitis C virus (HCV), ART may attenuate liver disease progression by preserving or restoring immune function and reducing HIV-related immune activation and inflammation.[39-41] Antiretroviral (ARV) drugs active against both HIV and HBV (such as tenofovir disoproxil fumarate [TDF], lamivudine [3TC], and emtricitabine [FTC]) also may prevent development of significant liver disease by directly suppressing HBV replication.[42-43] Although ARV drugs do not inhibit HCV replication directly, HCV treatment outcomes typically improve when HIV replication is controlled or CD4 counts are increased.[44] Chronic viral hepatitis increases the risk of ARV-induced liver injury; however, the majority of coinfected persons do not develop clinically significant liver injury.[45-47] 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 (HSR) and associated hepatotoxicity to this drug are more frequent in patients with higher pretreatment CD4 cell counts.[48] Collectively, these data suggest earlier treatment of HIV infection in persons coinfected with HBV, and likely HCV, may reduce the risk of liver disease progression. Thus, ART is recommended for patients coinfected with HBV **(AII)**. ART for patients coinfected with HBV should include drugs with activity against both HIV and HBV **(AII)** (also see Hepatitis B Virus/HIV Coinfection). ART also is recommended for most patients coinfected with HCV **(BII)**, including those with high CD4 counts and those with cirrhosis. Combined HIV/HCV treatment can be complicated by large pill burden, drug interactions, and overlapping toxicities. Although ART should be considered for HIV/HCV-coinfected patients regardless of CD4 cell count, for patients infected with HCV genotype 1, some clinicians may choose to defer ART in HIV treatment-naive patients with CD4 counts >500 cells/mm^3 until HCV treatment that includes the HCV NS3/4A protease inhibitors (PIs) is completed (also see HIV/Hepatitis C Virus Coinfection).

Cardiovascular disease

Among HIV-infected patients, CVD is a major cause of morbidity and mortality, accounting for a third of serious non-AIDS conditions and at least 10% of deaths.[49-50] Studies link exposure to specific ARV drugs to a higher risk of CVD.[51-52] In one study, compared with HIV-uninfected controls, HIV-infected men on ART had a more atherogenic lipid profile as assessed by lipoprotein particle size analysis.[53] Untreated HIV infection also may be associated with an increased risk of CVD. In several cross-sectional studies, levels of markers of inflammation and endothelial dysfunction were higher in HIV-infected patients than in HIV-uninfected controls.[54-56] In two randomized trials, markers of inflammation and coagulation increased following treatment interruption.[57-58] One study suggests that ART may improve endothelial function.[59]

In the SMART study, the risk of cardiovascular events was greater in participants randomized to CD4-guided treatment interruption than in participants who received continuous ART.[60] In other studies, ART resulted in marked improvement in parameters associated with CVD, including markers of inflammation (such as interleukin 6 [IL-6] and high-sensitivity C-reactive protein [hsCRP]) and endothelial dysfunction.[55-59] A modest association between lower CD4 count while on therapy and short-term risk of CVD also exists.[56, 61-62] 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 adjusted 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 CVD and CD4 cell depletion suggest that early control of HIV replication with ART can be used as a strategy to reduce risk of CVD. Therefore, ART should be considered for HIV-infected individuals with a significant risk of CVD, as assessed by medical history and established estimated risk calculations **(BII)**. Consideration of risk of CVD in the selection of specific ART is discussed in What to Start.

Malignancies

Several population-based analyses suggest that the incidence of non-AIDS-associated malignancies is increased in chronic HIV infection. The incidence of non-AIDS-defining malignancies is higher in HIV-infected subjects than in matched HIV-uninfected controls.[63] Large cohort studies enrolling mainly 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 malignancies.[7, 61, 64-67] 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, regardless of CD4 count, a protective effect of ART for HIV-associated malignancies.[64] This potential effect of HIV-associated immunodeficiency is striking particularly with regard to cancers associated with chronic viral infections such as HBV, HCV, human papilloma virus (HPV), Epstein-Barr virus (EBV), and human herpes virus-8 (HHV-8).[68-69] Cumulative HIV viremia, independent of other factors, may also be associated with the risk of non-Hodgkin lymphoma and other AIDS-defining malignancies.[67, 70] Since the early 1990s, incidence rates for many cancers, including Kaposi sarcoma, diffuse large B-cell lymphoma, and primary central nervous system (CNS) lymphoma, have declined markedly in HIV-infected individuals in the United States. However, for other cancers, such as Burkitt lymphoma, Hodgkin lymphoma, cervical cancer, and anal cancer, similar reductions in incidence have not been observed.[71-72] Declines in overall mortality and aging of HIV-infected cohorts increase overall cancer incidence, which may confound a clear assessment of the impact of ART on preventing the development of malignancies.[73-74] Taken together this evidence suggests that initiating ART to suppress HIV replication and maintain CD4 counts at levels >350 to 500 cells/mm^3 may reduce the overall incidence of both AIDS-defining and non-AIDS-defining malignancies **(CIII)**, although the effect on incidence is most likely to be heterogeneous across various cancer types.

Neurological diseases

Although HIV RNA can be detected in the cerebrospinal fluid (CSF) of most untreated patients,[75-76] these patients usually do not present with overt symptoms of HIV-associated neurological disease.[77] In some patients CNS infection progresses to HIV encephalitis and can present as HIV-associated dementia (HAD).[78-80] This progression is usually in the context of more advanced untreated systemic HIV infection when severe CNS opportunistic infections (OIs) also cause high morbidity and mortality.[81]

ART has had a profound impact on the nervous system complications of HIV infection. Effective viral suppression resulting from ART has dramatically reduced the incidence of HAD and severe CNS OIs.[82-84] Suppressive ART usually reduces CSF HIV RNA to undetectable levels.[85-86] Exceptional cases of symptomatic and asymptomatic CNS viral escape, in which HIV RNA is detectable in CSF despite viral suppression in plasma, have been documented.[87-88] This suggests that in some settings monitoring CSF HIV RNA may be useful.

Recent attention has turned to milder forms of CNS dysfunction, defined by impairment on formal neuropsychological testing.[80, 89] It is unclear whether this impairment is a consequence of injury sustained before treatment initiation or whether neurologic damage can continue or develop despite systemically effective ART.[90] The association of cognitive impairment with low nadir CD4 counts supports pretreatment injury and bolsters the argument that earlier initiation of ART may prevent subsequent brain dysfunction.[91-92]

The peripheral nervous system (PNS) also is a target in HIV infection, and several types of neuropathies have been identified.[93] Most common is HIV-associated polyneuropathy, a chronic, predominantly sensory and sometimes painful neuropathy. The impact of early treatment on this and other forms of neuropathy is not as clearly defined as on HAD.[94-95]

Age and treatment-related immune reconstitution (also see HIV and the Older Patient)

The CD4 cell response to ART is an important predictor of short- 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.[96-99]

T-cell activation and inflammation

Early untreated HIV infection is associated with sustained high-level inflammation and T-cell activation.[100-102] 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 peripheral CD4 T-cell count.[103-104] ART results in a rapid, but often incomplete, decrease in most markers of HIV-associated immune activation.[105-109] Persistent T-cell activation and/or T-cell dysfunction is particularly evident in patients who delay therapy until later stage disease (CD4 count <350 cells/mm^3).[106, 109-110] The degree of persistent inflammation during treatment, as represented by the levels of IL-6, may be independently associated with risk of death.[58] 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.[58, 111-112] 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,[106, 109-110] earlier treatment may result in less residual immunological perturbations on therapy and, hence, less risk for AIDS- and non-AIDS-related complications **(CIII)**.

Antiretroviral Therapy for Prevention of HIV Transmission

Prevention of perinatal 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 perinatal transmission of HIV. Effective suppression of HIV replication, as reflected in plasma HIV RNA, is a key determinant in reducing perinatal transmission. In the setting of ART initiation prior to 28 weeks' gestation and an HIV RNA level <50 copies/mL near delivery, use of combination ART during pregnancy has reduced the rate of perinatal transmission of HIV from approximately 20% to 30% to <0.5%.[113] Thus, use of combination ART drug regimens is recommended for all HIV-infected pregnant women **(AI)**. Following delivery, in the absence of breastfeeding, considerations regarding continuation of the ARV regimen for maternal therapeutic indications are the same as those regarding ART for other non-pregnant individuals. For detailed recommendations, see the perinatal guidelines.[114]

Prevention of sexual transmission

Recent study results provide strong support for the premise that treatment of the HIV-infected individual can significantly reduce sexual transmission of HIV. Lower plasma HIV RNA levels are associated with decreases in the concentration of the virus in genital secretions.[115-116] Studies of HIV-serodiscordant heterosexual couples have demonstrated a relationship between level of plasma viremia and risk of transmission of HIV: when plasma HIV RNA levels are lower, transmission events are less common.[117-121]

HPTN 052 was a multicontinental trial that enrolled 1,763 HIV-serodiscordant couples, in which the HIV-infected partner was ART naive and had a CD4 count of 350 to 550 cells/mm^3 at enrollment. The study compared immediate ART with delayed therapy (not started until CD4 count <250 cells/mm^3) for the HIV-infected partner.[14] At study entry, 98% of the participants were in heterosexual monogamous relationships. All study participants were counseled on behavioral modification and condom use. Twenty-eight linked HIV transmission events were identified during the study period but only 1 event occurred in the early therapy arm. This 96% reduction in transmission associated with early ART was statistically significant (HR 0.04, 95% CI: 0.01–0.27, P <0.001). These results show that early ART is more effective at preventing transmission of HIV than all other behavioral and biomedical prevention interventions studied to date, including condom use, male circumcision, vaginal microbicides, HIV vaccination, and pre-exposure prophylaxis. This study, as well as other observational studies, and modeling analyses showing a decreased rate of HIV transmission among serodiscordant heterosexual couples following the introduction of ART, demonstrate that suppression of viremia in ART-adherent patients with no concomitant sexually transmitted diseases (STDs) substantially reduces the risk of transmission of HIV.[120-125] HPTN 052 was conducted in heterosexual couples and not in populations at risk of transmission via homosexual exposure or needle sharing. However, the prevention benefits of effective ART probably will apply to these populations as well. Therefore, the Panel recommends that ART be offered to patients who are at risk of transmitting HIV to sexual partners. (The strength of this recommendation varies according to mode of sexual transmission: **AI** for heterosexual transmission and **AIII** for male-to-male and other modes of sexual transmission.) Clinicians

should discuss with patients the potential individual and public health benefits of therapy and the need for adherence to the prescribed regimen and counsel patients that ART is not a substitute for condom use and behavioral modification and that ART does not protect against other STDs (also see Preventing Secondary Transmission of HIV).

Potential Limitations of Earlier Initiation of Therapy

Although there are benefits associated with earlier initiation of ART, there also are some limitations to using this approach in all patients. Concerns about long-term toxicity and development of resistance to ARV drugs have served as a rationale for deferral of HIV therapy. However, evidence thus far indicates that resistance occurs more frequently in individuals who initiate therapy later in the course of infection than in those who initiate ART earlier. Earlier initiation of ART at higher CD4 counts (e.g., >500 cells/mm^3) results in greater cumulative time on therapy. Nevertheless, assuming treatment will continue for several decades regardless of when therapy is initiated, the incremental increase in drug exposure associated with starting therapy at higher CD4 counts will represent a small percentage of the total time on ART for most patients.

Newer ARV drugs are generally better tolerated, more convenient, and more effective than drugs used in older regimens but there are fewer longer term safety data for the newer agents. Analyses supporting initiation of ART at CD4 counts >350 cells/mm^3 (e.g., NA-ACCORD and ART-CC) were based on observational cohort data where patients were largely treated with regimens less commonly used in current clinical practice. In addition, these studies reported on clinical endpoints of death and/or AIDS disease progression but lacked information on drug toxicities, emergent drug 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 CVD associated with cumulative exposure to some drugs in the nucleoside reverse transcriptase inhibitor (NRTI) and PI drug classes.[52, 126] In the SMART study, compared with interruption or deferral of therapy, continuous exposure to ART was associated with significantly greater loss of bone density.[60] 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.

ART frequently improves quality of life for symptomatic patients. However, some side effects of ART may impair the quality of life for some patients, especially those who are asymptomatic at initiation of therapy. For example, efavirenz (EFV) can cause neurocognitive or psychiatric side effects and all the PIs have been associated with gastrointestinal (GI) side effects. Furthermore, some patients may find that the inconvenience of taking medication every day outweighs the overall benefit of early ART and may choose to delay therapy.

Nonadherence to Antiretroviral Therapy

At any CD4 count, adherence to therapy is essential to achieve viral suppression and prevent emergence of drug-resistance mutations. Several behavioral and social factors associated with poor adherence, such as untreated major psychiatric disorders, active substance abuse, unfavorable 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 to Antiretroviral Therapy.

Cost

In resource-rich countries, the cost of ART exceeds $10,000 per year (see Appendix C). Several modeling studies support the cost effectiveness of HIV therapy initiated soon after diagnosis.[127-129] One study reported that the annual cost of care is 2.5 times higher for patients with CD4 counts <50 cells/mm^3 than for patients

with CD4 counts >350 cells/mm^3.[130] A large proportion of the health care expenditure in patients with advanced infection is from non-ARV drugs and hospitalization. However, no comparisons of costs for patients starting ART with CD4 count 350 to 500 cells/mm^3 and those for patients starting ART at >500 cells/mm^3 have been reported.

Historically, concerns about long-term toxicity, reduced quality of life, and the potential for emerging drug resistance served as key reasons to defer HIV therapy in asymptomatic patients for as long as possible. Inherent in this reasoning was the assumption that in asymptomatic patients the harm associated with viral replication was less than the harm associated with the toxicities of ART. There is now more evidence that untreated HIV infection has negative consequences on health at all stages of disease. Also, the currently preferred ART regimens are better tolerated than previous regimens, leading to greater effectiveness, improved adherence,[131] and lower frequency of emerging drug resistance. Therefore, the current guidelines emphasize avoiding adverse consequences of untreated HIV infection while managing potential drug toxicity associated with ART.

Conditions Favoring More Rapid Initiation of Therapy

Several conditions increase the urgency for therapy, including:

- Pregnancy **(AI)** (Clinicians should refer to the perinatal guidelines for more detailed recommendations on the management of HIV-infected pregnant women.[114])
- AIDS-defining conditions **(AI)**
- Acute OIs (see discussion below)
- Lower CD4 counts (e.g., <200 cells/mm^3) **(AI)**
- HIVAN **(AII)**
- HIV/HBV coinfection **(AII)**
- Rapidly declining CD4 counts (e.g., >100 cells/mm^3 decrease per year) **(AIII)**
- Higher viral loads (e.g., >100,000 copies/mL) **(BII)**

Acute opportunistic infections

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

In the setting of some OIs, such as cryptococcal meningitis or nontuberculous mycobacterial infections, for which immediate therapy may increase the risk of immune reconstitution inflammatory syndrome (IRIS), a short delay before initiating ART may be warranted **(CIII)**.[132-133] In the setting of other OIs, such as *Pneumocystis jiroveci* pneumonia (PCP), early initiation of ART is associated with increased survival;[3] therefore, therapy should not be delayed **(AI)**.

In patients who have active TB, initiating ART during treatment for TB confers a significant survival advantage;[134-138] therefore, ART should be initiated as recommended in 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[139] for more detailed discussion on when to initiate ART in the setting of a specific OI.

Conditions Where Deferral of Therapy May be Considered

Some patients and their clinicians may decide to defer therapy for a period of time on the basis of clinical or

personal circumstances. Deferring therapy for the reasons discussed below may be reasonable in patients with high CD4 counts (e.g., >500 cells/mm^3) but deferring therapy in 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 to allow a patient more time to prepare for lifelong treatment may be considered.

When there are significant barriers to adherence (also see Adherence to Antiretroviral Therapy)
In patients with higher CD4 counts who are at risk of poor adherence, it may be prudent to defer treatment while addressing the barriers to adherence. However, in patients with conditions that require urgent initiation of ART (see above), therapy should be started while simultaneously addressing the barriers to 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.[140-141] If other objective measures (e.g., pharmacy refill data, pill count) are available, these methods should be used to assess adherence at each follow-up visit.[142-144] Continuous assessment and counseling make it possible for the clinician to intervene early to address barriers to adherence occurring at any point during treatment (see Adherence to Antiretroviral Therapy).

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:

- Surgery that may result in an extended interruption of ART.
- Treatment with medications that have clinically significant drug interactions with ART and for which alternative medications are not available.

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

Some less common situations exist in which ART may not be indicated at any time while CD4 counts remain high. In particular, such situations include that of 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 to make 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 sarcoma) and in patients with liver disease due to chronic HBV or HCV.

Long-term nonprogressors and elite HIV controllers
A small subset of ARV-untreated HIV-infected individuals (~3%−5%) can maintain normal CD4 cell counts for many years (long-term nonprogressors), and an even smaller subset (~1%) can maintain suppressed viral loads for years (elite controllers).[145-146] Although therapy theoretically may be 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 ART 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.[147-150] Despite the 2006 Centers for Disease Control and Prevention (CDC) recommendations for routine, opt-out HIV screening in the health care setting regardless of perceptions about a patient's risk of

infection,[151] the median CD4 count of 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. Compared with other groups, nonwhites, IDUs, and older patients more often receive a delayed diagnosis of HIV infection and a substantial proportion of these individuals develop AIDS-defining illnesses within 1 year of diagnosis.[147-150] Therefore, for the current treatment guidelines to have maximum impact, routine HIV screening per current CDC recommendations is essential. It is also critical that all newly diagnosed patients be educated about HIV disease and linked to care for full evaluation, follow-up, and management. Once patients are in care, focused effort is required to retain them in the health care system if the full benefits of early diagnosis and treatment are to be achieved both for the infected individuals and their sexual partners.

Conclusion

The current recommendations are based on greater evidence supporting earlier initiation of ART than was advocated in previous guidelines. The strength of the recommendations varies according to the quality and availability of existing evidence supporting each recommendation. In addition to the benefit of earlier initiation of therapy for the health of the HIV-infected individual, the reduction in sexual transmission to HIV-uninfected individuals provides further reason for earlier initiation of ART. 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-Naive Patient (Last updated March 27, 2012; last reviewed March 27, 2012)

Panel's Recommendations

- The Panel recommends the following as preferred regimens for antiretroviral (ARV)-naive 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 on the basis of 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*

More than 20 approved antiretroviral (ARV) drugs in 6 mechanistic classes are available 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-naive patients are listed in Table 6 to guide prescribers in choosing the regimen best suited for an individual patient. Table 7 provides a list of agents or components not recommended for initial treatment.

Considerations When Selecting A First Antiretroviral Regimen for Antiretroviral Therapy-Naive Patients

Data Used for Making Recommendations

The Panel's recommendations are primarily based on clinical trial data published in peer-reviewed journals and data prepared by manufacturers for Food and Drug Administration (FDA) review. In selected cases, the Panel considers data presented in abstract format at major scientific meetings. The first criterion for selection of evidence on which to base recommendations 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 noted in Tables 5a and 5b. "Preferred regimens" are those regimens 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 with preferred regimens. In certain situations and based on individual patient characteristics and needs, a regimen listed as an alternative may actually be the preferred regimen for a specific patient. Compared with preferred or alternative regimens, 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, pill burden, drug interaction potential, or need for additional testing).

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

Factors to Consider When Selecting an Initial Regimen

Regimen selection should be individualized on the basis of a number of factors, including the following:

- comorbid conditions (e.g., cardiovascular disease [CVD], chemical dependency, liver disease, psychiatric disease, renal diseases, or tuberculosis [TB]);
- potential adverse drug effects;
- potential drug interactions with other medications;
- pregnancy or pregnancy potential;
- result 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

Appendix B, Tables 1–6 provide a listing of characteristics, such as formulations, dosing recommendations, pharmacokinetics (PKs), and common adverse effects, of individual ARV agents. Additionally, Appendix B, Table 7 provides clinicians with ARV dosing recommendations for patients who have renal or hepatic insufficiency.

An initial ARV regimen generally consists of two NRTIs in combination 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 HIV RNA decreases and CD4 cell increases in a large majority of patients.[1-7]

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

Table 5a. Preferred and Alternative Antiretroviral Regimens for Antiretroviral Therapy-Naive Patients

A combination ART regimen generally consists of two NRTIs + one active drug from one of the following classes: NNRTI, PI (generally boosted with RTV), INSTI, or a CCR5 antagonist. Selection of a regimen should be individualized on the basis of virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance testing results, and the patient's 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) The preferred regimens for non-pregnant patients are arranged by chronological order of FDA approval of components other than nucleosides and, thus, by duration of clinical experience.	
NNRTI-Based Regimen • EFV/TDF/FTC[a] **(AI)** *PI-Based Regimens (in alphabetical order)* • ATV/r + TDF/FTC[a] **(AI)** • DRV/r (once daily) + TDF/FTC[a] **(AI)** *INSTI-Based Regimen* • RAL + TDF/FTC[a] **(AI)** *Preferred Regimen for Pregnant Women*[b] • LPV/r (twice daily) + ZDV/3TC[a] **(AI)**	*Comments* **EFV** should not be used during the first trimester of pregnancy or in women of childbearing potential who are trying to conceive or not using effective and consistent contraception. **TDF** should be used with caution in patients with renal insufficiency. **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) • EFV + ABC/3TC[a] **(BI)** • RPV/TDF/FTC[a] **(BI)** • RPV + ABC/3TC[a] **(BIII)** *PI-Based Regimens (in alphabetical order)* • ATV/r + ABC/3TC[a] **(BI)** • DRV/r + ABC/3TC[a] **(BIII)** • FPV/r (once or twice daily) + ABC/3TC[a] or TDF/FTC[a] **(BI)** • LPV/r (once or twice daily) + ABC/3TC[a] or TDF/FTC[a] **(BI)** *INSTI-Based Regimen* • RAL + ABC/3TC[a] **(BIII)**	*Comments* • Use **RPV** with caution in patients with pretreatment HIV RNA >100,000 copies/mL. • Use of PPIs with **RPV** is contraindicated. • **ABC** should not be used in patients who test positive for HLA-B*5701. • Use **ABC** with caution in patients with known high risk of CVD or with pretreatment HIV RNA >100,000 copies/mL. (See text.) **Once-daily LPV/r** is not recommended for use in pregnant women.

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

[b] 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.

The following combinations in the recommended list above are available as coformulated fixed-dose combinations: ABC/3TC, EFV/TDF/FTC, LPV/r, RPV/TDF/FTC, TDF/FTC, and ZDV/3TC.

Key to Abbreviations: 3TC = lamivudine, ABC = abacavir, ART = antiretroviral therapy, ARV = antiretroviral, ATV/r = atazanavir/ritonavir, CVD = cardiovascular disease, DRV/r = darunavir/ritonavir, EFV = efavirenz, FDA = Food and Drug Administration, FPV/r = fosamprenavir/ritonavir, FTC = emtricitabine, INSTI = integrase strand transfer inhibitor, LPV/r = lopinavir/ritonavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleos(t)ide reverse transcriptase inhibitor, PI = protease inhibitor, PPI = proton pump inhibitor, RAL = raltegravir, RPV = rilpivirine, RTV = ritonavir, TDF = tenofovir, ZDV = zidovudine

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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*

Table 5b. Acceptable Antiretroviral Regimens for Treatment-Naive Patients

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 • EFV + ZDV/3TC[a] **(CI)** • NVP + (TDF/FTC[a] or ZDV/3TC[a]) **(CI)** • NVP + ABC/3TC[a] **(CIII)** • RPV + ZDV/3TC[a] **(CIII)** *PI-Based Regimens* • ATV + (ABC or ZDV)/3TC[a] **(CI)** • ATV/r + ZDV/3TC[a] **(CI)** • DRV/r + ZDV/3TC[a] **(CIII)** • FPV/r + ZDV/3TC[a] **(CI)** • LPV/r + ZDV/3TC[a] **(CIII)** *INSTI-Based Regimen* • RAL + ZDV/3TC[a] **(CIII)** *CCR5 Antagonist-Based Regimens* • MVC + ZDV/3TC[a] **(CI)** • MVC + TDF/FTC[a] or ABC/3TC[a] **(CIII)**	*Comments* • **NVP** should not be used in patients with moderate to severe hepatic impairment (Child-Pugh B or C).[b] • **NVP** should not be used in women with pre-ART CD4 count >250 cells/mm^3 or in men with pre-ART CD4 count >400 cells/mm^3. Use **NVP** and **ABC** together with caution because both can cause HSRs within the first few weeks after initiation of therapy. **ZDV** can cause bone marrow suppression, lipoatrophy, and rarely lactic acidosis with hepatic steatosis. **LPV/r (twice daily) + ZDV/3TC** is the preferred regimen for use in pregnant women. **ATV/r** is generally preferred over **unboosted ATV**. **Unboosted ATV** may be used when RTV boosting is not possible. Perform tropism testing before initiation of therapy with **MVC**. **MVC** may be considered in patients who have only CCR5-tropic virus.
Regimens that may be acceptable but should be used with caution (Regimens that have demonstrated virologic efficacy in some studies but are associated with concerns about safety, resistance, or efficacy. See comments below.)	
PI-Based Regimens • SQV/r + TDF/FTC[a] **(CI)** • SQV/r + (ABC or ZDV)/3TC[a] **(CIII)**	*Comments* • **SQV/r** was associated with PR and QT prolongation in a healthy volunteer study. • Baseline ECG is recommended before initiation of **SQV/r**. • **SQV/r** is not recommended in patients with any of the following: 1. pretreatment QT interval >450 msec 2. refractory hypokalemia or hypomagnesemia 3. concomitant therapy with other drugs that prolong QT interval 4. complete AV block without implanted pacemaker 5. risk of complete AV block

[a] 3TC may substitute for FTC or vice versa.
[b] Refer to Appendix B, Table 7 for the criteria for Child-Pugh classification

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

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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*

Non-Nucleoside Reverse Transcriptase Inhibitor- versus Protease Inhibitor- versus Integrase Strand Transfer Inhibitor- versus CCR5 Antagonist-Based Regimens

Efavirenz (EFV) has been compared with a number of other drugs (other NNRTIs, PIs, RAL, MVC) in combination regimens containing two NRTIs.[3-9] To date, no regimen has proven superior to EFV-based regimens with respect to virologic responses.

Non-Nucleoside Reverse Transcriptase Inhibitor- versus Protease Inhibitor-Based Regimens

RTV-boosted PI-based regimens have shown good virologic and immunologic responses but are often associated with more gastrointestinal (GI) symptoms than EFV-based regimens, which are associated with more rash and central nervous system (CNS) 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 seldom develops after early virologic failure,[11] especially when RTV boosting is used. At least partial resistance to EFV, NVP, or rilpivirine (RPV), however, is conferred by a single mutation in the reverse transcriptase gene, and it may develop rapidly after virologic failure. 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 antiretroviral therapy (ART)-naive population, genotypic testing results should be used to guide the selection of the initial ARV regimen. (See Drug-Resistance Testing.) In terms of convenience, coformulation of EFV/tenofovir (TDF)/emtricitabine (FTC) or RPV/TDF/FTC allows for once-daily dosing with a single tablet. Most PI-based regimens include RTV, may be dosed once or twice daily, and have a higher pill burden than NNRTI regimens. Drug-drug interactions are important with both kinds of regimens, but more clinically significant interactions are seen with RTV-boosted PI regimens than with NNRTI-based regimens.

Other Treatment Options

Another option for initial therapy is the combination of TDF/FTC and RAL.[6] This combination showed virologic efficacy similar to that of TDF/FTC/EFV up to 156 weeks[13] and is generally well tolerated. No clinical trial data comparing INSTI-based with PI-based regimens exist. 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-naive 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.

Non-Nucleoside Reverse Transcriptase Inhibitor-Based Regimens (One Non-Nucleoside Reverse Transcriptase Inhibitor + Two Nucleoside Reverse Transcriptase Inhibitors)

Summary: Non-Nucleoside Reverse Transcriptase Inhibitor-Based Regimens

Five NNRTIs (delavirdine [DLV], EFV, etravirine [ETR], NVP, and RPV) are currently FDA approved.

NNRTI-based regimens have demonstrated virologic potency and durability. The major disadvantages of currently available NNRTIs involve the prevalence of NNRTI-resistant viral strains in ART-naive patients[12, 14-16] and the low genetic barrier of NNRTIs for development of resistance. Resistance testing should be performed to guide therapy selection for ART-naive patients (see Drug-Resistance Testing). All NNRTIs except for ETR require only a single mutation to confer resistance, and cross resistance affecting these 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] However, in RPV-treated patients, the presence of RPV-resistant mutations at virologic failure is common and may confer cross resistance to ETR.[18]

On the basis of clinical trial results and safety data, the Panel recommends that EFV, RPV, or NVP may be used as part of an initial regimen. In most instances, EFV is preferred on the basis of 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.

RPV may be used as an alternative NNRTI option in treatment-naive patients, whereas NVP may be used as an acceptable NNRTI option in women with pretreatment CD4 counts ≤250 cells/mm^3 or in men with pretreatment CD4 counts ≤400 cells/mm^3. (See discussions below.)

Among the NNRTIs, 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 at a dose of 200 mg twice daily is approved for use in treatment-experienced patients with virologic failure.[19] In a small, randomized, double-blind, placebo-controlled trial, ETR 400 mg once daily was compared with EFV 600 mg once daily (both in combination with two NRTIs) in treatment-naive subjects. Seventy-nine and 78 participants were randomized to the ETR and EFV arms, respectively. At 48 weeks, 76% of the ETR recipients and 74% of the EFV recipients achieved plasma HIV RNA <50 copies/mL. Neuropsychiatric side effects were more frequently reported in the EFV recipients than in the ETR recipients.[20] These results suggest that once-daily ETR may be a potential NNRTI option in treatment-naive patients. However, more data are required and, pending results from larger trials, the panel cannot recommend ETR as initial therapy at this time.

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

Efavirenz as Preferred Non-Nucleoside Reverse Transcriptase Inhibitor

Large randomized, controlled trials and cohort studies of ART-naive 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, 21] Studies that compared EFV-based regimens with other regimens demonstrated that 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.[22-23] EFV-based regimens also had virologic activity comparable to that of NVP-,[24-25] 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, but 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-naive patients. Virologic responses were similar for both drugs but compared with EFV, NVP was associated with greater toxicity and did not meet criteria for noninferiority.[24] Two randomized controlled trials compared EFV + two NRTIs with RPV + two NRTIs. Most patients received TDF/FTC as the NRTI pair. Pooled data evaluated at 48 weeks demonstrated comparable virologic efficacy for the two study groups, except in participants in each group who had baseline HIV RNA >100,000 copies/mL. Among participants who had baseline viremia at this level, a greater proportion of subjects randomized to RPV than to EFV experienced virologic failure.[18]

Limitations of EFV are its CNS adverse effects, which usually resolve over a few weeks, and its potential teratogenic effects. In animal reproductive studies, EFV at drug exposure levels similar to those achieved in humans caused major congenital anomalies in the CNS of nonhuman primates.[26] In humans, several cases of neural tube defects in newborns of mothers exposed to EFV during the first trimester of pregnancy have been reported.[27-28] 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-Nucleoside Reverse Transcriptase Inhibitor 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)**.

Rilpivirine as Alternative Non-Nucleoside Reverse Transcriptase Inhibitor

In two large, multinational, randomized, double-blind clinical trials, RPV (25 mg once daily) was compared with EFV (600 mg once daily), each in combination with two NRTIs. In a pooled analysis of the two studies, 83% of RPV-treated subjects and 80% of EFV-treated subjects had plasma HIV RNA <50 copies/mL at 48 weeks.[18, 29-30] Although overall RPV demonstrated noninferiority to EFV, among participants with higher pretreatment HIV RNA (>100,000 copies/mL), virologic failure occurred more frequently in those randomized to receive RPV. Subjects with virologic failure on RPV were also more likely to have genotypic resistance to other NNRTIs (EFV, ETR, and NVP) and to have resistance to their prescribed NRTIs.

Drug discontinuations because of adverse effects were more common with EFV than with RPV. The frequency of depressive disorders and discontinuations due to depressive disorders were similar between the two arms, whereas dizziness, abnormal dreams, rash, and hyperlipidemia were more frequent with EFV than with RPV.

At higher than the approved dose of 25 mg, RPV (75 mg once daily or 300 mg once daily) may prolong the QTc interval. As a result, RPV should be used cautiously when coadministered with a drug having a known risk of torsades de pointes. Although RPV has shown no teratogenicity in animal studies, data on PKs and safety of RPV in pregnant HIV-infected women are insufficient at this time. RPV should not be given to adolescents younger than 18 years of age because appropriate dosing information in this age group is lacking.

A fixed-dose combination tablet of RPV/TDF/FTC allows for one-tablet once-daily dosing. RPV must be administered with a meal. Because the oral bioavailability of RPV may be significantly reduced in the presence of acid-lowering agents, the ARV should be used with caution with antacids and H2 receptor antagonists. RPV use with proton pump inhibitors (PPIs) is contraindicated. Table 15b provides guidance on the timing of RPV administration when the agent is used together with antacids or H2 receptor antagonists.

Based on limited data on durability of treatment responses (48 weeks) and the lower virologic response to RPV compared with EFV in patients with high pretreatment viral loads, the panel recommends RPV/TDF/FTC as an alternative regimen for initial therapy **(BI)**. Caution should be exercised when using RPV in patients with plasma HIV RNA >100,000 copies/mL, given the higher RPV virologic failure rates and the greater probability of ETR resistance at the time of failure observed in this population during clinical trials.

Nevirapine as Acceptable Non-Nucleoside Reverse Transcriptase Inhibitor

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.[24] Two deaths were attributed to NVP use. One resulted from fulminant hepatitis and one from staphylococcal sepsis as a complication of Stevens-Johnson syndrome (SJS).

In the ARTEN trial, ART-naive participants were randomized to NVP 200 mg twice daily or NVP 400 mg once daily or RTV-boosted ATV (ATV/r), all in combination with TDF/FTC. The proportion of participants in each arm who achieved the primary endpoint of having at least two consecutive plasma HIV RNA levels <50 copies/mL before Week 48 was similar (66.8% for NVP vs. 65.3% for ATV/r). However, more participants in the NVP

arms than in the ATV/r arm discontinued study drugs before Week 48 because of adverse events (13.6% vs. 2.6%, respectively) or lack of efficacy (8.4% vs. 1.6%, respectively). NNRTI- and/or NRTI-resistance mutations were selected in 29 of 44 (65.9%) participants who experienced virologic failure while on NVP, whereas resistance mutations were not detected in any of the 28 participants who had virologic failure on ATV/r.[31]

Serious hepatic events have been observed when NVP was initiated in ART-naive 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.[31-33] 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 than in women with CD4 counts ≤250 cells/mm^3 (11.0% vs. 0.9%, respectively). 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%, respectively). Most of these patients had no identifiable underlying hepatic abnormalities. In some cases, hepatic injuries continued to progress despite discontinuation of NVP.[33-34] In contrast, other studies have not shown an association between baseline CD4 counts and severe NVP hepatotoxicity.[35-36] 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 safety and efficacy data discussed above, the Panel recommends that NVP be considered as an acceptable NNRTI **(C)** as initial therapy for women with pretreatment CD4 counts ≤250 cells/mm^3 or in men with pretreatment 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.[37]

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 400 mg per day (as an extended-release 400-mg tablet once daily or 200-mg immediate-release tablet twice daily). Some experts recommend monitoring serum transaminases at baseline, at 2 weeks, then 2 weeks after dose escalation, and then monthly for the first 18 weeks. Clinical and laboratory parameters should be assessed at each visit.

Protease Inhibitor-Based Regimens (Ritonavir-Boosted or Unboosted Protease Inhibitor + Two Nucleoside Reverse Transcriptase Inhibitors)

Summary: Protease Inhibitor-Based Regimens

PI-based regimens (particularly with RTV-boosting) have demonstrated virologic potency and durability in treatment-naive subjects. Unlike with NNRTI- and INSTI-based regimens, with PI-based regimens resistance mutations are seldom detected at virologic failure. In patients who experience virologic failure while on their first PI-based regimen, few or no PI mutations are detected at failure.[31, 38] Each PI has its own virologic potency, adverse effect profile, and pharmacokinetic (PK) properties. The characteristics, advantages, and disadvantages of each PI are listed in Table 6 and Appendix B, Table 3. When selecting a boosted PI-based regimen for an ART-naive patient, clinicians should consider factors such as dosing frequency, food requirements, pill burden, daily RTV dose, drug interaction potential, toxicity profile of the individual PI, and baseline lipid profile and pregnancy status of the patient. (See the perinatal guidelines for specific recommendations in pregnancy[39]).

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 PK boosting agent. Two large observational cohort

studies suggested that LPV/r, IDV, fosamprenavir (FPV), or ritonavir-boosted fosamprenavir (FPV/r) may be associated with increased rates of myocardial infarction (MI) or stroke.[40-41] Both studies had too few patients receiving ATV/r or ritonavir-boosted darunavir (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 seen with SQV/r 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.[42]

The potent inhibitory effect of RTV on the cytochrome P (CYP) 450 3A4 isoenzyme allows the addition of low-dose RTV to other PIs as a PK booster to increase drug exposure and prolong the plasma half-life of the active PI. Boosting with RTV 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[43-45] and also may contribute to the lower risk of resistance at virologic failure with boosted PIs than 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, support for the use of once-daily boosted PI regimens that use only 100 mg per day of RTV is growing. This is because these regimens tend to cause fewer GI side effects and less metabolic toxicity than regimens that use RTV at a dose of 200 mg per day.

The Panel uses the following criteria to distinguish between preferred and alternative PIs in ART-naive 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/r (once daily) and DRV/r (once daily) as preferred PIs.

Preferred Protease Inhibitor (in alphabetical order, by active protease inhibitor component)

Ritonavir-Boosted Atazanavir. 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.[46]

The CASTLE study compared once-daily ATV/r with twice-daily LPV/r, each in combination with TDF/FTC, in 883 ARV-naive participants. In this open-label, noninferiority study, analysis at 48 weeks[47] and at 96 weeks[48] showed similar virologic and CD4 responses of the two regimens. More hyperbilirubinemia and less GI toxicity were seen in the ATV/r arm than in the LPV/r arm. This study supports the designation of ATV/r + TDF/FTC as a preferred PI-based regimen **(AI)**.

The main adverse effect associated with ATV/r is indirect hyperbilirubinemia, with or without jaundice or scleral icterus, but without concomitant hepatic transaminase elevations. Nephrolithiasis also has been reported in patients who received RTV-boosted or unboosted ATV.[49] ATV/r requires acidic gastric pH for dissolution. Thus, concomitant use of drugs that raise gastric pH, such as antacids, H2 antagonists, and particularly PPIs, may impair absorption of ATV. Table 15a provides recommendations for use of ATV/r with these agents.

Ritonavir-Boosted Darunavir. The ARTEMIS study compared DRV/r (800/100 mg once daily) 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-naive participants. At 48 weeks, DRV/r was noninferior to LPV/r. Among those participants whose baseline HIV RNA levels were >100,000 copies/mL, the virologic response rates were lower in the LPV/r arm than in the DRV/r arm. Grades 2 to 4 adverse events, primarily diarrhea, were seen more frequently in LPV/r recipients than in DRV/r recipients.[50] At virologic failure, no major PI mutations were detected in participants randomized to either arm.[38] At 96 weeks, virologic response to DRV/r was

superior to response to LPV/r.[51] Based on these data, the Panel recommends DRV/r + TDF/FTC as a preferred PI-based regimen **(AI)**. No randomized controlled trial to evaluate the efficacy of DRV/r with other 2-NRTI combinations exists. A small retrospective study suggested that DRV/r plus ABC/3TC may be effective in treatment-naive patients for up to 48 weeks.[52] Based on this preliminary information, the Panel recommends this combination as an alternative PI-based regimen **(BIII)**.

Alternative Protease Inhibitor (in alphabetical order, by active protease inhibitor component)

Ritonavir-Boosted Fosamprenavir (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-naive patients. At Weeks 48 and 144, similar percentages of subjects achieved viral loads of <400 copies/mL.[53-54] The frequency and severity of adverse events did not differ between the regimens. Twice-daily FPV/r was noninferior to twice-daily LPV/r. Based on the preference for 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 (1400 mg with RTV 200 mg once daily) with NFV,[55] similar virologic efficacy was reported in both arms. A comparative trial of once-daily FPV/r (1400/100 mg) with once-daily ATV/r, both in combination with TDF/FTC, was conducted in 106 ARV-naive participants.[56] 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 alternative PI-based regimens.

Ritonavir-Boosted Lopinavir (coformulated). LPV/r is the only available coformulated boosted PI. It can be given once or twice daily. However, because compared with boosted PIs using RTV 100 mg/day, LPV/r must be boosted with 200 mg/day of RTV and is associated with higher rates of GI side effects and hyperlipidemia, LPV/r is recommended as an alternative rather than preferred PI for ART-naive patients. Early studies showed that LPV/r was superior to NFV in maintaining suppressed viral loads.[57] 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.[58] 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.[50, 59-60] In the largest trial that compared once-daily with twice-daily LPV/r, both in combination with TDF/FTC, 664 ART-naive 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.[61] 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.[40-41] 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 **(A)**.[39] Once-daily dosing should not be used in pregnant women, 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.[39]

Acceptable Protease Inhibitor-Based Component

Atazanavir. 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 that ATV 400 mg once daily and both comparator treatments had similar virologic efficacy in ARV-naive patients after 48 weeks of therapy.[5, 46, 62-63]

Unboosted ATV may be an acceptable 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 **(C)**. Concomitant use of TDF or EFV with ATV can lower the concentrations of ATV. Therefore, ATV should be boosted with RTV when coadministered with these two agents. ATV requires acidic gastric pH for dissolution. Thus, concomitant use of drugs that raise gastric pH, such as antacids, H2 antagonists, and PPIs, may significantly impair ATV absorption. PPIs should not be used in patients who are taking unboosted ATV. H2 antagonists and antacids should be used with caution and with careful dose separation. (See Tables 14 and 15a.)

Protease Inhibitor Component that May be Acceptable but Should be Used with Caution

Ritonavir-Boosted Saquinavir. The GEMINI study compared SQV/r (1000/100 mg twice daily) with LPV/r, both given twice daily, in combination with TDF/FTC given once daily, in 337 ART-naive participants who were monitored over 48 weeks. Similar levels of viral suppression and increases in CD4 counts were seen in both arms.[64] Triglyceride (TG) levels were higher in the LPV/r arm than in the SQV/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 at the recommended dose was associated with increases in both QT and PR intervals. The degree of QT prolongation with SQV/r was greater than that seen with some other boosted PIs used at their recommended doses. Rare cases of torsades de pointes and complete heart block have been reported in post-marketing surveillance. Based on these findings, an ECG before initiation of SQV/r is recommended. 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.[42] 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-naive patients **(C)**.

Integrase Strand Transfer Inhibitor-Based Regimens (Integrase Strand Transfer Inhibitor + Two Nucleoside Reverse Transcriptase Inhibitors)

Raltegravir. RAL is an INSTI that is approved for use in ART-naive patients on the basis of 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-naive subjects. This multinational double-blind, placebo-controlled study enrolled 563 subjects with plasma HIV-1 RNA levels >5,000 copies/mL. At Week 48, a similar percentage 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. The frequency of serious adverse events was similar in both groups.[6] At 156 weeks, virologic and immunologic responses remained similar in both groups with no new safety concerns identified.[13] On the basis of these data, the Panel recommends RAL + TDF/FTC (or 3TC) as a preferred regimen for ART-naive patients **(AI)**. In a small single-arm pilot study of 35 subjects who received a regimen of RAL + ABC/3TC, 91% of subjects had HIV RNA levels <50 copies/mL at Week 48.[65] On the basis of these preliminary data, RAL + ABC/3TC may be used as an alternative INSTI-based regimen **(BIII)**. RAL use has been associated

with creatine kinase elevations. Myositis and rhabdomyolysis have been reported. Rare cases of severe skin reactions and systemic hypersensitivity reactions (HSRs) in patients who received RAL have been reported during post-marketing surveillance of the agent.[66]

Comparisons of RAL-based regimens and boosted PI-based regimens in ART-naive subjects have not been reported. RAL must be administered twice daily, a potential disadvantage when comparing RAL-based regimens with some other regimens. RAL, like EFV, has a lower genetic barrier to resistance than RTV-boosted PIs, and in the STARTMRK comparative trial, resistance mutations were observed at approximately the same frequency in RAL- and EFV-treated participants.

CCR5 Antagonist-Based Regimens (CCR5-Antagonist + Two Nucleoside Reverse Transcriptase Inhibitors)

The MERIT study compared the CCR5 antagonist MVC with EFV, both in combination with ZDV/3TC, in a randomized, double-blind trial in ART-naive 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 level <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, compared with participants receiving EFV, more participants discontinued MVC 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 for both ARVs.[67] 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-naive patients. Because MVC requires twice-daily dosing, requires an expensive tropism assay prior to use, and experience with regimens other than ZDV/3TC is limited, the Panel recommends MVC + ZDV/3TC as an acceptable regimen for use in ART-naive patients **(CI)**. Although the MERIT trial used ZDV/3TC as its NRTI backbone, pending further data, many clinicians would favor the combination of MVC with TDF/FTC or ABC/3TC **(CIII)**.

Dual-Nucleoside Reverse Transcriptase Inhibitor Options as Part of Initial Combination Therapy

Summary: Dual-Nucleoside Reverse Transcriptase Inhibitor 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.[68]

All NRTIs except ddI can be taken with or without food. 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 RPV), 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-Nucleoside Reverse Transcriptase Inhibitor

Tenofovir/Emtricitabine (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-naive patients, demonstrated potent virologic suppression[21] and was superior to ZDV/3TC in virologic efficacy up to 144 weeks.[69] In the 934 study, more participants in the ZDV/3TC arm than in the TDF/FTC arm developed loss of limb fat (as assessed by dual-energy x-ray absorptiometry [DXA]) and anemia at 96 and 144 weeks.[69] Emergence of the M184V mutation was less frequent with TDF/FTC 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 in combination with several boosted PIs and RAL has been studied in randomized clinical trials; all such trials demonstrate good virologic benefit.[6, 47, 50, 56, 60]

TDF/FTC was compared with ABC/3TC in the ACTG 5202 study[70] and the HEAT trial.[71] 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 for more detailed discussion.)

Renal impairment, manifested by increases in serum creatinine, glycosuria, hypophosphatemia, and acute tubular necrosis, with TDF use has been reported.[72-73] Risk factors may include advanced HIV disease, greater treatment experience, and pre-existing renal impairment.[74] 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 available dosage adjustment guidelines for renal dysfunction are based on PK studies only and not on safety and efficacy data, the use of alternative NRTIs (especially ABC) may be preferred over dose-adjusted TDF in this setting.

Concomitant use of some PIs can increase TDF concentrations, and studies have suggested a greater risk of renal dysfunction when TDF is used in PI-based regimens.[72, 75-78] TDF has been used in combination with PIs without renal toxicity in several clinical trials that involved patients who had CrCl >50 to 60 mL/min. Furthermore, in two randomized studies comparing TDF/FTC with ABC/3TC, participants receiving TDF/FTC experienced a significantly greater decline in bone mineral density.[79-80]

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 HIV/Hepatitis B Coinfection.)

Alternative Dual Nucleoside Reverse Transcriptase Inhibitor

Abacavir/Lamivudine (coformulated) for Patients who Test Negative for HLA-B*5701.
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. CD4 T-cell increase at 48 weeks was greater in the ABC-treated participants than in the ZDV-treated participants.[81] 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 on the basis of a screening HIV RNA of <100,000 copies/mL or >100,000 copies/mL. HLA-B*5701 testing was not required prior to study entry, which may have influenced the results of the trial with respect to some of the safety and tolerability endpoints. A 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 than in the TDF/FTC arm.[70] This difference in virologic failure

between arms was observed regardless of whether the third active drug was EFV or ATV/r. There was no difference between ABC/3TC and TDF/FTC in time to virologic failure for participants who had plasma HIV RNA <100,000 copies/mL at screening. TDF/FTC has a more favorable safety and tolerability profile than ABC/3TC.[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).[71] The ASSERT study compared open label ABC/3TC with TDF/FTC in 385 HLA-B*5701-negative, ART-naive patients; all study subjects also received EFV. At 48 weeks, the proportion of participants with HIV RNA <50 copies was lower among ABC/3TC-treated subjects (59%) than among TDF/FTC subjects (71%) (difference 11.6%, 95% confidence interval [CI]: 2.2–21.1).[83]

ABC has the potential for serious HSRs. Clinically suspected HSRs have been observed in 5% to 8% of patients who start ABC. The risk of this reaction is highly associated with the presence of the HLA-B*5701 allele.[84-85] (See HLA-B*5701 Screening.) HLA-B*5701 testing should precede 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 HLA-B*5701 negative are less likely to experience an HSR, but they should be counseled about the symptoms of the reaction.

An association between ABC use and MI was first reported in the D:A:D study. This large, multinational observational study group found that recent (within 6 months) or current use of ABC, but not TDF, was associated with an increased risk of MI, particularly in participants with pre-existing cardiac risk factors.[40, 86] Since this D:A:D study, multiple studies have explored this association. Some studies have found an association;[87-90] others have found a weak association or no association.[41, 91-94] Multiple studies have also been conducted to evaluate potential mechanistic pathways, including endothelial dysfunction, increased platelet reactivity, leukocyte adhesion, inflammation, and hypercoagulability[95-102] that may underlie the association between ABC use and an increased risk of MI. However, to date, no consensus either on the association of ABC use with MI risk or a possible mechanism for the association has been reached.

The fixed-dose combination of ABC/3TC allows for once-daily dosing. Pending additional data, ABC/3TC should be used with caution in individuals who have plasma HIV RNA levels ≥100,000 copies/mL and in persons at higher risk of CVD. However, the combination of ABC/3TC remains a good alternative dual-NRTI option for some ART-naive patients **(BI)**.

Acceptable Dual Nucleoside Reverse Transcriptase Inhibitor

Zidovudine/Lamivudine (coformulated). The dual-NRTI combination of ZDV/3TC has extensive durability, safety, and tolerability experience.[3, 5, 8, 22, 103-105] 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 and 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 GI toxicity, fatigue, and possibly mitochondrial toxicity, including lactic acidosis/hepatic steatosis and lipoatrophy. Because ZDV/3TC has greater toxicity than TDF/FTC or ABC/3TC and requires twice-daily dosing, the Panel recommends ZDV/3TC as an acceptable, rather than a preferred or alternative, dual-NRTI option **(CI)**.

ZDV/3TC remains a preferred option in pregnant women. This dual NRTI has the most PK, 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.[39]

Nucleoside Reverse Transcriptase Inhibitors and Hepatitis B Virus. Three of the currently approved NRTIs—FTC, 3TC, and TDF—have activity against HBV. Most HIV/HBV-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. Importantly, patients who have HIV/HBV coinfection may be at risk of acute exacerbation of hepatitis after initiation or upon discontinuation of TDF, 3TC, or FTC.[106-108] Thus, these patients should be monitored closely for clinical or chemical hepatitis if these drugs are initiated or discontinued. (See HIV/Hepatitis B Coinfection and Initiating Antiretroviral Therapy.)

All-Nucleoside Reverse Transcriptase Inhibitor Regimens

Triple-NRTI regimens studied in several clinical trials have shown suboptimal virologic activity.[22-23, 109-112]

Abacavir/Lamivudine/Zidovudine (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[104-105] and NFV-based regimens[112] but was inferior virologically to an EFV-based regimen.[22] This combination is **generally not recommended (BI)** and should be used only when a preferred, an alternative, or an acceptable NNRTI-, PI-, or INSTI- based regimen is less desirable because of concerns about toxicities, drug interactions, or regimen complexity.

Zidovudine/Lamivudine + Tenofovir. The DART study demonstrated that the combination of ZDV/3TC + TDF has antiviral activity.[113] However, because comparative data with standard regimens are not available, this combination **cannot be recommended** in routine clinical practice **(BIII)**.

Zidovudine/Lamivudine + Abacavir + Tenofovir. A quadruple-NRTI regimen of ZDV/3TC + ABC + TDF first showed comparable virologic responses to an EFV-based regimen in a small pilot study.[114] 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.[115] Thus, this regimen **cannot be recommended (BI)**.

Table 6. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 1 of 4)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
NNRTIs (in alphabetical order)		**NNRTI Class Advantages:** • Long half-lives	**NNRTI Class Disadvantages:** • Greater risk of resistance at the time of treatment failure with NNRTIs than with PIs • Potential for cross resistance • Skin rash • Potential for CYP450 drug interactions (See Tables 14, 15b, and 16b.) • Transmitted resistance more common with NNRTIs than with PIs
	EFV	• Virologic responses equivalent or superior to all comparators to date • Once-daily dosing • Coformulated with TDF/FTC	• Neuropsychiatric side effects • Teratogenic in nonhuman primates. Several cases of neural tube defect in infants born to women who were exposed to EFV in the first trimester of pregnancy reported. EFV use should be avoided in women with potential for pregnancy and is contraindicated in the first trimester. • Dyslipidemia
	NVP	• No food effect • Fewer lipid effects than EFV • Once-daily dosing with extended-release tablet formulation	• Higher incidence of rash, including rare but serious HSRs (SJS or TEN), than with other NNRTIs • Higher incidence of hepatotoxicity, including serious and even fatal cases of hepatic necrosis, than with other NNRTIs • Contraindicated in patients with moderate or severe (Child-Pugh B or C) hepatic impairment • Some data suggest that ART-naive 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. • Early virologic failure of NVP + TDF + (FTC or 3TC) in small clinical trials

	RPV	• Once-daily dosing
		• Coformulated with TDF/FTC
		• Compared with EFV:
		  • Fewer discontinuations for CNS adverse effects
		  • Fewer lipid effects
		  • Fewer rashes
			• More virologic failures in patients with pretreatment HIV RNA >100,000 copies/mL than with EFV-based regimen
			• More NNRTI- and 3TC-associated mutations at virological failure than with regimen containing EFV + two NRTIs
			• Food requirement
			• Absorption depends on lower gastric pH. (See Table 15a for detailed information regarding interactions with H2 antagonists and antacids.)
			• Contraindicated with PPIs
			• RPV-associated depression reported
			• Use RPV with caution when coadministered with a drug having a known risk of torsades de pointes.

Table 6. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 2 of 4)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
PIs (in alphabetical order)		**PI Class Advantages:** • Higher genetic barrier to resistance than NNRTIs and RAL • PI resistance uncommon with failure while on first PI regimen	**PI Class Disadvantages:** • Metabolic complications such as dyslipidemia, insulin resistance, hepatotoxicity • GI adverse effects • 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 PIs • Once-daily dosing • Low pill burden • Good GI tolerability • Signature mutation (I50L) not associated with broad PI cross resistance	• Indirect hyperbilirubinemia sometimes leading to jaundice or scleral icterus • PR interval prolongation: generally inconsequential unless ATV combined with another drug with similar effect • Cannot be coadministered with TDF, EFV, or NVP (See ATV/r.) • Nephrolithiasis • Skin rash • Food requirement • Absorption depends on food and low gastric pH. (See Table 15a for detailed information regarding interactions with H2 antagonists, antacids, and PPIs.)
	ATV/r	• RTV boosting: higher trough ATV concentration and greater antiviral effect • Once-daily dosing • Low pill burden	• More adverse effects on lipids than unboosted ATV • More hyperbilirubinemia and jaundice than unboosted ATV • Food requirement • Absorption depends on food and low gastric pH. (See Table 15a for interactions with H2 antagonists, antacids, and PPIs.) • RTV boosting required with TDF and EFV. With EFV, use ATV 400 mg and RTV 100 mg once daily (PI-naive patients only). • Should not be coadministered with NVP
	DRV/r	• Once-daily dosing • Potent virologic efficacy	• Skin rash • Food requirement
	FPV/r	• Twice-daily dosing resulted in efficacy comparable to LPV/r • RTV boosting results in higher trough APV concentration and greater antiviral effect • Once-daily dosing possible with RTV 100 mg or 200 mg daily • No food effect	• Skin rash • Hyperlipidemia • Once-daily dosing results in lower APV concentrations than twice-daily dosing • For FPV 1400 mg + RTV 200 mg: requires 200 mg of RTV and no coformulation • Fewer data on FPV 1400 mg + RTV 100 mg dose than on DRV/r and ATV/r

Table 6. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 3 of 4)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
PIs (in alphabetical order)	**LPV/r**	• Coformulated • No food requirement • Recommended PI in pregnant women (twice daily only) • Greater CD4 count increase than with EFV-based regimens	• Requires 200 mg per day of RTV • Lower drug exposure in pregnant women—may need dose increase in third trimester • Once-daily dosing not recommended in pregnant women • Once-daily dosing results in lower trough concentration than twice-daily dosing • Possible higher risk of MI associated with cumulative use of LPV/r • PR and QT interval prolongation have been reported. Use with caution in patients at risk of cardiac conduction abnormalities or receiving other drugs with similar effect.
	SQV/r	• Similar efficacy but less hyperlipidemia than with LPV/r	• Highest pill burden (6 pills per day) among available PI regimens • Requires 200 mg of RTV • Food requirement • PR and/or QT interval prolongations in a healthy volunteer study • Pretreatment ECG recommended • 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 • Fewer drug-related adverse events and lipid changes than EFV • No food effect • Fewer drug-drug interactions than PI- or NNRTI-based regimens	• Twice-daily dosing • Lower genetic barrier to resistance than with boosted PI-based regimens • No data with NRTIs other than TDF/FTC in ART-naive patients • Increase in creatine kinase, myopathy, and rhabdomyolysis have been reported • Rare cases of severe skin reactions (including SJS and TEN) have been reported and systemic HSRs with rash and constitutional symptoms, with or without hepatitis, have been reported.
CCR5 Antagonist	**MVC**	• Virologic response noninferior to EFV in post hoc analysis of MERIT study (See text.) • Fewer adverse effects than EFV	• Requires viral tropism testing prior to initiation of therapy, which results in additional cost and possible delay in initiation of therapy • More MVC-treated than EFV-treated patients discontinued therapy due to lack of efficacy in MERIT study • Less long-term experience in ART-naive patients than with boosted PI- or NNRTI-based regimens • Limited experience with dual-NRTIs other than ZDV/3TC • Twice-daily dosing • CYP 3A4 substrate; dosing depends on presence or absence of concomitant CYP3A4 inducer(s) or inhibitor(s)

Table 6. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (page 4 of 4)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
Dual-NRTI pairs (in alphabetical order)	**ABC/3TC**	• Virologic response noninferior to ZDV/3TC • Better CD4 count responses than with ZDV/3TC • Once-daily dosing • Coformulation • No food effect • No cumulative TAM-mediated resistance	• Potential for ABC HSR in patients with HLA-B*5701 • Increased potential for cardiovascular events, especially in patients with cardiovascular risk factors • Inferior virologic responses in patients with baseline HIV RNA >100,000 copies/mL when compared with TDF/FTC in ACTG 5202 study; however, this was not seen in the HEAT study.
	TDF/FTC	• Better virologic responses than with ZDV/3TC • Better virologic responses than with ABC/3TC in patients with baseline HIV RNA >100,000 copies/mL in ACTG 5202 study; however, this was not seen in the HEAT study. • Active against HBV; recommended dual-NRTI for HIV/HBV coinfection • Once-daily dosing • No food effect • Coformulated (TDF/FTC, EFV/TDF/FTC, and RPV/TDF/FTC) • No cumulative TAM-mediated resistance	• Potential for renal impairment, including Fanconi syndrome and acute renal insufficiency • Early virologic failure of NVP + TDF + (FTC or 3TC) in small clinical trials • Potential for decrease in BMD
	ZDV/3TC	• Coformulated (ZDV/3TC and ZDV/3TC/ABC) • No food effect (although better tolerated with food) • Preferred dual NRTI in pregnant women	• Bone marrow suppression, especially anemia and neutropenia • GI intolerance, headache • Mitochondrial toxicity, including lipoatrophy, lactic acidosis, hepatic steatosis • Compared with TDF/FTC, inferior in combination with EFV • Less CD4 increase compared with ABC/3TC • Twice-daily dosing

Key to Abbreviations: 3TC = lamivudine, ABC = abacavir, APV = amprenavir, ART = antiretroviral therapy, ARV = antiretroviral, ATV = atazanavir, ATV/r = atazanavir/ritonavir, AV = atrioventricular, BMD = bone mineral density, CNS = central nervous system, CYP = cytochrome P, d4T = stavudine, ddI = didanosine, 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, RAL = raltegravir, RPV = rilpivirine, RTV = ritonavir, SJS = Stevens-Johnson syndrome, SQV/r = saquinavir/ritonavir, TAM = thymidine analogue mutation, TDF = tenofovir, TEN = toxic epidermal necrosis, ZDV = zidovudine

Table 7. Antiretroviral Components or Regimens Not Recommended as Initial Therapy

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 regimen **(BI)**	• Inferior virologic efficacy
DRV (unboosted)	• Use without RTV has not been studied
DLV **(BIII)**	• Inferior virologic efficacy • Inconvenient (three times daily) dosing
ddI + 3TC (or FTC) **(BIII)**	• Inferior virologic efficacy • Least clinical trial experience in ART-naive patients
ddI + TDF **(BII)**	• High rate of early virologic failure • Rapid selection of resistance mutations • Potential for immunologic nonresponse/CD4 T-cell decline • Increased ddI drug exposure and toxicities
T20 **(BIII)**	• No clinical trial experience in ART-naive patients • Requires twice-daily subcutaneous injections
ETR **(BIII)**	• Insufficient data in ART-naive patients
FPV (unboosted) **(BIII)**	• Less potent than RTV-boosted FPV • Virologic failure with unboosted FPV-based regimen may select mutations that confer resistance to DRV
IDV (unboosted) **(BIII)**	• Inconvenient dosing (three times daily with meal restrictions) • Fluid requirement
IDV (RTV-boosted) **(BIII)**	• High incidence of nephrolithiasis
NFV **(BI)**	• Inferior virologic efficacy • High incidence of diarrhea
RTV as sole PI **(BIII)**	• High pill burden • GI 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 (RTV-boosted) **(BI)**	• Inferior virologic efficacy

Key to Abbreviations: 3TC = lamivudine, ABC = abacavir, ART = antiretroviral therapy, ARV = antiretroviral, d4T = stavudine, ddI = didanosine, DLV = delavirdine, DRV = darunavir, ETR = etravirine, FPV = fosamprenavir, FTC = emtricitabine, GI = gastrointestinal, IDV = indinavir, NFV = nelfinavir, NRTI = nucleoside reverse transcriptase inhibitor, PI = protease inhibitor, RTV = ritonavir, SQV = saquinavir, T20 = enfuvirtide, TDF = tenofovir, TPV = tipranavir, ZDV = zidovudine

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What Not to Use (Last updated March 27, 2012; last reviewed March 27, 2012)

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-naive 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-naive women with CD4 counts >250 cells/mm^3 or in ARV-naive 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 (page 1 of 2)

	Rationale	Exception
Antiretroviral Regimens Not Recommended		
Monotherapy with NRTI (AII)	• Rapid development of resistance • Inferior ARV activity when compared with combination of three or more ARV agents	• No exception
Dual-NRTI regimens (AI)	• Rapid development of resistance • 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-naive patients. • 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 • Reports of serious, even fatal, cases of lactic acidosis with hepatic steatosis with or without pancreatitis in pregnant women	• No exception
ddI + TDF (AII)	• Increased ddI concentrations and serious ddI-associated toxicities • Potential for immunologic nonresponse and/or CD4 cell count decline • High rate of early virologic failure • 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. • 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 • 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

Table 8. Antiretroviral Regimens or Components That Should Not Be Offered At Any Time (page 2 of 2)

	Rationale	Exception
NVP in ARV-naive 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 (Last updated January 10, 2011; last reviewed 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-naive 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 (Last updated January 10, 2011; last reviewed 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)-naive 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 (Last updated January 10, 2011; last reviewed 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

Drug	Concentration (ng/mL)
Suggested minimum target trough concentrations in patients with HIV-1 susceptible to the ARV drugs[2-9]	
Fosamprenavir (FPV)	400 (measured as amprenavir concentration)
Atazanavir (ATV)	150
Indinavir (IDV)	100
Lopinavir (LPV)	1000
Nelfinavir[a] (NFV)	800
Saquinavir (SQV)	100–250
Efavirenz (EFV)	1000
Nevirapine (NVP)	3000

[a] Measurable active (M8) metabolite

Table 9b. Trough Concentrations of Antiretroviral Drugs for Treatment-Experienced Patients with Virologic Failure

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)	3300 (1255–7368)
Etravirine (ETR)	275 (81–2980)
Raltegravir (RAL)	72 (29–118)

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Discontinuation or Interruption of Antiretroviral Therapy (Last updated January 10, 2011; last reviewed January 10, 2011)

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 (Last updated January 10, 2011; last reviewed 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)-naive 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-naive 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-naive 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

- **Suspecting acute HIV infection:** Signs or symptoms of acute HIV infection with recent (within 2–6 weeks) high risk of exposure to HIV[a]
  - 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.[a]
- **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.[b]
  - Positive virologic test[b] 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.

[a] 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.

[b] 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 (Last updated January 10, 2011; last reviewed 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 naive 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 (Last updated March 27, 2012; last reviewed March 27, 2012)

Treatment Challenges of HIV-Infected Illicit Drug Users

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 [i.e., poppers]). 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 individuals who have HIV infection or who are at risk of HIV infection. The association between club drugs and high-risk sexual behavior in men who have sex with men (MSM) is strongest for methamphetamine and amyl nitrate; this association is less consistent with the other club drugs.[1]

Illicit drug use has 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] Treatment of HIV disease in illicit drug users can be successful but HIV-infected illicit drug users present special treatment challenges. These challenges 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 in 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 (TB), 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 illicit drug users with HIV disease than in HIV-uninfected illicit drug users, due in part to respiratory, hepatic, and neurological impairments associated with HIV infection.[4] Successful HIV therapy for illicit drug users often depends on clinicians becoming familiar with and managing these comorbid conditions and providing overdose prevention support.

Illicit drug users 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 use among illicit drug users include active drug use, younger age, female gender, suboptimal health care, recent incarceration, lack of access to rehabilitation programs, and health care providers' lack of expertise in HIV treatment.[5-6] The typically unstable, chaotic life patterns of many illicit drug users; 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 illicit drug users.[8-9] The first step in provision of care and treatment for these individuals is to recognize the existence of a substance abuse problem. It is often obvious that the problem exists, but some patients may hide these problem behaviors from clinicians. Assessment of a patient for substance abuse should be part of routine medical history taking and should be done in a professional, straightforward, and nonjudgmental manner.

Treatment Efficacy in HIV-Infected Illicit Drug Use Populations

Although illicit drug users are underrepresented in HIV therapy clinical trials, available data indicate that efficacy of ART in illicit drug users—when they are not actively using drugs—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 of disruptions caused by drug use on the patient both before and while receiving ART. Although many illicit drug users can sufficiently control their drug use for long enough 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, 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] These strategies should include, if available, the use of adherence support mechanisms such as modified directly observed therapy (mDOT), which has shown promise in this population.[12]

Antiretroviral Agents and Opioid Substitution Therapy

Compared with noninjection drug users receiving ART, injection drug users (IDUs) receiving ART 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 (GI), and hematologic disorders are highly prevalent among IDUs. These comorbid conditions should be considered when selecting antiretroviral (ARV) agents in this population. 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 Antiretroviral Therapy. 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. Patients and substance abuse treatment facilities should be informed 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 to 10-mg increments daily until the desired effect is achieved.

Buprenorphine and Antiretroviral Therapy. Buprenorphine, a partial μ-opioid agonist, is administrated sublingually and is often coformulated with naloxone. It is increasingly used for opioid dependence treatment. Compared with methadone, buprenorphine has a lower risk of respiratory depression and overdose. This allows physicians in primary care to prescribe buprenorphine for the treatment of opioid dependency. The flexibility of the primary care setting can 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 ARV agents.[13-14] Findings from available studies show that the drug interaction profile of buprenorphine is more favorable than that of methadone.

Naltrexone and Antiretroviral Therapy. 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 CYP450 enzyme system and is not expected to interact with protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs).[15]

Table 11 provides the currently available pharmacokinetic (PK) 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 CYP450 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 and needle and syringe exchange programs, strategies to reduce 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 those who do not abuse drugs.

Important considerations in the selection of successful regimens and the provision of appropriate patient monitoring in this population include need for 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 (page 1 of 2)

Concomitant Drug	Antiretroviral Drug	Pharmacokinetic Interactions Clinical Comments/Recommendations
Buprenorphine	EFV	buprenorphine AUC ↓ 50%; norbuprenorphine[a] AUC ↓ 71% No withdrawal symptoms reported. No dosage adjustment recommended; however, monitor for withdrawal symptoms.
	ETR	buprenorphine AUC ↓ 25% No dosage adjustment necessary.
	ATV	buprenorphine AUC ↑ 93%; norbuprenorphine AUC ↑ 76%; ↓ ATV levels possible Do not coadminister buprenorphine with unboosted ATV.
	ATV/r	buprenorphine AUC ↑ 66%; norbuprenorphine AUC ↑ 105% Monitor for sedation. Buprenorphine dose reduction may be necessary.
	DRV/r	buprenorphine: no significant effect; norbuprenorphine AUC ↑ 46% and C_{min} ↑ 71% No dose adjustment necessary.
	FPV/r	buprenorphine: no significant effect; norbuprenorphine AUC ↓ 15% No dosage adjustment necessary.
	TPV/r	buprenorphine: no significant effect; norbuprenorphine AUC, C_{max}, and C_{min} ↓ 80%; TPV C_{min} ↓ 19%–40% Consider monitoring TPV level.
	3TC, ddI, TDF, ZDV, NVP, LPV/r, NFV	No significant effect No dosage adjustment necessary.
	ABC, d4T, FTC, ETR, IDV +/- RTV, SQV/r, RAL, MVC, T20	No data
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.
	EFV	methadone AUC ↓ 52% Opioid withdrawal common; increased methadone dose often necessary.

Table 11. Drug Interactions between Antiretroviral Agents and Drugs Used to Treat Opioid Addiction (page 2 of 2)

Methadone, cont'd	NVP	methadone AUC ↓ 41% NVP: no significant effect 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[b] AUC ↓ 16%–18%; With LPV/r: methadone AUC ↓ 26%–53%; With SQV/r 1000/100 mg BID: R-methadone AUC ↓ 19%; With TPV/r: R-methadone AUC ↓ 48% Opioid withdrawal unlikely but may occur. Adjustment of methadone dose usually not required; however, monitor for opioid withdrawal and increase methadone dose as clinically indicated.
	FPV	No data with FPV (unboosted) With APV: R-methadone C_{min} ↓ 21%, no significant change in AUC Monitor and titrate methadone as clinically indicated. The interaction with FPV is presumed to be similar.
	NFV	methadone AUC ↓ 40% 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 No dosage adjustment necessary.
	FTC, MVC, T20	No data

[a] Norbuprenorphine is an active metabolite of buprenorphine.
[b] R-methadone is the active form of methadone.

Key to Abbreviations: 3TC = lamivudine, ABC = abacavir, APV = amprenavir, ATV = atazanavir, ATV/r = atazanavir/ ritonavair, 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, 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, T20 = enfuvirtide, TDF = tenofovir, TPV = tipranavir, TPV/r = tipranavir/ritonavir, ZDV = zidovudine

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HIV-Infected Women (Last updated March 27, 2012; last reviewed March 27, 2012)

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 to prevent unintended pregnancy **(AIII)**.
- In pregnant women, an additional goal of therapy is prevention of perinatal transmission of HIV, with a goal of maximal viral suppression to reduce the risk of transmission of HIV to the fetus and newborn **(AI)**.
- When selecting an ARV combination regimen for a pregnant woman, clinicians should consider the known safety, efficacy, and pharmacokinetic data on use during pregnancy for each agent **(AIII)**.
- Use of 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, including during pregnancy. Clinicians who provide care for pregnant women should consult the current Perinatal Guidelines[1] for in-depth discussion and management assistance. Additional guidance on the management of HIV-infected women can be found at: http://hab.hrsa.gov/deliverhivaidscare/clinicalguide11/.

Gender Considerations in Antiretroviral Therapy

In general, studies to date have not shown gender differences in virologic responses to ART,[2-4] although a number of studies have suggested that gender may influence the frequency, presentation, and severity of selected ARV-related adverse events.[5] Although data are limited, there is also evidence that pharmacokinetics for some ARV drugs may differ between men and women, possibly due to variations between men and women in factors such as body weight, plasma volume, gastric emptying time, plasma protein levels, cytochrome P (CYP) 450 activity, drug transporter function, and excretion activity.[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 in ARV-naive individuals; women with higher CD4 counts (>250 cells/mm^3) or elevated baseline transaminase levels appear to be at greatest risk.[9-12] It is generally recommended that NVP not be prescribed to ARV-naive 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 is 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) but 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. Compared with HIV-infected men, 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 is exacerbated by HIV and ART.[16-17] At the present time, none of these differences requires women-specific 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. Counseling should include discussion of special considerations pertaining to ARV use when trying to conceive and during pregnancy (see Perinatal Guidelines[1]). Sexual activity, reproductive desires and plans, HIV status of sexual partner(s), and use of effective contraception to prevent unintended pregnancy should be discussed. An HIV-infected woman who wishes to conceive with an HIV-uninfected male partner should be informed of options to prevent sexual transmission of HIV while attempting conception. Interventions include initiation of maximally suppressive ART, which has been shown to significantly decrease the risk of sexual transmission (see Preventing Secondary Transmission of HIV), and artificial insemination including the option to self-inseminate with the partner's sperm during the periovulatory period[18]. More extensive discussion can been found in the Reproductive Options for HIV-Concordant and Serodiscordant Couples section of the Perinatal Guidelines.[1] 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 or may engage in sexual activity that could result in pregnancy **(AIII)**. The most vulnerable period in fetal organogenesis is early in gestation, often before pregnancy is recognized.

Hormonal Contraception

Safe and effective reproductive health and family planning services to reduce unintended pregnancy and perinatal transmission of HIV are an essential component of care for HIV-infected women of childbearing age. Counseling about reproductive issues should be provided on an ongoing basis.

Providers should be aware of potential interactions between ARV drugs and hormonal contraceptives that could lower contraceptive efficacy. 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 decreases contraceptive efficacy or increases estrogen- or progestin-related adverse effects (e.g., thromboembolism). In small studies of HIV-infected women receiving injectable depot-medroxyprogesterone acetate (DMPA) while on ART, there were no significant interactions between DMPA and efavirenz (EFV), NVP, nelfinavir (NFV), or NRTI drugs.[19-21] Contraceptive failure of the etonogestrel implant in two patients on EFV-based therapy has been reported and a study has shown EFV may decrease plasma progestin concentrations of COCs containing ethinyl estradiol and norgestimate.[22-23] Several RTV-boosted PIs decrease oral contraceptive estradiol levels.[24-25] A small study from Malawi showed that NVP use did not significantly affect estradiol or progestin levels in HIV-infected women.[26] Overall, data are relatively limited and the clinical implications of these findings are unclear. The magnitudes of change in drug levels that may reduce contraceptive efficacy or increase adverse effects are unknown. Concerns about pharmacokinetic interactions between hormonal contraceptives and ARVs should not prevent clinicians from prescribing hormonal contraceptives for women on ART. However, when women wish to use hormonal contraceptives and drug interactions with ARVs are known, additional or alternative contraceptive methods may be recommended (see drug interaction Tables 15a, 15b, and 15d and Perinatal Guidelines[1]). Consistent use of male or female condoms to prevent transmission of HIV and protect against other sexually transmitted

diseases (STDs) is recommended for all HIV-infected women and their partners, regardless of contraceptive use.

The data on the association between hormonal contraception and the risk of acquisition of HIV are conflicting.[27] A retrospective secondary analysis of two studies of serodiscordant couples in Africa in which the HIV-infected partner was not receiving ART found that women using hormonal contraception (the vast majority using injectable DMPA) had a twofold increased risk of acquiring HIV (for HIV-infected male/HIV-uninfected female couples) or transmitting HIV (HIV-infected female/HIV- uninfected male couples).[28] HIV-infected women using hormonal contraception had higher genital HIV RNA concentrations than did women not using hormonal contraceptives.[28] Oral contraceptive use was not significantly associated with transmission of HIV; however, the number of women using oral contraceptives in this study was insufficient to adequately assess risk. It is important to note that not all studies have supported a link between hormonal contraception and transmission or acquisition of HIV and that individuals in this study were not receiving ART. Further research is needed to definitively determine if hormonal contraceptive use is an independent risk factor for acquisition and transmission of HIV.[27,29]

Intrauterine devices (IUDs) appear to be a safe and effective contraceptive option for HIV-infected women.[30-33] Although studies have focused primarily on non-hormone-containing IUDs (e.g., copper IUD), several small studies have also found levonorgestrel-releasing IUDs to be safe.[31, 34-35]

Pregnant Women

Clinicians should review the Perinatal Guidelines[1] for a detailed discussion of the management of HIV-infected pregnant women. The use of combination ARV regimens is recommended for all HIV-infected pregnant women, regardless of virologic, immunologic, or clinical parameters **(AI)**. Pregnant HIV-infected women should be counseled regarding the known benefits versus risks of ARV use during pregnancy to the woman, fetus, and newborn. A woman's decision regarding ARV use should be respected. Coercive and punitive approaches 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 Perinatal Transmission of HIV. Both reduction of HIV RNA levels and use of ARVs appear to have an independent effect on reduction of perinatal transmission of HIV.[36-38] The goal of ARV use is to achieve maximal and sustained suppression of HIV RNA levels during pregnancy.

As in non-pregnant individuals, genotypic resistance testing is recommended for all pregnant women before ARV initiation **(AIII)** and for pregnant women 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 (see the Perinatal Guidelines[1]).

Regimen Considerations. Pregnancy should not preclude the use of optimal drug regimens. Because recommendations on ARVs to use for treatment of HIV-infected pregnant women are subject to unique considerations, recommendations specific to the timing of therapy initiation and the choice of ARVs for pregnant women may differ from those for non-pregnant individuals. 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 and the woman's ability to adhere to a particular regimen during pregnancy;
- potential short- and long-term effects of the ARV on the fetus and newborn, which are unknown for many drugs.

Combination drug regimens are considered the standard of care in pregnancy, both for the treatment of HIV infection and for the prevention of perinatal transmission of HIV. ZDV by intravenous infusion to the mother during labor and neonatal ZDV prophylaxis for 6 weeks are recommended irrespective of antenatal regimen chosen. Recommendations on ARV choice in pregnancy are discussed in detail in the Perinatal Guidelines (see Perinatal Guidelines[1]).

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 Food and Drug Administration (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]

Postpartum Management

Following delivery, clinical, immunologic, and virologic follow-up should continue as recommended for non-pregnant adults and adolescents. Because maternal ART reduces but does not eliminate the risk of transmission of HIV in breast milk and postnatal transmission can occur despite maternal ART, women should also be counseled to avoid breastfeeding.[1] HIV-infected women should avoid premastication of food for the infant because the practice has been associated with transmission of HIV from mother to child.[39] Considerations regarding continuation of ART for maternal therapeutic indications are the same as considerations regarding ART use for other non-pregnant individuals. For more information regarding postpartum discontinuation of ART, refer to the Perinatal Guidelines.[1] Several studies have demonstrated that women's adherence to ART may worsen in the postpartum period.[40-44] Clinicians caring for postpartum women receiving ART should specifically address adherence, including evaluating specific facilitators and barriers to adherence, and consider offering an adherence intervention (see Adherence to Antiretroviral Therapy).

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HIV-2 Infection (Last updated January 10, 2011; last reviewed 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-naive 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-naive 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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HIV and the Older Patient (Last updated March 27, 2012; last reviewed March 27, 2012)

Key Considerations When Caring for Older HIV-Infected Patients
• Antiretroviral therapy (ART) is recommended in patients >50 years of age, regardless of CD4 cell count **(BIII)**, because the risk of non-AIDS related complications may increase and the immunologic response to ART may be reduced in older HIV-infected patients.
• ART-associated adverse events may occur more frequently in older HIV-infected adults than in younger HIV-infected individuals. Therefore, the bone, kidney, metabolic, cardiovascular, and liver health of older HIV-infected adults should be monitored closely.
• The increased risk of drug-drug interactions between antiretroviral (ARV) drugs and other medications commonly used in older HIV-infected patients should be assessed regularly, especially when starting or switching ART and concomitant medications.
• HIV experts and primary care providers should work together to optimize the medical care of older HIV-infected patients with complex comorbidities.
• Counseling to prevent secondary transmission of HIV remains an important aspect of the care of the older HIV-infected 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*

Effective antiretroviral therapy (ART) has increased survival in HIV-infected individuals, resulting in an increasing number of older individuals living with HIV infection. In the United States, approximately 30% of people currently living with HIV/AIDS are age 50 years or older and trends suggest that the proportion of older persons living with HIV/AIDS will increase steadily.[1] Care of HIV-infected patients increasingly will involve adults 60 to 80 years of age, a population for which data from clinical trials or pharmacokinetic studies are very limited.

There are several distinct areas of concern regarding the association between age and HIV disease.[2] First, older HIV-infected patients may suffer from aging-related comorbid illnesses that can complicate the management of HIV infection, as outlined in detail below. Second, HIV disease may affect the biology of aging, possibly resulting in early manifestations of many clinical syndromes generally associated with advanced age. Third, reduced mucosal and immunologic defenses (such as post-menopausal atrophic vaginitis) and changes in risk behaviors (for example, decrease in condom use because of less concern about pregnancy and increased use of erectile dysfunction drugs) in older adults could lead to increased risk of acquisition and transmission of HIV.[3-4] Finally, because older adults generally are perceived to be at low risk of HIV infection, screening for HIV in this population remains low. For these reasons, HIV infection in many older adults may not be diagnosed until late in the disease process. This section focuses on HIV diagnosis and treatment considerations in the older HIV-infected patient.

HIV Diagnosis and Prevention

Even though many older individuals are engaged in risk behaviors associated with acquisition of HIV, they may be perceived to be at low risk of infection and, as a result, they are less likely to be tested for HIV than younger persons.[5] According to one U.S. survey, 71% of men and 51% of women age 60 years and older continue to be sexually active,[6] with less concern about the possibility of pregnancy contributing to less

condom use. Another national survey reported that among individuals age 50 years or older, condoms were not used during most recent intercourse with 91% of casual partners or 70% of new partners.[7] In addition, results from a CDC survey[8] show that in 2008 only 35% of adults age 45 to 64 years had ever been tested for HIV infection despite the 2006 CDC recommendation that individuals age 13 to 64 years be tested at least once and more often if sexually active.[9] Clinicians must be attuned to the possibility of HIV infection in older patients, including those older than 64 years of age who, based on CDC recommendations, would not be screened for HIV. Furthermore, sexual history taking, risk-reduction counseling, and screening for sexually transmitted diseases (STDs) (if indicated), are important components of general health care for HIV-infected and -uninfected older patients.

Failure to consider a diagnosis of HIV in older persons likely contributes to later disease presentation and initiation of ART.[10] One surveillance report showed that the proportion of patients who progressed to AIDS within 1 year of diagnosis was greater among patients >60 years of age (52%) than among patients younger than 25 years (16%).[1] When individuals >50 years of age present with severe illnesses, AIDS-related opportunistic infections (OIs) need to be considered in the differential diagnosis of the illness.

Initiating Antiretroviral Therapy

Concerns about decreased immune recovery and increased risk of serious non-AIDS events are factors that favor initiating ART in patients >50 years of age regardless of CD4 cell count **(BIII)**. (See Initiating Antiretroviral Therapy in Treatment-Naive Patients.) Data that would favor use of any one of the Panel's recommended initial ART regimens (see What to Start) on the basis of age are not available. The choice of regimen should be informed by a comprehensive review of the patient's other medical conditions and medications. A noteworthy limitation of currently available information is lack of data on the long-term safety of specific antiretroviral (ARV) drugs in older patients, such as use of tenofovir disoproxil fumarate (TDF) in older patients with declining renal function. The recommendations on how frequently to monitor parameters of ART effectiveness and safety for adults age >50 years are similar to those for the general HIV-infected population; however, the recommendations for older adults focus particularly on the adverse events of ART pertaining to renal, liver, cardiovascular, metabolic, and bone health (see Table 13).

HIV, Aging, and Antiretroviral Therapy

The efficacy, pharmacokinetics, adverse effects, and drug interaction potentials of ART in the older adult have not been studied systematically. There is no evidence that the virologic response to ART is different in older patients than in younger patients. However, CD4 T-cell recovery after starting ART generally is less robust in older patients than in younger patients.[11-14] This observation suggests that starting ART at a younger age will result in better immunologic and possibly clinical outcomes.

Hepatic metabolism and renal elimination are the major routes of drug clearance, including the clearance of ARV drugs. Both liver and kidney function may decrease with age, which may result in impaired drug elimination and drug accumulation.[15] Current ARV drug doses are based on pharmacokinetic and pharmacodynamic data derived from studies conducted in subjects with normal organ function. Most clinical trials include only a small proportion of study participants >50 years of age. Whether drug accumulation in the older patient may lead to greater incidence and severity of adverse effects than seen in younger patients is unknown.

HIV-infected patients with aging-associated comorbidities may require additional pharmacologic intervention, making therapeutic management increasingly complex. In addition to taking medications to manage HIV infection and comorbid conditions, many older HIV-infected patients also are taking medications to ameliorate discomfort (e.g., pain medications, sedatives) or to manage adverse effects of

medications (e.g., anti-emetics). They also may self-medicate with over-the-counter medicines or supplements. In the HIV-negative population, polypharmacy is a major cause of iatrogenic problems in geriatric patients.[16] This may be the result of medication errors (by prescribers or patients), nonadherence, additive drug toxicities, and drug-drug interactions. Older HIV-infected patients probably are at an even greater risk of polypharmacy and its attendant adverse consequences than younger HIV-infected or similarly aged HIV-uninfected patients.

Drug-drug interactions are common with ART and easily can be overlooked by prescribers.[17] The available drug interaction information on ARV agents is derived primarily from pharmacokinetic studies performed in a small number of relatively young, HIV-uninfected subjects with normal organ function (see Tables 14-16b). Data from these studies provide clinicians with a basis to assess whether a significant interaction may exist. However, the magnitude of the interaction may be different in older HIV-infected patients than in younger HIV-infected patients.

Nonadherence is the most common cause of treatment failure. Complex dosing requirements, high pill burden, inability to access medications because of cost or availability, limited health literacy including lack of numeracy skills, misunderstanding of instructions, depression, and neurocognitive impairment are among the key reasons for nonadherence.[18] Although many of these factors likely will be more prevalent in an aging HIV-infected population, some data suggest that older HIV-infected patients may be more adherent to ART than younger HIV-infected patients.[19-21] Clinicians should assess adherence regularly to identify any factors, such as neurocognitive deficits, that may make adherence a challenge. One or more interventions such as discontinuation of unnecessary medications; regimen simplification; or use of adherence tools, including pillboxes, daily calendars, and evidence-based behavioral approaches may be necessary to facilitate medication adherence (see Adherence to Antiretroviral Therapy).

Non-AIDS HIV-Related Complications and other Comorbidities

With the reduction in AIDS-related morbidity and mortality observed with effective use of ART, non-AIDS conditions constitute an increasing proportion of serious illnesses in ART-treated HIV-infected populations.[22-24] Heart disease and cancer are the leading causes of death in older Americans.[25] Similarly, for HIV-infected patients on ART, non-AIDS events such as heart disease, liver disease, and cancer have emerged as major causes of morbidity and mortality. Neurocognitive impairment, already a major health problem in aging patients, may be exacerbated by the effect of HIV infection on the brain.[26] That the presence of multiple non-AIDS comorbidities coupled with the immunologic effects of HIV infection could add to the disease burden of an aging HIV-infected person is a concern.[27-29] At present, primary care recommendations are the same for HIV-infected and HIV-uninfected adults and focus on identifying and managing risks of conditions such as heart, liver, and renal disease; cancer; and bone demineralization.[30-32]

Discontinuing Antiretroviral Therapy in Older Patients

Important issues to discuss with aging HIV-infected patients are living wills, advance directives, and long-term care planning including financial concerns. Health care cost sharing (e.g., co-pays, out-of-pocket costs), loss of employment, and other financial-related factors can cause interruptions in treatment. Clinic systems can minimize loss of treatment by helping patients maintain access to insurance.

For the severely debilitated or terminally ill HIV-infected patient, adding palliative care medications, while perhaps beneficial, further increases the complexity and risk of negative drug interactions. For such patients, a balanced consideration of both the expected benefits of ART and the toxicities and negative quality-of-life effects of ART is needed.

Few data exist on the use of ART in severely debilitated patients with chronic, severe, or non-AIDS terminal conditions.[33-34] Withdrawal of ART usually results in rebound viremia and a decline in CD4 cell count. Acute retroviral syndrome after abrupt discontinuation of ART has been reported. In very debilitated patients, if there are no significant adverse reactions to ART, most clinicians would continue therapy. In cases where ART negatively affects quality of life, the decision to continue therapy should be made together with the patient and/or family members after a discussion on the risks and benefits of continuing or withdrawing ART.

Conclusion

HIV infection may increase the risk of many major health conditions experienced by aging adults and possibly accelerate the aging process.[35] As HIV-infected adults age, their health problems become increasingly complex, placing additional demands on the health care system. This adds to the concern that outpatient clinics providing HIV care in the United States share the same financial problems as other chronic disease and primary care clinics and that reimbursement for care is not sufficient to maintain care at a sustainable level.[36] Continued involvement of HIV experts in the care of older HIV-infected patients is warranted. However, given that the current shortage of primary care providers and geriatricians is projected to continue, current HIV providers will need to adapt to the shifting need for expertise in geriatrics through continuing education and ongoing assessment of the evolving health needs of aging HIV-infected patients.[37] The aging of the HIV-infected population also signals a need for more information on long-term safety and efficacy of ARV drugs in older patients.

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Considerations for Antiretroviral Use in Patients with Coinfections

HIV/Hepatitis B Virus (HBV) Coinfection (Last updated January 10, 2011; last reviewed January 10, 2011)

Panel's Recommendations

- Prior to initiation 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 naive 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 **(AII)**.[17-19]

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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HIV/Hepatitis C Virus (HCV) Coinfection (Last updated March 27, 2012; last reviewed March 27, 2012)

Key Considerations When Managing Patients Coinfected with HIV and Hepatitis C Virus

- All HIV-infected patients should be screened for hepatitis C virus (HCV) infection, preferably before starting antiretroviral therapy (ART).
- ART may slow the progression of liver disease by preserving or restoring immune function and reducing HIV-related immune activation and inflammation. For most HIV/HCV-coinfected patients, including those with cirrhosis, the benefits of ART outweigh concerns regarding drug-induced liver injury (DILI). Therefore, ART should be considered for HIV/HCV-coinfected patients, regardless of CD4 count **(BII)**.
- Initial ART combination regimens for most HIV/HCV-coinfected patients are the same as those for individuals without HCV infection. However, when treatment for both HIV and HCV is indicated, consideration of potential drug-drug interactions and overlapping toxicities should guide ART regimen selection or modification (see discussion in the text).
- Combined treatment of HIV and HCV can be complicated by large pill burden, drug interactions, and overlapping toxicities. Although ART should be initiated for most HIV/HCV-coinfected patients regardless of CD4 cell count, in ART-naive patients with CD4 counts >500 cells/mm^3 some clinicians may choose to defer ART until completion of HCV treatment.
- In patients with lower CD4 counts (e.g., <200 cells/mm^3), it may be preferable to initiate ART and delay HCV therapy until CD4 counts increase as a result of ART.

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 one-third of patients with chronic hepatitis C virus (HCV) infection progress to cirrhosis at a median time of less than 20 years.[1, 2] The rate of progression increases with older age, alcoholism, male sex, and HIV infection.[3-6] In a meta-analysis, individuals coinfected with HIV/HCV were found to have three times greater risk of progression to cirrhosis or decompensated liver disease than were HCV-monoinfected patients.[5] This accelerated rate is magnified in HIV/HCV-coinfected patients with low CD4 counts. Although ART appears to slow the rate of HCV disease progression in HIV/HCV-coinfected patients, several studies have demonstrated that the rate continues to exceed that observed in those without HIV infection.[7, 8] Whether HCV infection accelerates HIV progression, as measured by AIDS-related opportunistic infections (OIs) or death,[9] is unclear. If such an increased risk of HIV progression exists, it may reflect the impact of injection drug use, which is strongly linked to HCV infection.[10,11] The increased frequency of antiretroviral (ARV)-associated hepatotoxicity with chronic HCV infection also complicates HIV treatment.[12, 13]

A combination regimen of peginterferon and ribavirin (PegIFN/RBV) has been the mainstay of treatment for HCV infection. In HCV genotype 1-infected patients without HIV, addition of an HCV NS3/4A protease inhibitor (PI) boceprevir or telaprevir to PegIFN/RBV significantly improves the rate of sustained virologic response (SVR).[14, 15] Clinical trials of these HCV PIs in combination with PegIFN/RBV for the treatment of HCV genotype 1 infection in HIV-infected patients are currently under way. Both boceprevir and telaprevir are substrates and inhibitors of cytochrome P (CYP) 3A4/5 and p-glycoprotein (p-gp); boceprevir is also metabolized by aldo-keto reductase. These drugs have significant interactions with certain ARV drugs that are metabolized by the same pathways. As such, the presence of HCV infection and the treatment of HCV may influence HIV treatment as discussed below.

Assessment of HIV/Hepatitis C Virus Coinfection Before Initiation of Antiretroviral Therapy

- All HIV-infected patients should be screened for HCV infection using sensitive immunoassays licensed for detection of antibody to HCV in blood.[16] HCV-seronegative patients at risk for the acquistion of HCV

infection should undergo repeat testing annually. HCV-seropositive patients should be tested for HCV RNA using a qualitative or quantitative assay to confirm the presence of active infection.[17]

- Patients with HIV/HCV coinfection should be counseled to avoid consuming alcohol and to use appropriate precautions to prevent transmission of HIV and/or HCV to others. HIV/HCV-coinfected patients who are susceptible to hepatitis A virus (HAV) or hepatitis B virus (HBV) infection should be vaccinated against these viruses.
- All patients with HIV/HCV coinfection should be evaluated for HCV therapy. HCV treatment is recommended according to standard guidelines.[18, 19] Strong preference should be given to commence HCV treatment in patients with higher CD4 counts. For patients with lower CD4 counts (e.g., <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.[17, 20-22]

Antiretroviral Therapy in HIV/Hepatitis C Virus Coinfection

- When to start antiretroviral therapy: The rate of liver disease (liver fibrosis) progression is accelerated in HIV/HCV-coinfected patients, particularly in individuals with low CD4 counts (≤350 cells/mm^3). Data largely from retrospective cohort studies are inconsistent regarding the effect of ART on the natural history of HCV disease.[6, 23, 24] However, ART may slow the progression of liver disease by preserving or restoring immune function and reducing HIV-related immune activation and inflammation.[25-27] Thus, for most coinfected patients, including those with high CD4 counts and those with cirrhosis, the benefits of ART outweigh concerns regarding DILI. Therefore, ART should be initiated for most HIV/HCV-coinfected patients, regardless of CD4 count **(BII)**. However, in HIV treatment-naive patients with CD4 counts >500 cells/mm^3, some clinicians may choose to defer ART until completion of HCV treatment.
- What antiretroviral to start and what antiretroviral not to use: Initial ARV combination regimens for most HIV treatment-naive patients with HCV are the same as those for patients without HCV infection. Special considerations for ARV selection in HIV/HCV-coinfected patients include:
  - When both HIV and HCV treatments are indicated, the choice of ARV regimen should be guided by the HCV treatment regimen selected with careful consideration of potential drug-drug interactions and overlapping toxicities (as discussed below).
  - 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.)
- Hepatotoxicity: DILI following initiation of ART is more common in HIV/HCV-coinfected patients than in those with HIV monoinfection. The greatest risk of DILI may be observed in coinfected individuals with advanced liver disease (e.g., cirrhosis or end-stage liver disease).[28] Eradication of HCV infection with treatment may decrease the likelihood of ARV-associated DILI.[29]
  - 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 significant elevations in liver enzyme levels (>5 times the upper limit of the laboratory reference range) have been observed during therapy with ARV drugs that are no longer commonly used in clinical practice, including stavudine (d4T) (with or without didanosine [ddI]), nevirapine (NVP), or full-dose ritonavir (RTV) (600 mg twice daily).[30] Additionally, certain ARV agents should be avoided if possible because they have been associated with higher incidence of serious liver-associated adverse effects, such as fatty liver disease with nucleoside reverse transcriptase inhibitors (NRTIs) such as d4T, ddI, or zidovudine (ZDV);[31] noncirrhotic portal hypertension associated with ddI;[32] and hepatotoxicity associated with RTV-boosted tipranavir.[33]

- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels should be monitored at 1 month after initiation of ART and then every 3 to 6 months. Mild to moderate fluctuations in ALT and/or AST are typical in individuals 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 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 the ART regimen or of the specific drug suspected to be responsible for the DILI may be required.[34]

Treating Both HIV and Hepatitis C Virus Infection

Concurrent treatment of HIV and HCV is feasible but may be complicated by high pill burden, drug interactions, and overlapping drug toxicities. In this context, the decision to treat chronic HCV should also include consideration of the medical need for such treatment on the basis of an assessment of HCV disease stage. Some clinicians may choose to defer HCV therapy in HIV/HCV-coinfected patients with no or minimal liver fibrosis. If treatment with PegIFN/RBV alone or in combination with one of the HCV NS3/4A PIs (boceprevir or telaprevir) is initiated, the ART regimen may need to be modified to reduce the potential for drug interactions and/or toxicities that may develop during the period of concurrent HIV and HCV treatment.

Considerations for using certain nucleoside reverse transcriptase inhibitors and hepatitis C virus treatments:

- ddI **should not be given** with RBV because of the potential for drug-drug interactions leading to life-threatening ddI-associated mitochondrial toxicity including hepatomegaly/steatosis, pancreatitis, and lactic acidosis **(AII)**.[35]
- Combined use of ZDV and RBV is associated with increased rates of anemia, making RBV dose reduction necessary. Therefore, this combination should be avoided when possible.[36] Because the risk of anemia may further increase when boceprevir or telaprevir is combined with PegIFN/RBV, ZDV **should not be given** with this combination **(AIII)**.
- Abacavir (ABC) has been associated with decreased response to PegIFN/RBV in some, but not all, retrospective studies; current evidence is insufficient to recommend avoiding this combination.[37-39]

Considerations for the use of HCV NS3/4A protease inhibitors (boceprevir or telaprevir) and antiretroviral therapy:

- Boceprevir is approved for the treatment of HCV genotype 1 infection in patients without HIV infection. After 4 weeks of PegIFN/RBV therapy, boceprevir is added to the regimen for 24, 32, or 44 additional weeks of HCV therapy. Data on the use of an HCV regimen containing boceprevir together with ART in HIV/HCV-coinfected individuals are limited. In 1 small study of coinfected patients, higher HCV response was observed with boceprevir plus PegIFN/RBV (64 patients) than with PegIFN/RBV alone (34 patients). In this study, patients received ART that included HIV-1 ritonavir-boosted atazanavir (ATV/r), darunavir (DRV/r), or lopinavir (LPV/r) or raltegravir (RAL) plus dual NRTIs.[40]

  Boceprevir is primarily metabolized by aldo-keto reductase, but because the drug is also a substrate and inhibitor of CYP3A4/5 and p-gp enzymes, it may interact with ARVs metabolized by these pathways. Based on drug interaction studies in healthy volunteers, boceprevir can be coadministered with RAL.[41] However, coadministration of boceprevir with ATV/r, DRV/r, LPV/r, or efavirenz (EFV) is not recommended because of bidirectional drug interactions (see Table 15a and 15b).[42, 43] Importantly, the pharmacokinetic (PK) interactions of HIV PIs with boceprevir were not identified before the approval of boceprevir and before participant enrollment in the HIV/HCV-coinfection trial; consequently, some

coinfected patients have received HIV PIs and boceprevir during HCV treatment. Patients who are currently receiving these drug combinations should be advised not to stop any medication until contacting their health care providers. If therapy with HIV PIs and boceprevir is continued, patients should be closely monitored for HIV and HCV responses and consideration should be given to switching the HIV PI or EFV to RAL during boceprevir therapy. Additional clinical trial data are needed to determine if other ARVs may be coadministered with boceprevir.

- Telaprevir is approved for the treatment of HCV genotype 1 infection in patients without HIV infection. Telaprevir is administered in combination with PegIFN/RBV for the initial 12 weeks of HCV therapy followed by 12 or 36 weeks of additional treatment with PegIFN/RBV. Data on the use of this regimen in HIV/HCV-coinfected individuals are limited. In 1 small study of coinfected patients, higher HCV response was observed with telaprevir plus PegIFN/RBV (38 patients) than with PegIFN/RBV alone (22 patients). In this study, patients received ART containing EFV or ATV/r plus tenofovir/emtricitabine (TDF/FTC) or no ART during the HCV therapy.[44]

  Because telaprevir is a substrate and an inhibitor of CYP3A4 and p-gp enzymes, the drug may interact with ARVs metabolized by these pathways. On the basis of drug interaction studies in healthy volunteers and data on responses in coinfected patients enrolled in the small clinical trial noted above, telaprevir can be coadministered with ATV/r[45] and RAL[46] at the standard recommended dose of telaprevir (750 mg every 7–9 hours) and with EFV at an increased dose of telaprevir (1125 mg every 7–9 hours) (see Table 15b); however, coadministration of telaprevir with DRV/r, fosamprenavir/ritonavir (FPV/r), or LPV/r is not recommended because of bidirectional drug interactions.[45] Data on PK interactions of telaprevir with other ARVs including non-nucleoside reverse transcriptase inhibitors (NNRTIs) other than EFV and with maraviroc (MVC) are not available; therefore, coadministration of telaprevir with other ARVs cannot be recommended.

Following are preliminary recommendations for the use of boceprevir or telaprevir in HIV patients coinfected with HCV genotype 1 based on current ART use. These recommendations may be modified as new drug interaction and clinical trial information become available.

Patients not on ART:	Use either boceprevir or telaprevir
Patients receiving RAL + 2-NRTI:	Use either boceprevir or telaprevir
Patients receiving ATV/r + 2-NRTI:	Use telaprevir at standard dose. Do not use boceprevir.
Patients receiving EFV + 2-NRTI:	Use telaprevir at increased dose of 1125 mg every 7–9 hours. Do not use boceprevir.

Patients receiving other ARV regimens:

- If HCV disease is minimal (i.e., no or mild portal fibrosis), consider deferring HCV treatment given rapidly evolving HCV drug development.
- If good prognostic factors for HCV treatment response are present—IL28B CC genotype or low HCV RNA level (<400,000 International Unit [IU]/mL)—consider use of PegIFN/RBV without HCV NS3/4A PI.
- On the basis of ART history and HIV genotype testing results, if possible, consider switching to the ART regimens listed above to permit the use of boceprevir or telaprevir.
- For patients with complex ART history or resistance to multiple classes of ART, consultation with experts regarding the optimal strategy to minimize the risk of HIV breakthrough may be needed. In such patients, telaprevir may be the preferred HCV NS3/4A PI because its duration of use (12 weeks) is shorter than that of boceprevir (24 to 44 weeks).

Summary:

In summary, HCV coinfection and use of PegIFN/RBV with or without HCV NS3/4A PIs (telaprevir or boceprevir) to treat HCV may impact the treatment of HIV because of increased pill burden, toxicities, and

drug-drug interactions. Because ART may slow the progression of HCV-related liver disease, ART should be considered for most HIV/HCV-coinfected patients, regardless of CD4 count. If treatment with PegIFN/RBV alone or in combination with one of the HCV NS3/4A PIs (telaprevir or boceprevir) is initiated, the ART regimen may need to be modified to reduce the potential for drug-drug interactions and/or drug toxicities that may develop during the period of concurrent HIV and HCV treatment. The science of HCV drug development is evolving rapidly. As new clinical trial data on the management of HIV/HCV-coinfected patients with newer HCV drugs become available, the Panel will modify its recommendations accordingly.

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Mycobacterium Tuberculosis Disease with HIV Coinfection (Last updated March 27, 2012; last reviewed March 27, 2012)

Panel's Recommendations
• The principles for treatment of active tuberculosis (TB) disease in HIV-infected patients are the same as those for HIV-uninfected patients **(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)**.
• In patients with CD4 counts <50 cells/mm^3, ART should be initiated within 2 weeks of starting TB treatment **(AI)**.

• In patients with CD4 counts ≥50 cells/mm^3 who present with clinical disease of major severity as indicated by clinical evaluation (including low Karnofsky score, low body mass index [BMI], low hemoglobin, low albumin, organ system dysfunction, or extent of disease), ART should be initiated within 2 to 4 weeks of starting TB treatment. The strength of this recommendation varies on the basis of CD4 cell count:
  • CD4 count 50 to 200 cells/mm^3 **(BI)**
  • CD4 count >200 cells/mm^3 **(BIII)**

• In patients with CD4 counts ≥50 cells/mm^3 who do not have severe clinical disease, ART can be delayed beyond 2 to 4 weeks of starting TB therapy but should be started within 8 to 12 weeks of TB therapy initiation. The strength of this recommendation also varies on the basis of CD4 cell count:
  • CD4 count 50 to 500 cells/mm^3 **(AI)**
  • CD4 count >500 cells/mm^3 **(BIII)**

• In all HIV-infected pregnant women with active TB, ART should be started as early as feasible, both for maternal health and for prevention of mother-to-child transmission (PMTCT) of HIV **(AIII)**.
• In HIV-infected patients with documented multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB, ART should be initiated within 2 to 4 weeks of confirmation of TB drug resistance and initiation of second-line TB therapy **(BIII)**.
• Despite pharmacokinetic drug interactions, a rifamycin (rifampin or rifabutin) should be included in TB regimens for patients receiving ART, with dosage adjustment if necessary **(AII)**.
• Rifabutin is the preferred rifamycin to use in HIV-infected patients with active TB disease on a protease inhibitor (PI)-based regimen because the risk of substantial drug interactions with PIs is lower with rifabutin than with rifampin **(AII)**.
• Coadministration of rifampin and PIs (with or without ritonavir [RTV] boosting) is not recommended **(AII)**.
• Rifapentine (RPT) is NOT recommended in HIV-infected patients receiving ART for treatment of latent TB infection (LTBI) or active TB, unless in the context of a clinical trial **(AIII)**.
• 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, which can include 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*

Treatment of Active Tuberculosis in HIV-Infected 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.[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 guiding treatment for individuals 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] The Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents[4] include a more complete discussion of the diagnosis and treatment of TB disease in HIV-infected patients.

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-drug interactions between rifamycins and some antiretroviral (ARV) agents, (3) the additive toxicities associated with concomitant ARV and TB drug use, (4) the development of TB-associated IRIS after ART initiation, and (5) the need for treatment support including DOT and the integration of HIV and TB care and treatment.

Antiretroviral Therapy in Patients with Active Tuberculosis

Patients Diagnosed with Tuberculosis While Receiving Antiretroviral Therapy

When TB is diagnosed in a patient 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 (see Tables 14–16 for dosing recommendations).

Patients Not Yet Receiving Antiretroviral Therapy

Until recently, when to start ART in patients with active TB has been a subject of debate. Survival is improved when ART is started early following initiation of TB therapy, but a delay in initiating ART often was favored because of the potential complications of high pill burden, additive toxicities, drug interactions, adherence, and the potential for development of IRIS.Recent studies primarily conducted in resource-limited settings, including three randomized controlled trials, have helped clarify the question of when to start ART in patients with active TB.[5-8]

The SAPiT study conducted in South Africa convincingly demonstrated that starting ART during rather than after concluding treatment for TB can significantly reduce mortality. In this study, ambulatory 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 first 8 weeks of TB treatment (i.e., during the continuation phase of TB therapy) or sequential therapy with ART initiated after the conclusion of standard TB therapy. The median CD4 cell count of participants at study entry was 150 cells/mm^3. The sequential therapy arm was stopped when an early analysis demonstrated that the mortality rate in the combined two integrated arms was 56% lower than the rate in the sequential therapy arm. Treatment was continued in the two integrated arms until study completion.[5]

With the completion of SAPiT and 2 other randomized controlled trials, CAMELIA and STRIDE, the question on the optimal time to initiate ART during TB therapy has been addressed. Findings from these trials now serve as the basis for the Panel's recommendations on when to start ART in patients with active TB.

In the final analysis of the SAPiT trial, there were no differences in rates of AIDS or death between the 2 integrated arms of the study (patients who started ART within 4 weeks after initiating TB treatment vs. those who started ART at 8–12 weeks [i.e., within 4 weeks after completing the intensive phase of TB treatment]).

However, in patients with baseline CD4 counts <50 cells/mm^3 (17% of the study population), the rate of AIDS or death was lower in the earlier therapy group than in the later therapy group (8.5 vs. 26.3 cases per 100 person-years, a strong trend favoring the earlier treatment arm, $P = 0.06$). For all patients, regardless of CD4 cell count, earlier therapy was associated with a higher incidence of IRIS and of adverse events that required a switch in ARV drugs than later therapy. Two deaths were attributed to IRIS.[6]

In the CAMELIA study, which was conducted in Cambodia[7], patients who had CD4 counts <200 cells/mm^3 were randomized to initiate ART at 2 weeks or 8 weeks after initiation of TB treatment. Study participants had advanced HIV disease, with a median entry CD4 count of 25 cells/mm^3; low BMIs (median = 16.8 kg/m^2), Karnofsky scores (87% <70), and hemoglobin levels (median = 8.7 g/dl); and high rates of disseminated TB disease. Compared with therapy initiated at 8 weeks, ART initiated at 2 weeks resulted in a 38% reduction in mortality ($P = 0.006$). A significant reduction in mortality was seen in patients with CD4 counts ≤50 cells/mm^3 and in patients with CD4 counts 51 to 200 cells/mm^3. Overall, 6 deaths associated with TB-IRIS were reported.

The ACTG 5221 (STRIDE) trial, a multinational study conducted at 28 sites, randomized ART-naive patients with confirmed or probable TB and CD4 counts <250 cells/mm^3 to earlier (<2 weeks) or later (8–12 weeks) ART.[8] At study entry, the participants' median CD4 count was 77 cells/mm^3. The rates of mortality and AIDS diagnoses were not different between the earlier and later arms, although higher rates of IRIS were seen in the earlier arm. However, a significant reduction in AIDS or death was seen in the subset of patients with CD4 counts <50 cells/mm^3 who were randomized to the earlier ART arm ($P = 0.02$).

In each of these 3 studies, IRIS was more common in patients initiating ART earlier than in patients starting ART later, but the syndrome was infrequently associated with mortality. Collectively these 3 trials demonstrate that in patients with active TB and with very low CD4 cell counts (i.e., <50 cells/mm^3), early initiation of ART can reduce mortality and AIDS progression, albeit at the risk of increased IRIS. These findings strongly favor initiation of ART within the first 2 weeks of TB treatment in patients with CD4 cell counts <50 cells/mm^3 **(AI)**.

The question of when to start ART in patients with CD4 counts ≥50 cells/mm^3 is also informed by these studies. The STRIDE and SAPiT studies—in which the patients with CD4 cell counts ≥50 cells/mm^3 were relatively healthy and with reasonable Karnofsky scores (note the SAPiT study excluded patients with Karnofsky scores <70) and BMIs—demonstrated that ART initiation in these patients can be delayed until 8 to 12 weeks after initiation of TB therapy (**AI** for CD4 counts 51–500 cells/mm^3 and **BIII** for CD4 counts >500 cells/mm^3).

However, the CAMELIA study, which included more patients who were severely ill than the STRIDE and SAPiT studies, showed that early initiation of ART improved survival both in patients with CD4 counts ≤50 cells/mm^3 and in patients with CD4 counts from 51 to 200 cells/mm^3. In a multivariate analysis, age >40 years, low BMI (<16), low Karnofsky score (<40), elevated aspartate aminotransferase (AST) level (>1.25 x the upper limit of normal [ULN]), disseminated and MDR TB were independently associated with poor survival; whereas in a univariate analysis, hemoglobin <10g/dl also was associated with poor survival.

Thus, recently published results from the three clinical trials are complementary in defining the need for ART and use of CD4 count and clinical status to inform decisions on the optimal time to initiate ART in patients with HIV and TB disease. Earlier initiation of ART within 2 to 4 weeks of TB treatment should be strongly considered for patients with CD4 cell counts from 50 to 200 cells/mm^3 who have evidence of clinical disease of major severity as indicated by clinical evaluation, low Karnofsky score, low BMI, low hemoglobin, low albumin, or organ system dysfunction **(BI)**. Initiation of ART within 2 to 4 weeks also should be considered for patients with CD4 counts >200 cells/mm^3 who present with evidence of severe disease **(BIII)**.

Of additional importance, each of the above studies demonstrated excellent responses to ART, with 90% and >95% of participants achieving suppressed viremia (HIV RNA <400 copies/mL) at 12 months in the SAPiT

and CAMELIA studies, respectively, and 74% of participants at 2 years in the STRIDE study.

Mortality rates in patients with MDR or XDR TB and HIV coinfection are very high.[9] Retrospective case control studies and case series provide growing evidence of better outcomes associated with receipt of ART in such coinfected patients,[10] but the optimal timing for initiation of ART is unknown. However, given the high rates and rapid mortality, most experts recommend that ART be initiated within 2 to 4 weeks after confirmation of the diagnosis of drug resistance and initiation of second-line TB therapy **(BIII)**.

All HIV-infected pregnant women with active TB should be started on ART as early as feasible, both for maternal health and to prevent perinatal transmission of HIV **(AIII)**. The choice of ART should be based on efficacy and safety in pregnancy and take into account potential drug-drug interactions between ARVs and rifamycins (see Perinatal Guidelines for more detailed discussions).[11]

TB meningitis often is associated with severe complications and high mortality rate. In a randomized study conducted in Vietnam, patients were randomized to immediate ART or to therapy deferred until 2 months after initiation of TB treatment. A higher rate of severe (Grade 4) adverse events was seen in patients who received immediate ART than in those who deferred therapy (80.3% vs. 69.1%, respectively; $P = 0.04$).[12] In this study 59.8% of the immediate ART patients and 55.5% of the delayed ART patients died within 9 months. However, in the United States, where patients may be more closely monitored and treated for severe adverse events such as central nervous system (CNS) IRIS, many experts feel that ART should be initiated as for other HIV/TB-coinfected patients **(CIII)**.

Drug Interaction Considerations

A rifamycin is a crucial component in 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 significant interactions with most ARV agents including all PIs, non-nucleoside reverse transcriptase inhibitors (NNRTIs), maraviroc (MVC), and raltegravir (RAL). Rifampin is a potent enzyme inducer, leading to accelerated drug clearance and significant reduction in ARV drug exposure. Despite these interactions, some observational studies suggest that good virologic, immunologic, and clinical outcomes may be achieved with standard doses of efavirenz (EFV)[13-14] and, to a lesser extent, nevirapine (NVP)[15-16] when combined with rifampin. However, rifampin is not recommended in combination with all PIs and the NNRTIs etravirine (ETR) and rilpivirine (RPV). When rifampin is used with MVC or RAL, increased dosage of the ARV is generally recommended. 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. Tables 14, 15a, 15b, 15d, and 15e 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, clinicians should monitor patients closely to assure good control of both TB and HIV infections. 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.

Rifapentine is a long-acting rifamycin that can be given once weekly with INH for the treatment of active or latent TB infection. Similar to rifampin and rifabutin, rifapentine is also a CYP3A4 inducer. No systematic study has been performed to assess the magnitude of the enzyme induction effect of rifapentine on the metabolism of ARV drugs and other concomitant drugs. Significant enzyme induction can result in reduced ARV drug exposure, which may compromise virologic efficacy. Rifapentine is **not recommended** for treatment of latent or active TB infection in patients receiving ART, unless given in the context of a clinical trial **(AIII)**.

Anti-Tuberculosis/Antiretroviral Drug Toxicities

ARV agents and TB drugs, particularly INH, rifamycin, and pyrazinamide, can cause drug-induced hepatitis. These first-line TB drugs should be used for treatment of active TB disease, even with coadministration of other potentially hepatotoxic drugs or when baseline liver disease is present **(AIII)**. Patients receiving potentially hepatotoxic drugs should be monitored frequently for clinical symptoms and signs of hepatitis and have laboratory monitoring for hepatotoxicity. Peripheral neuropathy can occur with administration of INH, didanosine (ddI), or stavudine (d4T) or may be a manifestation of HIV infection. All patients receiving INH also should receive supplemental pyridoxine to reduce peripheral neuropathy. Patients should be monitored closely for signs of drug-related toxicities and receive alternative ARVs to ddI or d4T.

Immune Reconstitution Inflammatory Syndrome with Tuberculosis and Antiretroviral Agents

IRIS occurs in two forms: unmasking and paradoxical. The mechanism of the syndrome is the same for both forms: restoration of immune competence by administration of ART, resulting in an exuberant host response to TB bacilli and/or antigens. Unmasking IRIS refers to the initial clinical manifestations of active TB that occurs soon after ART is started. Paradoxical IRIS refers to the worsening of TB clinical symptoms after ART is 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 more than 40% of patients starting ART after TB is diagnosed, although the incidence depends on the definition of IRIS and the intensity of monitoring.[17-18]

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.[19-22] Most IRIS in HIV/TB disease occurs within 3 months of the start of TB treatment. Delaying initiation of ART for 2 to 8 weeks may reduce the incidence and severity of IRIS. However, this possible advantage of delayed ART must be weighed against the potential benefit of earlier ART in improving immune function and preventing progression of HIV disease and mortality.

Patients with mild or moderately severe IRIS can be managed symptomatically or treated with nonsteroidal anti-inflammatory agents. Patients with more severe IRIS can be treated successfully with corticosteroids. A recent randomized, placebo-controlled trial demonstrated benefit of corticosteroids in the management of IRIS symptoms (as measured by decreasing days of hospitalization and Karnofsky performance score) without adverse consequences.[23] 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 Antiretroviral Therapy: Conversion to Positive Tuberculin Skin Test and Interferon-Gamma Release Assay

Immune reconstitution with ART may result in unmasking LTBI (i.e., conversion of a previously negative tuberculin skin test [TST] to a positive TST or a positive interferon-gamma [IFN-γ] release assay [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.[24] 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 **(BII)**.[25]

Caring for Patients with HIV and Tuberculosis

Close collaboration among clinicians, health care institutions, and public health programs involved in the diagnosis and treatment of HIV-infected patients with active TB disease is necessary in order to integrate care and improve medication adherence and TB treatment completion rates, reduce drug toxicities, and maximize HIV outcomes. HIV-infected patients with active TB disease should receive treatment support, including adherence counseling and DOT, corresponding to their needs **(AII)**. ART simplification or use of coformulated fixed-dose combinations also may help to improve drug adherence.

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Limitations to Treatment Safety and Efficacy

Adherence to Antiretroviral Therapy (Last updated March 27, 2012; last reviewed March 27, 2012)

Adherence to antiretroviral therapy (ART) has been correlated strongly with HIV viral suppression, reduced rates of resistance, an increase in survival, and improved quality of life.[1-2] In the past few years, ART regimens have been greatly simplified. Although newer regimens include more fixed-dose combination products and offer once-daily dosing, adherence remains a challenge. Because HIV treatment is a lifelong endeavor, and because many patients will initiate therapy when they are generally in good health, feel well, and demonstrate no obvious signs or symptoms of HIV disease, adherence poses a special challenge and requires commitment from the patient and the health care team.

Adherence remains a challenging and complicated topic. This section provides clinicians with some guidance in their approaches to assist patients in maintaining adherence.

Factors Associated with Nonadherence

Adherence to ART can be influenced by characteristics of the patient, the regimen, the clinical setting, and the provider/patient relationship.[3] To assure adherence, it is critical that the patient receive and understand information about HIV disease, the goal of therapy, and the specific regimen prescribed. A number of factors have been associated with poor adherence, including the following:

- low levels of health literacy[4] or numeracy (ability to understand numerical-related health information);[5]
- certain age-related challenges (e.g., polypharmacy, vision loss, cognitive impairment)[6];
- younger age;
- psychosocial issues (e.g., depression, homelessness, low social support, stressful life events, or psychosis);[7]
- nondisclosure of HIV serostatus[8]
- neurocognitive issues (e.g., cognitive impairment, dementia)
- active (but not history of) substance abuse, particularly for patients who have experienced recent relapse;
- stigma[9];
- difficulty with taking medication (e.g., trouble swallowing pills, daily schedule issues);
- complex regimens (e.g., high pill burden, high-frequency dosing, food requirements);
- adverse drug effects;
- nonadherence to clinic appointments[10]
- cost and insurance coverage issues; and
- treatment fatigue.

Adherence studies conducted in the early era of combination ART with unboosted protease inhibitors (PIs) found that virologic failure is much less likely to occur in patients who adhere to more than 95% of their prescribed doses than in those who are less adherent.[11] More recent adherence studies were conducted using boosted PIs and non-nucleoside reverse transcriptase inhibitors (NNRTIs). These studies suggest that the longer half-lives of boosted PIs and efavirenz may make the drugs more forgiving of lapses in adherence.[12-13] Nonetheless, clinicians should encourage patients to adhere as closely as possible to the prescribed doses and schedules for all ART 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%,[14] this measure still is associated with viral load responses.[15] 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 missed 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 also may 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 about the frequency of missed doses or to estimate the percentage of doses taken during the previous 3 or 7 days.[16] Pharmacy records and pill counts also can be used in addition to simply asking the patient about adherence.[17] 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

Before writing the first prescriptions, the clinician should assess the patient's readiness to take medication, including information such as factors that may limit adherence (psychiatric illness, active drug use, etc.) and make additional support necessary; the patient's understanding of the disease and the regimen; and the patient's social support, housing, work and home situation, and daily schedules.

During the past several years, a number of advances have simplified many regimens dramatically, particularly those for treatment-naive patients. Prescribing regimens that are simple to take, have a low pill burden and low-frequency dosing, have no food requirements, and have low incidence and severity of adverse effects will facilitate adherence.[18] The Panel considered both regimen simplicity and effectiveness when making current treatment recommendations (see What to Start).

Patients should understand that their first regimen usually offers the best chance for a simple regimen that affords long-term treatment success and prevention of drug resistance. Given that effective response to ART is dependent on good adherence, clinicians should identify barriers to adherence such as a patient's schedule, competing psychosocial needs, learning needs, and literacy level before treatment is initiated. As appropriate, resources and strategies that will help the patient to achieve and maintain good adherence should be employed.

Individualizing treatment with involvement of the patient in decision making is the cornerstone of any treatment plan.[17] The first principle of successful treatment is negotiation of an understandable plan to which the patient can commit.[19-20] Establishing a trusting relationship over time and maintaining good communication will help to improve adherence and long-term outcomes.

An increasing number of interventions have demonstrated efficacy in improving adherence to ART. A meta-analysis of 19 randomized controlled trials of ART 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 as participants in comparison conditions.[21]

In a more recent synthesis, CDC provides new guidance to assist providers in selecting from among the many possible adherence interventions. According to efficacy criteria described by the CDC HIV/AIDS Prevention Research Synthesis (PRS) project, CDC has identified a subset of best-evidence medication adherence interventions. In December 2010, CDC published a new online Medication Adherence chapter of

the Compendium of Evidence-Based HIV Behavioral Interventions that includes eight medication adherence behavioral interventions identified from the scientific literature published or in press from January 1996 through December 2009. For descriptions of the interventions, see: http://www.cdc.gov/hiv/topics/research/prs/ma-good-evidence-interventions.htm.[22] Since these reviews have been conducted, additional evidence also has accumulated regarding the efficacy and benefits of motivational interviewing.[23]

In summary, effective adherence interventions vary in their modality and duration, providing clinics, providers, and patients with options to suit a range of needs and settings. Some effective interventions identified include multiple nurse home visits, five-session group intervention, pager messaging, and couples-based interventions. Substance abuse therapy and strengthening social support also can improve adherence. All health care team members, including nurses, nurse practitioners, pharmacists, medication managers, and social workers, have integral roles in successful adherence programs.[24-27] Directly observed therapy (DOT) has been shown to be effective in provision of ART to active drug users.[28] However, the benefits cannot be sustained after transitioning the drug users out of the methadone clinics and halting the provision of ART by DOT.[29]

To routinely determine whether such additional adherence intervention is warranted, assessments should be done at each clinical encounter and should be the responsibility of the entire health care team. Routine monitoring of HIV viral load and pharmacy records are useful determinants for the need of intensified efforts.

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 the treatment setting, resources available, and patient population. The complexity and the importance of adherence encourage clinicians to continue to seek novel, patient-centered ways to improve adherence and to tailor adherence interventions. Early detection of nonadherence and prompt intervention can reduce greatly 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 Provide an accessible, trusting health care team	• Nurses, social workers, pharmacists, and medications managers
Establish a trusting relationship with the patient	
Establish patient readiness to start ART	
Assess and simplify the regimen, if possible	
Identify potential barriers to adherence before starting ART	• Psychosocial issues • Active substance abuse or at high risk of relapse • Low literacy • Low numeracy • Busy daily schedule and/or travel away from home • Nondisclosure of HIV diagnosis • Skepticism about ART • Lack of prescription drug coverage • Lack of continuous access to medications
Provide resources for the patient	• Referrals for mental health and/or substance abuse treatment • Resources to obtain prescription drug coverage • Pillboxes
Involve the patient in ARV regimen selection	• For each option, review regimen potency, 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 that the patient can complete in the waiting room • Ensure that other members of the health care team also assess adherence • 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) • Failure to take the right dose(s) at the right time(s) • Nonadherence to food requirements
Identify reasons for nonadherence	• Adverse effects from medications • Complexity of regimen (pill burden, dosing frequency, etc.) • Difficulty swallowing large pills • Forgetfulness • Failure to understand dosing instructions • Inadequate understanding of drug resistance and its relationship to adherence • Pill fatigue • Other potential barriers
If resources allow, select from among available effective interventions	• See http://www.cdc.gov/hiv/topics/research/prs/ma-good-evidence-interventions.htm

Key to Abbreviations: ART = antiretroviral therapy; ARV = antiretroviral

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Adverse Effects of Antiretroviral Agents (Last updated March 27, 2012; last reviewed March 27, 2012)

Adverse effects have been reported with use of 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)-naive patients enrolled in randomized trials appear to be declining with use of newer ARV regimens and are generally now occurring in less than 10% of study participants. 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, compared with men, women (ART-naive women with CD4 counts >250 cells/mm^3) seem to have a higher propensity of developing Stevens-Johnson syndrome, rashes, and hepatotoxicity from nevirapine (NVP)[3-5] and have 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 drug toxicities (e.g., interactions that result from concomitant use of statins with protease inhibitors [PIs]); or genetic factors predisposing patients to abacavir (ABC) hypersensitivity reaction (HSR).[13-14]

Although the therapeutic goals of ART include achieving and maintaining viral suppression and improving immune function, an overarching goal should be to select a regimen that is not 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 prior history of drug intolerances.

In addition, it should be appreciated that in general the overall benefits of HIV therapy outweigh its risks and that some conditions such as anemia, cardiovascular disease (CVD), and renal impairment may be more likely in the absence of ART.[15-16]

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.[17-20]

Table 13. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects
(See Appendix B for additional information listed by drug.) (Page 1 of 4)

Adverse Effects	NRTIs	NNRTIs	PIs	INSTI	EI
Bleeding events			**All PIs:** ↑ spontaneous bleeding, hematuria in patients with hemophilia **TPV:** Reports of intracranial hemorrhage. Risks include CNS lesions, trauma, surgery, hypertension, alcohol abuse, coagulopathy, and concomitant use of anti-coagulant or anti-platelet agents including vitamin E		
Bone marrow suppression	**ZDV:** Anemia, neutropenia				
Cardiovascular disease (CVD)	**ABC and ddI:** Associated with MI in some but not all cohort studies. Absolute risk greatest among patients with traditional CVD risk factors.		**PIs:** Associated with MI and stroke in some cohort studies. Data on newer PIs (ATV, DRV, and TPV) are limited. **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. **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. Symptoms usually 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 increased plasma EFV concentrations due to genetic factors or increased absorption with food.			

Table 13. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects
(See Appendix B for additional information listed by drug.) (Page 2 of 4)

Adverse Effects	NRTIs	NNRTIs	PIs	INSTI	EI
Diabetes mellitus (DM)/insulin resistance	**ZDV, d4T, and ddI**		• Reported for some **PIs (IDV, LPV/r)**, but not all PIs studied • **ATV +/- RTV** not found to alter insulin sensitivity of HIV-uninfected individuals in short-term studies.		
Dyslipidemia	**d4T > ZDV > ABC:** • ↑ LDL and TG	**EFV** • ↑ TG • ↑ LDL • ↑ HDL	**↑ LDL, ↑ TG, ↑ HDL: all RTV-boosted PIs** **↑ TG:** **LPV/r = FPV/r and LPV/r > DRV/r and ATV/r**		
Gastrointestinal (GI) effects	**Nausea and vomiting:** **ddI and ZDV > other NRTIs** **Pancreatitis: ddI**		GI intolerance (diarrhea, nausea, vomiting) **Diarrhea:** common with **NFV**. **LPV/r** > **DRV/r** and **ATV/r**		
Hepatic effects	Reported for most **NRTIs** **ddI:** Prolonged exposure linked to noncirrhotic portal hypertension, some cases with esophageal varicees **Steatosis:** Most commonly seen with **ZDV**, **d4T**, or **ddI** **Flares:** HIV/HBV-coinfected patients may develop severe hepatic flare when **TDF**, **3TC**, and **FTC** are withdrawn or when HBV resistance develops.	**NVP > other NNRTIs** **NVP:** • Severe hepatic toxicity with **NVP** is often associated with skin rash or symptoms of hypersensitivity. • For ARV-naive 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. Overall risk is higher for women than men. • Risk is greatest in the first few months of treatment. • 2-week dose escalation of **NVP** reduces risk of rash and possibly hepatotoxicity if related to hypersensitivity. • **NVP** is contraindicated in patients with Child-Pugh classification B or C. • Liver failure observed in HIV-uninfected individuals receiving **NVP** for post-exposure prophylaxis. **NVP** should never be used for this indication.	**All PIs:** Drug-induced hepatitis and hepatic decompensation (and rare cases of fatalities) have been reported with all PIs to varying degrees. The frequency of hepatic events is higher with TPV/r than with other PIs. **IDV, ATV:** Jaundice due to indirect hyperbilirubinemia **TPV/r:** Contraindicated in patients with moderate to severe hepatic insufficiency (Child-Pugh classification B or C)		**MVC:** Hepatotoxicity with or without rash or HSRs reported

Table 13. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects
(See Appendix B for additional information listed by drug.) (Page 3 of 4)

Adverse Effects	NRTIs	NNRTIs	PIs	INSTI	EI
Hypersensitivity reaction (HSR) (excluding rash alone or Stevens Johnson syndrome[SJS])	**ABC:** • HLA-B*5701 screening should be performed prior to initiation of **ABC** and **ABC** should not be started if HLA-B*5701 is positive. • Symptoms of HSR include (in descending frequency): fever, skin rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, and respiratory symptoms. • Symptoms worsen with continuation of **ABC** • Median onset of reactions is 9 days; ~ 90% of reactions within first 6 weeks • Onset of rechallenge reactions is within hours of rechallenge dose • Patients, regardless of HLA-B*5701 status, should not be rechallenged with **ABC** if HSR suspected.	**NVP:** • 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. • In ARV-naive 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. Overall, risk is higher for women than men. • 2-week dose escalation of **NVP** reduces risk.		**RAL**	**MVC:** reported as part of a syndrome related to hepatotoxicity
Lactic acidosis	**NRTIs**, especially **d4T**, **ZDV**, and **ddI** • 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. • Mortality up to 50% in some case series, especially in patients with serum lactate >10 mmol/L • Females and obese patients at increased risk. **Laboratory findings:** • ↑ lactate (often >5 mmol/L), anion gap, AST, ALT, PT, bilirubin • ↑ amylase and lipase in patients with pancreatitis • ↓ arterial pH, serum bicarbonate, serum albumin				

Table 13. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects
(See Appendix B for additional information listed by drug.) (Page 4 of 4)

Adverse Effects	NRTIs	NNRTIs	PIs	INSTI	EI
Lipodystrophy	**Lipoatrophy: Thymidine analogs** (**d4T** > **ZDV**). May be more likely when combined with **EFV** than with a ritonavir-boosted **PI**.	**Lipohypertophy:** Trunk fat increase observed with **EFV**-, **PI**-, and **RAL**-containing regimens; however, causal relationship has not been established.			
Myopathy/elevated creatine phosphokinase (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 Concurrent use of **PI** may increase risk.		**IDV:** ↑ serum creatinine, pyuria; hydronephrosis or renal atrophy **IDV, ATV:** Stone, crystal formation; adequate hydration may reduce risk.		
Osteopenia/ osteoporosis	**TDF:** Associated with greater loss of BMD than 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)				
Rash		**All NNRTIs**	**ATV, DRV, FPV**	**RAL:** Uncommon	**MVC**
Stevens-Johnson syndrome (SJS)/ toxic epidermal necrosis (TEN)	**ddI, ZDV:** Reported cases	**NVP > DLV, EFV, ETR, RPV**	**FPV, DRV, IDV, LPV/r, ATV:** Reported cases	**RAL**	

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

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Drug Interactions (Last updated March 29, 2012; last reviewed March 27, 2012)

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 (t½) 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 (IC50) 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 Protease Inhibitors, Non-Nucleoside Reverse Transcriptase Inhibitors, or CCR5 Antagonist (page 1 of 2)

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 PK interaction data.

Drug Categories										
Antiretroviral Agents[a,b]	**Cardiac Agents**	**Lipid-Lowering Agents**	**Antimycobacterials**	**Gastrointestinal Drugs**	**Neuroleptics**	**Psychotropics**	**Ergot Derivatives (vasoconstrictors)**	**Herbs**	**Antiretroviral Agents**	**Others**
ATV +/– RTV	none	lovastatin simvastatin	rifampin rifapentine[c]	cisapride[e]	pimozide	midazolam[f] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	ETR NVP	alfuzosin irinotecan salmeterol sildenafil for PAH
DRV/r	none	lovastatin simvastatin	rifampin rifapentine[c]	cisapride[e]	pimozide	midazolam[f] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	none	alfuzosin salmeterol sildenafil for PAH
FPV +/– RTV	flecainide propafenone	lovastatin simvastatin	rifampin rifapentine[c]	cisapride[e]	pimozide	midazolam[f] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	ETR	alfuzosin salmeterol sildenafil for PAH
LPV/r	none	lovastatin simvastatin	rifampin[d] rifapentine[c]	cisapride[e]	pimozide	midazolam[f] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	none	alfuzosin salmeterol sildenafil for PAH
SQV/r	amiodarone dofetilide flecainide lidocaine propafenone quinidine	lovastatin simvastatin	rifampin[d] rifapentine[c]	cisapride[e]	pimozide	midazolam[f] triazolam trazodone	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort garlic supplements	none	alfuzosin salmeterol sildenafil for PAH
TPV/r	amiodarone flecainide propafenone quinidine	lovastatin simvastatin	rifampin rifapentine[c]	cisapride[e]	pimozide	midazolam[f] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	ETR	alfuzosin salmeterol sildenafil for PAH
EFV	none	none	rifapentine[c]	cisapride[e]	pimozide	midazolam[f] triazolam	dihydroergotamine ergonovine ergotamine methylergonovine	St. John's wort	other NNRTIs	none
ETR	none	none	rifampin rifapentine[c]	none	none	none	none	St John's wort	unboosted PIs ATV/r, FPV/r, or TPV/r other NNRTIs	carbamazepine phenobarbital phenytoin clopidogrel
NVP	none	none	rifapentine[c]	none	none	none	none	St. John's wort	ATV +/– RTV other NNRTIs	ketoconazole
RPV	none	none	rifabutin rifampin rifapentine[c]	proton pump inhibitors	none	none	none	St. John's wort	other NNRTIs	carbamazepine oxcarbazepine phenobarbital phenytoin
MVC	none	none	rifapentine[c]	none	none	none	none	St. John's wort	none	none

Table 14. Drugs That Should Not Be Used With Protease Inhibitors, Non-Nucleoside Reverse Transcriptase Inhibitors, or CCR5 Antagonist (page 2 of 2)

[a] DLV, IDV, NFV, and RTV (as sole PI) are not included in this table. Refer to the FDA package insert for information regarding DLV-, IDV-, NFV-, and RTV (as sole PI)-related drug interactions.

[b] Certain listed drugs are contraindicated on the basis of 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.

[c] HIV-infected patients treated with rifapentine have a higher rate of TB relapse than those treated with other rifamycin-based regimens. Therefore an alternative agent to rifapentine is recommended.

[d] 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.

[e] The manufacturer of cisapride has a limited-access protocol for patients who meet specific clinical eligibility criteria.

[f] 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: Fluvastatin, pitavastatin, and pravastatin 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

Key to Abbreviations: ATV +/- RTV = atazanavir +/- ritonavir, ATV/r = atazanavir/ritonavir, CYP = cytochrome P, DLV = delavirdine, DRV/r = darunavir/ritonavir, EFV = efavirenz, ETR = etravirine, FDA = Food and Drug Administration, FPV +/- RTV = fosamprenavir +/- ritonavir, FPV/r = fosamprenavir/ritonavir, 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, PK = pharmacokinetic, RPV = rilpivirine, RTV = ritonavir, SQV = saquinavir, SQV/r = saquinavir/ritonavir, TB = tuberculosis, TPV/r = tipranavir/ritonavir

Table 15a. Drug Interactions between Protease Inhibitors and Other Drugs (Page 1 of 11)*

This table provides information relating to PK 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.

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

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Antacids	ATV +/– RTV	When given simultaneously, ↓ ATV expected	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.
H2 Receptor Antagonists	**RTV-boosted PIs**		
	ATV/r	↓ ATV	H2 receptor antagonist dose should not exceed a dose equivalent to famotidine 40 mg BID in ART-naive patients or 20 mg BID in ART-experienced patients. Give ATV 300 mg + RTV 100 mg simultaneously with and/or ≥10 hours after the H2 receptor antagonist. If using TDF and H2 receptor antagonist in ART-experienced patients, use ATV 400 mg + RTV 100 mg.
	DRV/r, LPV/r	No significant effect	No dosage adjustment necessary.
	PIs without RTV		
	ATV	↓ ATV	H2 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-naive patients. Give ATV at least 2 hours before and at least 10 hours after the H2 receptor antagonist.
	FPV	APV AUC ↓ 30%; no significant change in APV C_{min}	Give FPV at least 2 hours before H2 receptor antagonist if concomitant use is necessary. Consider boosting with RTV.

Table 15a. Drug Interactions between Protease Inhibitors and Other Drugs (Page 2 of 11)*

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
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-naive patients. PPIs should be administered at least 12 hours before ATV/r. **PPIs are not recommended in PI-experienced patients.**
	DRV/r, TPV/r	↓ omeprazole PI: no significant effect	May need to increase omeprazole dose when using TPV/r.
	FPV +/- RTV, LPV/r	No significant effect	No dosage adjustment necessary.
	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 DRV/r ↓ S-warfarin AUC 21%	Monitor INR closely when stopping or starting PI and adjust warfarin dose accordingly.
Anticonvulsants			
Carbamazepine	**RTV-boosted PIs**		
	ATV/r, FPV/r, LPV/r, SQV/r, TPV/r	↑ carbamazepine possible TPV/r ↑ carbamazepine AUC 26% May ↓ PI levels substantially	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. **Do not coadminister with LPV/r once daily.**
	DRV/r	carbamazepine AUC ↑ 45% DRV: no significant change	Monitor anticonvulsant level and adjust dose accordingly.
	PIs without RTV		
	ATV, FPV	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% LPV: no significant change	Titrate lamotrigine dose to effect or consider alternative anticonvulsant. 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.**

Table 15a. Drug Interactions between Protease Inhibitors and Other Drugs (Page 3 of 11)*

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Phenytoin	**RTV-boosted PIs**		
	ATV/r, DRV/r, SQV/r, TPV/r	↓ phenytoin possible ↓ PI possible	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response.
	FPV/r	phenytoin AUC ↓ 22% APV AUC ↑ 20%	Monitor phenytoin level and adjust dose accordingly. No change in FPV/r dose recommended.
	LPV/r	phenytoin AUC ↓ 31% LPV/r AUC ↓ 33%	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. **Do not coadminister with LPV/r once daily.**
	PIs without RTV		
	ATV, FPV	May ↓ PI levels substantially	Consider alternative anticonvulsant, RTV boosting for ATV and FPV, and/or monitoring PI level. Monitor anticonvulsant level and virologic response.
Valproic Acid (VPA)	LPV/r	↓VPA possible LPV AUC ↑ 75%	Monitor VPA levels and virologic 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 ↓ 55%	
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) ↑ 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.

Table 15a. Drug Interactions between Protease Inhibitors and Other Drugs (Page 4 of 11)*

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	No dosage adjustment necessary.
	SQV/r	No data with RTV boosting SQV (1200 mg TID) AUC ↑ 50%	No dosage adjustment necessary.
	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 ↑ PI possible	Consider monitoring itraconazole level to guide dosage adjustments. High doses (>200 mg/day) are not recommended unless dose is guided by itraconazole 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 ↑ 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% RTV 100 mg BID ↓ voriconazole AUC 39%	**Do not coadminister** voriconazole and RTV unless benefit outweighs risk. If administered, consider monitoring voriconazole level and adjust dose accordingly.
	PIs without RTV		
	ATV, FPV	↑ voriconazole possible ↑ PI possible	Monitor for toxicities.

Table 15a. Drug Interactions between Protease Inhibitors and Other Drugs (Page 5 of 11)*

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Anti-mycobacterials			
Clarithromycin	ATV +/– RTV	clarithromycin AUC ↑ 94%	May cause QTc prolongation. Reduce clarithromycin dose by 50%. Consider alternative therapy (e.g., azithromycin).
	DRV/r, FPV/r, LPV/r, SQV/r, TPV/r	DRV/r ↑ clarithromycin AUC 57% FPV/r ↑ clarithromycin possible LPV/r ↑ clarithromycin expected RTV 500 mg BID ↑ clarithromycin 77% SQV unboosted ↑ clarithromycin 45% TPV/r ↑ clarithromycin 19% clarithromycin ↑ unboosted SQV 177% clarithromycin ↑ TPV 66%	Monitor for clarithromycin-related toxicities or consider alternative macrolide (e.g., azithromycin). Reduce clarithromycin dose by 50% in patients with CrCl 30–60 mL/min. Reduce clarithromycin dose by 75% in patients with CrCl <30 mL/min.
	FPV	APV AUC ↑ 18%	No dosage adjustment necessary.
Rifabutin	**RTV-boosted PIs**		
	ATV/r	rifabutin (150 mg once daily) AUC ↑ 110% and metabolite AUC ↑ 2101% compared with rifabutin (300 mg daily) administered alone	Rifabutin 150 mg once daily or 300 mg three times a week. Monitor for antimycobacterial activity and consider therapeutic drug monitoring. PK data reported in this table are results from healthy volunteer studies. Lower rifabutin exposure has been reported in HIV-infected patients than in the healthy study participants.
	DRV/r	rifabutin (150 mg every other day) AUC not significantly changed and metabolite AUC ↑ 881% compared with rifabutin (300 mg once daily) administered alone	
	FPV/r	rifabutin (150 mg every other day) and metabolite AUC ↑ 64% compared with rifabutin (300 mg once daily) administered alone	
	LPV/r	rifabutin (150 mg once daily) and metabolite AUC ↑ 473% compared with rifabutin (300 mg daily) administered alone	
	SQV/r	↑ rifabutin with unboosted SQV	
	TPV/r	rifabutin (150 mg x 1 dose) and metabolite AUC ↑ 333%	
	PIs without RTV		
	ATV, FPV	↑ rifabutin AUC expected	Rifabutin 150 mg daily or 300 mg three times a week

Table 15a. Drug Interactions between Protease Inhibitors and Other Drugs (Page 6 of 11)*

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Rifampin	All PIs	↓ PI >75% approximately	**Do not coadminister rifampin and PIs.** Additional RTV does not overcome this interaction and increases hepatotoxicity.
Rifapentine	All PIs	↓ PI expected	**Do not coadminister rifapentine and PIs.**
Benzodiazepines			
Alprazolam **Diazepam**	All PIs	↑ benzodiazepine possible RTV (200 mg BID for 2 days) ↑ alprazolam half-life 222% and AUC 248%	Consider alternative benzodiazepines such as lorazepam, oxazepam, or temazepam.
Lorazepam **Oxazepam** **Temazepam**	All PIs	No data	These benzodiazepines metabolized via non-CYP450 pathways; less interaction potential compared with other benzodiazepines.
Midazolam	All PIs	↑ midazolam expected SQV/r ↑ midazolam (oral) AUC 1144% and C_{max} 327%	**Do not coadminister oral midazolam and PIs.** Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation.
Triazolam	All PIs	↑ triazolam expected RTV (200 mg BID) ↑ triazolam half-life 1200% and AUC 2000%	**Do not coadminister triazolam and PIs.**
Cardiac Medications			
Bosentan	All PIs	LPV/r ↑ bosentan 48-fold (Day 4) and 5-fold (Day 10) ↓ ATV expected	**Do not coadminister bosentan and ATV without RTV.** In patients on a PI (other than unboosted ATV) >10 days: start bosentan at 62.5 mg once daily or every other day. In patients on bosentan who require a PI (other than unboosted ATV): stop bosentan >36 hours before PI initiation and restart 10 days after PI initiation at 62.5 mg once daily or every other day.
Digoxin	RTV, SQV/r	RTV (200 mg BID) ↑ digoxin AUC 29% and half-life 43% 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 CCB 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.

Table 15a. Drug Interactions between Protease Inhibitors and Other Drugs (Page 7 of 11)*

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
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 benefits of inhaled fluticasone outweigh the risks of systemic corticosteroid adverse effects.**
Prednisone	LPV/r	↑ prednisolone AUC 31%	No dosage adjustment necessary.
Hepatitis C NS3/4A Protease Inhibitors			
Boceprevir	ATV/r	ATV AUC ↓ 35%, C_{min} ↓ 49% RTV AUC ↓ 36% boceprevir AUC ↔	**Coadministration is not recommended.**
	DRV/r	DRV AUC ↓ 44%, C_{min} ↓ 59% RTV AUC ↓ 26% boceprevir AUC ↓ 29%, C_{min} ↓ 35%	**Coadministration is not recommended.**
	LPV/r	LPV AUC ↓ 34%, C_{min} ↓ 43% RTV AUC ↓ 23% boceprevir AUC ↓ 44%, C_{min} ↓ 35%	**Coadministration is not recommended.**
Telaprevir	ATV/r	telaprevir AUC ↓ 20%	No dose adjustment necessary.
	DRV/r	telaprevir AUC ↓ 35% DRV AUC ↓ 40%	**Coadministration is not recommended.**
	FPV/r	telaprevir AUC ↓ 32% APV AUC ↓ 47%	**Coadministration is not recommended.**
	LPV/r	telaprevir AUC ↓ 54% LPV: no significant change	**Coadministration is not recommended.**
Herbal Products			
St. John's Wort	All PIs	↓ PI expected	**Do not coadminister.**
Hormonal Contraceptives			
Hormonal Contraceptives	**RTV-boosted PIs**		
	ATV/r	ethinyl estradiol AUC ↓ 19% and C_{min} ↓ 37% norgestimate ↑ 85%	Oral contraceptive should contain at least 35 mcg of ethinyl estradiol. Oral contraceptives containing progestins other than norethindrone or norgestimate have not been studied.[a]
	DRV/r	ethinyl estradiol AUC ↓ 44% norethindrone AUC ↓ 14%	Use alternative or additional contraceptive method.

Table 15a. Drug Interactions between Protease Inhibitors and Other Drugs (Page 8 of 11)*

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hormonal Contraceptives	FPV/r	ethinyl estradiol AUC ↓ 37% norethindrone AUC ↓ 34%	Use alternative or additional contraceptive method.
	LPV/r	ethinyl estradiol AUC ↓ 42% norethindrone AUC ↓ 17%	Use alternative or additional contraceptive method.
	SQV/r	↓ ethinyl estradiol	Use alternative or additional contraceptive method.
	TPV/r	ethinyl estradiol AUC ↓ 48% norethindrone: no significant change	Use alternative or additional contraceptive method.
	PIs without RTV		
	ATV	ethinyl estradiol AUC ↑ 48% norethindrone AUC ↑ 110%	Use oral contraceptive that contains no more than 30 mcg of ethinyl estradiol or use alternative contraceptive method. Oral contraceptives containing less than 25 mcg of ethinyl estradiol or progestins other than norethindrone or norgestimate have not been studied.[b]
	FPV	With APV: ↑ ethinyl estradiol and ↑ norethindrone C_{min} ; APV C_{min} ↓ 20%	Use alternative method.
HMG-CoA Reductase Inhibitors			
Atorvastatin	ATV +/- RTV	↑ atorvastatin possible	Titrate atorvastatin dose carefully and use lowest dose necessary.
	DRV/r FPV +/- RTV SQV/r	DRV/r + atorvastatin 10 mg similar to atorvastatin 40 mg administered alone; FPV +/– RTV ↑ atorvastatin AUC 130%–153%; SQV/r ↑ atorvastatin AUC 79%	Titrate atorvastatin dose carefully and use the lowest necessary dose. Do not exceed 20 mg atorvastatin daily.
	LPV/r	LPV/r ↑ atorvastatin AUC 488%	Use with caution and use the lowest atorvastatin dose necessary.
	TPV/r	↑ atorvastatin AUC 836%	**Do not coadminister.**
Lovastatin	All PIs	Significant ↑ lovastatin expected	**Contraindicated. Do not coadminister.**
Pitavastatin	All PIs	ATV ↑ pitavastatin AUC 31% and C_{max} ↑ 60% ATV: no significant effect DRV ↓ pitavastatin AUC 26% DRV: no significant effect LPV/r ↓ pitavastatin AUC 20% LPV: no significant effect	No dose adjustment necessary.
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.

Table 15a. Drug Interactions between Protease Inhibitors and Other Drugs (Page 9 of 11)*

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Rosuvastatin	ATV/r, LPV/r	ATV/r ↑ rosuvastatin AUC 213% and C_{max} ↑ 600% LPV/r ↑ rosuvastatin AUC 108% and C_{max} ↑ 366%	Titrate rosuvastatin dose carefully and use the lowest necessary dose. Do not exceed 10 mg rosuvastatin daily.
	DRV/r	rosuvastatin AUC ↑ 48% and C_{max} ↑ 139%	Titrate rosuvastatin dose carefully and use the lowest necessary dose while monitoring for toxicities.
	FPV +/- RTV	No significant effect on rosuvastatin	No dosage adjustment necessary
	SQV/r	No data available	Titrate rosuvastatin dose carefully and use the lowest necessary dose while monitoring for toxicities.
	TPV/r	rosuvastatin AUC ↑ 26% and C_{max} ↑ 123%	No dosage adjustment necessary.
Simvastatin	All PIs	Significant ↑ simvastatin level; SQV/r 400 mg/400 mg BID ↑ simvastatin AUC 3059%	**Contraindicated. Do not coadminister.**
Narcotics/Treatment for Opioid Dependence			
Buprenorphine	ATV	buprenorphine AUC ↑ 93% norbuprenorphine[c] AUC ↑ 76% ↓ ATV possible	**Do not coadminister buprenorphine with unboosted ATV.**
	ATV/r	buprenorphine AUC ↑ 66% norbuprenorphine[c] AUC ↑ 105%	Monitor for sedation. Buprenorphine dose reduction may be necessary.
	DRV/r	buprenorphine: no significant effect norbuprenorphine[c] AUC ↑ 46% and C_{min} ↑ 71%	No dosage adjustment necessary. Clinical monitoring is recommended.
	FPV/r	buprenorphine: no significant effect norbuprenorphine[c] AUC ↓ 15%	No dosage adjustment necessary. Clinical monitoring is recommended.
	LPV/r	No significant effect	No dosage adjustment necessary
	TPV/r	buprenorphine: no significant effect norbuprenorphine[c] AUC, C_{max}, and C_{min} ↓ 80% TPV C_{min} ↓ 19%–40%	Consider monitoring TPV level.

Table 15a. Drug Interactions between Protease Inhibitors and Other Drugs (Page 10 of 11)*

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Methadone	**RTV-boosted PIs**		
	ATV/r, DRV/r, FPV/r, LPV/r, SQV/r, TPV/r	ATV/r, DRV/r, FPV/r ↓ R-methadone[d] AUC 16%–18%; LPV/r ↓ methadone AUC 26%–53%; SQV/r 1000/100 mg BID ↓ R-methadone[d] AUC 19%; TPV/r ↓ R-methadone[d] 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.
	PIs without RTV		
	ATV	No significant effect	No dosage adjustment necessary.
	FPV	No data with unboosted FPV APV ↓ R-methadone[d] C_{min} 21%, AUC no significant change	Monitor and titrate methadone as clinically indicated. The interaction with FPV is presumed to be similar.
Phosphodiesterase Type 5 (PDE5) Inhibitors			
Sildenafil	All PIs	DRV/r + sildenafil 25 mg similar to sildenafil 100 mg alone; RTV 500 mg BID ↑ sildenafil AUC 1000%; SQV unboosted ↑ sildenafil AUC 210%	For treatment of erectile dysfunction Start with sildenafil 25 mg every 48 hours and monitor for adverse effects of sildenafil. For treatment of PAH **Contraindicated**
Tadalafil	All PIs	RTV 200 mg BID ↑ tadalafil AUC 124%; TPV/r (1st dose) ↑ tadalafil AUC 133%; TPV/r steady state: no significant effect	For treatment of erectile dysfunction 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. For treatment of PAH *In patients on a PI >7 days:* Start with tadalafil 20 mg once daily and increase to 40 mg once daily based on tolerability. *In patients on tadalafil who require a PI:* 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. For treatment of benign prostatic hyperplasia Maximum recommended daily dose is 2.5 mg per day
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.

Table 15a. Drug Interactions between Protease Inhibitors and Other Drugs (Page 11 of 11)*

Concomitant Drug	PI	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Miscellaneous Interactions			
Colchicine	All PIs	RTV 100 mg BID ↑ colchicine AUC 296%, C_{max} 184% With all PIs: significant ↑ in colchicine AUC expected	For treatment of gout flares Colchicine 0.6 mg x 1 dose, followed by 0.3 mg 1 hour later. Do not repeat dose for at least 3 days. *With FPV without RTV:* 1.2 mg x 1 dose and no repeat dose for at least 3 days For prophylaxis of gout flares Colchicine 0.3 mg once daily or every other day *With FPV without RTV:* colchicine 0.3 mg BID or 0.6 mg once daily or 0.3 mg once daily For treatment of familial Mediterranean fever Do not exceed colchicine 0.6 mg once daily or 0.3 mg BID. *With FPV without RTV:* Do not exceed 1.2 mg once daily or 0.6 mg BID. **Do not coadminister in patients with hepatic or renal impairment.**
Salmeterol	All PIs	↑ salmeterol possible	**Do not coadminister** because of potential increased risk of salmeterol-associated cardiovascular events, including QT prolongation, palpitations, and sinus tachycardia.
Atovaquone/ proguanil	ATV/r, LPV/r	ATV/r ↓ atovaquone AUC 46% and ↓ proguanil AUC 41% LPV/r ↓ atovaquone AUC 74% and ↓ proguanil AUC 38%	No dosage recommendation. Consider alternative drug for malaria prophylaxis, if possible.

[a] The following products contain at least 35 mcg of ethinyl estradiol combined with norethindrone or norgestimate (generic formulation may also be available): Ovcon 35, 50; Femcon Fe; Brevicon; Modicon; Ortho-Novum 1/35, 10/11, 7/7/7; Norinyl 1/35; Tri-Norinyl; Ortho-Cyclen; Ortho Tri-Cyclen.

[b] The following products contain no more than 30 mcg of ethinyl estradiol combined with norethindrone or norgestimate (generic formulation may also be available): Loestrin 1/20, 1.5/30; Loestrin Fe 1/20, 1.5/30; Loestrin 24 Fe; Ortho Tri-Cyclen Lo.

[c] Norbuprenorphine is an active metabolite of buprenorphine.

[d] R-methadone is the active form of methadone.

Key to Abbreviations: APV = amprenavir, ART = antiretroviral therapy, 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 = darunavir, 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, INR = international normalized ratio, LPV = lopinavir, LPV/r = lopinavir + ritonavir, NFV = nelfinavir, PAH = pulmonary arterial hypertension, PDE5 = phosphodiesterase type 5, PI = protease inhibitor, PK = pharmacokinetic, PPI = proton pump inhibitor, RTV = ritonavir, SQV = saquinavir, SQV/r = saquinavir + ritonavir, TCA = tricyclic antidepressant, TDF = tenofovir, TID = three times a day, TPV = tipranavir, TPV/r = tipranavir + ritonavir, VPA = valproic acid

Table 15b. Drug Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Page 1 of 6)*

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

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

Concomitant Drug Class/Name	NNRTI[a]	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Antacids	RPV	↓ RPV expected when given simultaneously	Give antacids at least 2 hours before or at least 4 hours after RPV.
H2 Receptor Antagonists	RPV	↓ RPV	Give H2 receptor antagonists at least 12 hours before or at least 4 hours after RPV.
Proton Pump Inhibitors (PPI)	RPV	↓ RPV	**Contraindicated. Do not coadminister.**
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 Phenobarbital Phenytoin	EFV	carbamazepine + EFV: carbamazepine AUC ↓ 27% and EFV AUC ↓ 36% phenytoin + EFV: ↓ EFV and ↓ phenytoin possible	Monitor anticonvulsant and EFV levels or, if possible, use alternative anticonvulsant to those listed.
	ETR	↓ anticonvulsant and ETR possible	**Do not coadminister.** Consider alternative anticonvulsant.
	NVP	↓ anticonvulsant and NVP possible	Monitor anticonvulsant and NVP levels and virologic responses or consider alternative anticonvulsant.
	RPV	↓ RPV possible	**Contraindicated. Do not coadminister.** Consider alternative anticonvulsant.
Antidepressants			
Bupropion	EFV	bupropion AUC ↓ 55%	Titrate bupropion dose based on clinical response.
Paroxetine	EFV, ETR	No significant effect	No dosage adjustment necessary.
Sertraline	EFV	sertraline AUC ↓ 39%	Titrate sertraline dose based on clinical response.

Table 15b. Drug Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Page 2 of 6)*

Concomitant Drug Class/Name	NNRTI[a]	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antifungals			
Fluconazole	EFV	No significant effect	No dosage adjustment necessary.
	ETR	ETR AUC ↑ 86%	No dosage adjustment necessary. Use with caution.
	NVP	NVP AUC ↑ 110%	Increased risk of hepatotoxicity possible with this combination. Monitor NVP toxicity or use alternative ARV agent.
	RPV	↑ RPV possible	No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection. (RPV 150 mg/day reduces ketoconazole exposure; no data on interaction with fluconazole.)
Itraconazole	EFV	itraconazole and OH-itraconazole AUC, C_{max}, and C_{min} ↓ 35%–44%	Failure to achieve therapeutic itraconazole concentrations has been reported. Avoid this combination if possible. If coadministered, closely monitor itraconazole concentration and adjust dose accordingly.
	ETR	↓ itraconazole possible ↑ ETR possible	Dose adjustments for itraconazole may be necessary. Monitor itraconazole level and antifungal response.
	NVP	↓ itraconazole possible ↑ NVP possible	Avoid combination if possible. If coadministered, monitor itraconazole concentration and adjust dose accordingly.
	RPV	↑ RPV possible	No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection. (RPV 150 mg/day reduces ketoconazole exposure; no data on interaction with itraconazole.)
Posaconazole	EFV	posaconazole AUC ↓ 50% ↔ EFV	Avoid concomitant use unless the benefit outweighs the risk. If coadministered, monitor posaconazole concentration and adjust dose accordingly.
	ETR	↑ ETR possible	No dosage adjustment necessary.
	RPV	↑ RPV possible	No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection. (RPV 150 mg/day reduces ketoconazole exposure; no data on interaction with posaconazole.)
Voriconazole	EFV	voriconazole AUC ↓ 77% EFV AUC ↑ 44%	**Contraindicated at standard doses.** Dose: voriconazole 400 mg BID, EFV 300 mg daily.
	ETR	voriconazole AUC ↑ 14% ETR AUC ↑ 36%	No dosage adjustment necessary; use with caution. Consider monitoring voriconazole level.
	NVP	↓ voriconazole possible ↑ NVP possible	Monitor for toxicity and antifungal response and/or voriconazole level.
	RPV	↑ RPV possible	No dosage adjustment necessary. Clinically monitor for breakthrough fungal infection. (RPV 150 mg/day reduces ketoconazole exposure; no data on interaction with voriconazole.)
Antimycobacterials			
Clarithromycin	EFV	clarithromycin AUC ↓ 39%	Monitor for effectiveness or consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment.

Table 15b. Drug Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Page 3 of 6)*

Concomitant Drug Class/Name	NNRTI[a]	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Antimycobacterials, cont'd			
Clarithromycin, cont'd	ETR	clarithromycin AUC ↓ 39% ETR AUC ↑ 42%	Consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
	NVP	clarithromycin AUC ↓ 31%	Monitor for effectiveness or use alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
	RPV	↔ clarithromycin expected ↑ RPV possible	Consider alternative macrolide, such as azithromycin, for MAC prophylaxis and treatment.
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% ETR AUC ↓ 37%	**If ETR is used with an RTV-boosted PI, rifabutin should not be coadministered.** Dose: rifabutin 300 mg once daily if ETR is not coadministered with an RTV-boosted PI.
	NVP	rifabutin AUC ↑ 17% and metabolite AUC ↑ 24% NVP C_{min} ↓ 16%	No dosage adjustment necessary. Use with caution.
	RPV	RPV AUC ↓ 46%	**Contraindicated. Do not coadminister.**
Rifampin	EFV	EFV AUC ↓ 26%	Maintain EFV dose at 600 mg once daily and monitor for virologic response. Consider therapeutic drug monitoring. Some clinicians suggest EFV 800 mg dose in patients who weigh more than 60 kg.
	ETR	Significant ↓ ETR possible	**Do not coadminister.**
	NVP	NVP ↓ 20%–58%	**Do not coadminister.**
	RPV	RPV AUC ↓ 80%	**Contraindicated. Do not coadminister.**
Rifapentine	EFV, ETR, NVP, RPV	↓ NNRTI expected	**Do not coadminister.**
Benzodiazepines			
Alprazolam	EFV, ETR, NVP, RPV	No data	Monitor for therapeutic effectiveness of alprazolam.
Diazepam	ETR	↑ diazepam possible	Decreased dose of diazepam may be necessary.
Lorazepam	EFV	lorazepam C_{max} ↑ 16%, AUC ↔	No dosage adjustment necessary.

Table 15b. Drug Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Page 4 of 6)*

Concomitant Drug Class/Name	NNRTI[a]	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Midazolam	EFV	Significant ↑ midazolam expected	**Do not coadminister with oral midazolam.** Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation.
Triazolam	EFV	Significant ↑ triazolam expected	**Do not coadminister.**
Cardiac Medications			
Dihydropyridine calcium channel blockers (CCBs)	EFV, NVP	↓ CCBs possible	Titrate CCB dose based on clinical response.
Diltiazem **Verapamil**	EFV	diltiazem AUC ↓ 69% ↓ verapamil possible	Titrate diltiazem or verapamil dose based on clinical response.
	NVP	↓ diltiazem or verapamil possible	
Corticosteroids			
Dexamethasone	EFV, ETR, NVP	↓ EFV, ETR, NVP possible	Consider alternative corticosteroid for long-term use. If dexamethasone is used with NNRTI, monitor virologic response.
	RPV	Significant ↓ RPV possible	**Contraindicated with more than a single dose of dexamethasone.**
Hepatitis C NS3/4A - Protease Inhibitors			
Boceprevir	EFV	EFV AUC ↑ 20% boceprevir AUC ↓ 19%, C_{min} ↓ 44%	**Coadministration is not recommended.**
Telaprevir	EFV	EFV AUC ↔ telaprevir AUC ↓ 26%, C_{min} ↓ 47% With TDF: EFV AUC ↓ 15%–18%, telaprevir AUC ↓ 18%–20%	Increase telaprevir dose to 1125 mg q8h.
Herbal Products			
St. John's wort	EFV, ETR, NVP, RPV	↓ NNRTI	**Do not coadminister.**

Table 15b. Drug Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Page 5 of 6)*

Concomitant Drug Class/Name	NNRTI[a]	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Hormonal Contraceptives			
Hormonal contraceptives	EFV	ethinyl estradiol ↔ levonorgestrel AUC ↓ 83% norelgestromin AUC ↓ 64% ↓ etonogestrel (implant) possible	Use alternative or additional contraceptive methods. Norelgestromin and levonorgestrel are active metabolites of norgestimate.
	ETR	ethinyl estradiol AUC ↑ 22% norethindrone: no significant effect	No dosage adjustment necessary.
	NVP	ethinyl estradiol AUC ↓ 20% norethindrone AUC ↓ 19%	Use alternative or additional contraceptive methods.
		DMPA: no significant change	No dosage adjustment necessary.
	RPV	ethinyl estradiol AUC ↑ 14% norethindrone: no significant change	No dosage adjustment necessary.
Levonorgestrel (for emergency contraception)	EFV levonorgestr	el AUC ↓ 58%	Effectiveness of emergency postcoital contraception may be diminished.
HMG-CoA Reductase Inhibitors			
Atorvastatin	EFV, ETR	atorvastatin AUC ↓ 32%–43%	Adjust atorvastatin according to lipid responses, not to exceed the maximum recommended dose.
	RPV	Atorvastatin AUC ↔ Atorvastatin metabolites ↑	No dosage adjustment necessary.
Fluvastatin	ETR	↑ fluvastatin possible	Dose adjustments for fluvastatin may be necessary.
Lovastatin **Simvastatin**	EFV	simvastatin AUC ↓ 68%	Adjust simvastatin dose according to lipid responses, not to exceed the maximum recommended dose. If EFV used with RTV-boosted PI, simvastatin and lovastatin should be avoided.
	ETR, NVP	↓ lovastatin possible ↓ simvastatin possible	Adjust lovastatin or simvastatin dose according to lipid responses, not to exceed the maximum recommended dose. If ETR or NVP used with RTV-boosted PI, simvastatin and lovastatin should be avoided.
Pitavastatin	EFV, ETR, NVP, RPV	No data	No dosage recommendation.
Pravastatin **Rosuvastatin**	EFV	pravastatin AUC ↓ 44% rosuvatatin: no data	Adjust statin dose according to lipid responses, not to exceed the maximum recommended dose.
	ETR	No significant effect expected	No dosage adjustment necessary.

Table 15b. Drug Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors and Other Drugs (Page 6 of 6)*

Concomitant Drug Class/Name	NNRTI[a]	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Narcotics/Treatment for Opioid Dependence			
Buprenorphine	EFV	buprenorphine AUC ↓ 50% norbuprenorphine[b] AUC ↓ 71%	No withdrawal symptoms reported. No dosage adjustment recommended, but monitor for withdrawal symptoms.
	ETR	buprenorphine AUC ↓ 25%	No dosage adjustment necessary.
	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 ↓ 37%–51% NVP: no significant effect	Opioid withdrawal common; increased methadone dose often necessary.
	RPV	R-methadone[c] AUC ↓ 16%	No dosage adjustment necessary, but monitor for withdrawal symptoms.
Phosphodiesterase Type 5 (PDE5) Inhibitors			
Sildenafil	ETR	sildenafil AUC ↓ 57%	May need to increase sildenafil dose based on clinical effect.
	RPV	sildenafil ↔	No dosage adjustment necessary.
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% ↓ progaunil AUC 43%	No dosage recommendation. Consider alternative drug for malaria prophylaxis, if possible.

[a] Approved dose for RPV is 25 mg once daily. Most PK interaction studies were performed using 75 to 150 mg per dose.

[b] Norbuprenorphine is an active metabolite of buprenorphine.

[c] R-methadone is the active form of methadone.

Key to Abbreviations: ARV = antiretroviral, AUC = area under the curve, BID = twice daily, CCB = calcium channel blocker, C_{max} = maximum plasma concentration, C_{min} = minimum plasma concentration, DLV = delavirdine, DMPA = depomedroxyprogesterone acetate, 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, PDE5 = phosphodiesterase type 5, PI = protease inhibitor, PPI = proton pump inhibitor, RPV = rilpivirine, RTV = ritonavir, TDF = tenofivir

Table 15c. Drug Interactions between Nucleoside Reverse Transriptase Inhibitors and Other Drugs (Including Antiretroviral Agents) (Page 1 of 2)

Concomitant Drug Class/ Name	NRTI	Effect on NRTI or Concomitant Drug Concentrations	Dosage Recommendations and Clinical Comments
Antivirals			
Boceprevir	TDF	No significant PK effects	No dose adjustment necessary.
Ganciclovir Valganciclovir	TDF	No data	Serum concentrations of these drugs and/or TDF may be increased. Monitor for dose-related toxicities.
	ZDV	No significant PK 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.
Telaprevir	TDF	TDF AUC ↑ 30%, C_{min} ↑ 6%–41%	Monitor for TDF-associated toxicity.
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%, 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% In patients with renal impairment: ddI AUC ↑ 312%	**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 RTV) 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 H2 receptor antagonist in ART-experienced patients, use ATV/r 400 mg/100 mg daily. Monitor for TDF-associated toxicity.
	ZDV	ZDV C_{min} ↓ 30%, no change in AUC	Clinical significance unknown.

Table 15c. Drug Interactions between Nucleoside Reverse Transriptase Inhibitors and Other Drugs (Including Antiretroviral Agents) (Page 2 of 2)

Concomitant Drug Class/ Name	NRTI	Effect on NRTI or Concomitant Drug Concentrations	Dosage Recommendations and Clinical Comments
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% TDF AUC ↑ 34%	Clinical significance unknown. Monitor for TDF toxicity.
TPV/r	ABC	ABC AUC ↓ 35%–44%	Appropriate doses for this combination have not been established.
	ddI	ddI-EC AUC ↔ and C_{min} ↓ 34% TPV/r ↔	Separate doses by at least 2 hours.
	TDF	TDF AUC ↔ TPV/r AUC ↓ 9%–18% and C_{min} ↓ 12%–21%	No dosage adjustment necessary.
	ZDV	ZDV AUC ↓ 35% TPV/r AUC ↓ 31%–43%	Appropriate doses for this combination have not been established.

Key to Abbreviations: 3TC = lamivudine, ABC = abacavir, ART = antiretroviral, ATV = atazanavir, ATV/r = atazanavir/ritonavir, AUC = area under the curve, 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

This table provides information relating to PK 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 Phenobarbital Phenytoin	MVC	↓ MVC possible	If used without a strong CYP3A inhibitor, use MVC 600 mg BID or an alternative antiepileptic agent.
Antifungals			
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. If used with a strong CYP3A inhibitor, use MVC 150 mg BID.
Rifampin	MVC	MVC AUC ↓ 64%	Coadministration is not recommended. If coadministration is necessary, use MVC 600 mg BID. If coadministered with a strong CYP3A inhibitor, use MVC 300 mg BID.
Rifapentine	MVC	↓ MVC expected	**Do not coadminister.**
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	

Key to Abbreviations: ARV = antiretroviral, AUC = area under the curve, BID = twice daily, CYP = cytochrome P, MVC = maraviroc, PK = pharmacokinetic

Table 15e. Drug Interactions between Integrase Inhibitor and Other Drugs

Concomitant Drug Class/Name	Integrase Inhibitor	Effect on Integrase Inhibitor or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Omeprazole	RAL	RAL AUC ↑ 212%, C_{max} ↑ 315%, and C_{min} ↑ 46%	No dosage adjustment necessary.
Antimycobacterials			
Rifabutin	RAL	RAL AUC ↑ 19%, C_{max} ↑ 39%, and C_{min} ↓ 20%	No dosage adjustment necessary.
Rifampin	RAL	RAL 400 mg: RAL AUC ↓ 40% and C_{min} ↓ 61% 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 Monitor closely for virologic response.
Hepatitis C NS3/4A – Protease Inhibitors			
Boceprevir	RAL	No significant effect	No dosage adjustment necessary.
Telaprevir	RAL	RAL AUC ↑ 31% Telaprevir ↔	No dosage adjustment necessary.
Hormonal Contraceptives			
Hormonal contraceptives	RAL	No clinically significant effect	Safe to use in combination
Narcotics/Treatment for Opioid Dependence			
Buprenorphine	RAL	No significant effect	No dosage adjustment necessary.
Methadone	RAL	No significant effect	No dosage adjustment necessary.

Key to Abbreviations: AUC = area under the curve, BID = twice daily, C_{max} = maximum plasma concentration, C_{min} = minimum plasma concentration, RAL = raltegravir

*Table 16a. Interactions Among Protease Inhibitors**

*NFV and IDV are not included in this table. Please refer to NFV and IDV FDA package inserts 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 1400 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	**Should not be coadministered because doses are not established**	•	LPV is coformulated with RTV as Kaletra.	Dose: SQV 1000 mg BID + LPV/r 400/100 mg BID	**Should not be coadministered because doses are not established**
RTV	Dose: (ATV 300 mg + RTV 100 mg) once daily	Dose: (FPV 1400 mg + RTV 100 mg or 200 mg) once daily; or (FPV 700 mg + RTV 100 mg) BID	LPV is coformulated with RTV and marketed as Kaletra.	•	Dose: (SQV 1000 mg + RTV 100 mg) BID	Dose: (TPV 500 mg + RTV 200 mg) BID
SQV	Dose: Insufficient data	Dose: Insufficient data	Dose: SQV 1000 mg BID + LPV/r 400/100 mg BID	Dose: (SQV 1000 mg + RTV 100 mg) BID	•	**Should not be coadministered because doses are not established**

Key to Abbreviations: 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 Non-Nucleoside Reverse Transcriptase Inhibitors, Maraviroc, Raltegravir, and Protease Inhibitors* (Page 1 of 3)*

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

		EFV	ETR	NVP	RPV[a]	MVC	RAL
ATV +/- RTV	**PK data**	With unboosted ATV ATV: AUC ↓ 74% EFV: no significant change With (ATV 300 mg + RTV 100 mg) once daily with food ATV concentrations similar to unboosted ATV without EFV	With unboosted ATV ETR: AUC ↑ 50%, C_{max} ↑ 47%, and C_{min} ↑ 58% ATV: AUC ↓ 17% and C_{min} ↓ 47% With (ATV 300 mg + RTV 100 mg) once daily ETR: AUC, C_{max}, and C_{min} ↑ approximately 30% ATV: AUC ↓ 14% and C_{min} ↓ 38%	With (ATV 300 mg + RTV 100 mg) once daily ATV: AUC ↓ 42% and C_{min} ↓ 72% NVP: AUC ↑ 25%	With boosted and unboosted ATV ↑ RPV possible	With unboosted ATV MVC: AUC ↑ 257% With (ATV 300 mg + RTV 100 mg) once daily MVC: AUC ↑ 388%	With unboosted ATV RAL: AUC ↑ 72% With (ATV 300 mg + RTV 100 mg) once daily RAL: AUC ↑ 41%
	Dose	**Do not coadminister with unboosted ATV.** In ART-naive patients (ATV 400 mg + RTV 100 mg) once daily **Do not coadminister in ART-experienced patients.**	**Do not coadminister with ATV +/– RTV.**	**Do not coadminister with ATV +/– RTV.**	Standard	MVC 150 mg BID with ATV +/– RTV	Standard
DRV – always use with RTV	**PK data**	With (DRV 300 mg + RTV 100 mg) BID DRV: AUC ↓ 13%, C_{min} ↓ 31% EFV: AUC ↑ 21%	ETR 100 mg BID with (DRV 600 mg + RTV 100 mg) BID DRV: no significant change ETR: AUC ↓ 37%, C_{min} ↓ 49%	With (DRV 400 mg + RTV 100 mg) BID DRV: AUC ↑ 24%[b] NVP: AUC ↑ 27% and C_{min} ↑ 47%	RPV 150 mg once daily with (DRV 800 mg + RTV 100 mg) once daily DRV: no significant change RPV: AUC ↑ 130% and C_{min} ↑ 178%	With (DRV 600 mg + RTV 100 mg) BID MVC: AUC ↑ 305% With (DRV 600 mg + RTV 100 mg) BID + ETR MVC: AUC ↑ 210%	With (DRV 600 mg + RTV 100 mg) BID RAL: AUC ↓ 29% and C_{min} ↑ 38%
	Dose	Clinical significance unknown. Use standard doses and monitor patient closely. Consider monitoring drug levels.	Standard (ETR 200 mg BID) Despite decreased ETR concentration, safety and efficacy of this combination have been established in a clinical trial.	Standard	Standard	MVC 150 mg BID	Standard
EFV	**PK data**	•	↓ ETR possible	NVP: no significant change EFV: AUC ↓ 22%	↓ RPV possible	MVC: AUC ↓ 45%	EFV: AUC ↓ 36%
	Dose		**Do not coadminister.**	**Do not coadminister.**	**Do not coadminister.**	MVC: 600 mg BID	Standard

Table 16b. Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors, Maraviroc, Raltegravir, and Protease Inhibitors* (Page 2 of 3)*

		EFV	ETR	NVP	RPV[a]	MVC	RAL
ETR	**PK data**	↓ ETR possible	•	↓ ETR possible	↓ RPV possible	MVC: AUC ↓ 53%, C_{max} ↓ 60%	ETR: C_{min} ↓ 17% RAL: C_{min} ↓ 34%
	Dose	**Do not coadminister.**		**Do not coadminister.**	**Do not coadminister.**	MVC 600 mg BID in the absence of a potent CYP3A inhibitor	Standard
FPV	**PK data**	With (FPV 1400 mg + RTV 200 mg) once daily APV: C_{min} ↓ 36%	With (FPV 700 mg + RTV 100 mg) BID APV: AUC ↑ 69%, C_{min} ↑ 77%	With unboosted FPV 1400 mg BID APV: AUC ↓ 33% NVP: AUC ↑ 29% With (FPV 700 mg + RTV 100 mg) BID NVP: C_{min} ↑ 22%	With boosted and unboosted FPV ↑ RPV possible	Unknown; ↑ MVC possible	No data
	Dose	(FPV 1400 mg + RTV 300 mg) once daily or (FPV 700 mg + RTV 100 mg) BID EFV standard	**Do not coadminister with FPV +/– RTV.**	(FPV 700 mg + RTV 100 mg) BID NVP standard	Standard	MVC 150 mg BID	Standard
LPV/r	**PK data**	With LPV/r tablets 500/125 mg[c] BID + EFV 600 mg LPV levels similar to LPV/r 400/100 mg BID without EFV	With LPV/r tablets ETR: levels ↓ 30%–45% (comparable to the decrease with DRV/r) LPV: levels ↓ 13%–20%	With LPV/r capsules LPV: AUC ↓ 27% and C_{min} ↓51%	RPV 150 mg once daily with LPV/r capsules LPV: no significant change RPV: AUC ↑ 52% and C_{min} ↑ 74%	MVC: AUC ↑ 295% With LPV/r + EFV MVC: AUC ↑ 153%	↓ RAL ↔ LPV/r
	Dose	LPV/r tablets 500/125 mg[c] BID; LPV/r oral solution 533/133 mg BID EFV standard	Standard	LPV/r tablets 500/125 mg[c] BID; LPV/r oral solution 533/133 mg BID NVP standard	Standard	MVC 150 mg BID	Standard
NVP	**PK data**	NVP: no significant change EFV: AUC ↓ 22%	↓ ETR possible	•	↓ RPV possible	MVC: AUC ↔ and C_{max} ↑ 54%	No data
	Dose	**Do not coadminister.**	**Do not coadminister.**		**Do not coadminister.**	Without PI MVC 300 mg BID With PI (except TPV/r) MVC 150 mg BID	Standard
RAL	**PK data**	RAL: AUC ↓ 36%	ETR: C_{min} ↑ 17% RAL: C_{min} ↓ 34%	No data	No data	RAL: AUC ↓ 37% MVC: AUC ↓ 21%	•
	Dose	Standard	Standard	No data	No data	Standard	

Table 16b. Interactions between Non-Nucleoside Reverse Transcriptase Inhibitors, Maraviroc, Raltegravir, and Protease Inhibitors* (Page 3 of 3)*

		EFV	ETR	NVP	RPV[a]	MVC	RAL
RPV	**PK data**	↓ RPV possible	↓ RPV possible	↓ RPV possible	•	No data	No data
	Dose	**Do not coadminister.**	**Do not coadminister.**	**Do not coadminister.**		No data	No data
RTV	**PK data**	Refer to information for boosted PI.	Refer to information for boosted PI.	Refer to information for boosted PI.	Refer to information for boosted PI.	With RTV 100 mg BID MVC: AUC ↑ 161%	With RTV 100 mg BID RAL: AUC ↓ 16%
	Dose					MVC 150 mg BID	Standard
SQV – always use with RTV	**PK data**	With SQV 1200 mg TID SQV: AUC ↓ 62% EFV: AUC ↓ 12%	With (SQV 1000 mg + RTV 100 mg) BID SQV: AUC unchanged ETR: AUC ↓ 33%, C_{min} ↓ 29% Reduced ETR levels similar to reduction with DRV/r	With 600 mg TID SQV: AUC ↓ 24% NVP: no significant change	↑ RPV possible	With (SQV 1000 mg + RTV 100 mg) BID MVC: AUC ↑ 877% With (SQV 1000 mg + RTV 100 mg) BID + EFV MVC: AUC ↑ 400%	No data
	Dose	(SQV 1000 mg + RTV 100 mg) BID	(SQV 1000 mg + RTV 100 mg) BID	Dose with SQV/r not established	Standard	MVC 150 mg BID	Standard
TPV – always use with RTV	**PK data**	With (TPV 500 mg + RTV 100 mg) BID TPV: AUC ↓ 31%, C_{min} ↓ 42% EFV: no significant change With (TPV 750 mg + RTV 200 mg) BID TPV: no significant change EFV: no significant change	With (TPV 500 mg + RTV 200 mg) BID ETR: AUC ↓ 76%, C_{min} ↓ 82% TPV: AUC ↑ 18%, C_{min} ↑ 24%	With (TPV 250 mg + RTV 200 mg) BID and with (TPV 750 mg + RTV 100 mg) BID NVP: no significant change TPV: no data	↑ RPV possible	With (TPV 500 mg + RTV 200 mg) BID MVC: no significant change in AUC TPV: no data	With (TPV 500 mg + RTV 200 mg) BID RAL: AUC ↓ 24%
	Dose	Standard	**Do not coadminister.**	Standard	Standard	MVC 300 mg BID	Standard

[a] Approved dose for RPV is 25 mg once daily. Most PK interaction studies were performed using 75 to 150 mg per dose.

[b] Based on between-study comparison.

[c] 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.

Key to Abbreviations: APV = amprenavir, ART = antiretroviral therapy, ATV = atazanavir, AUC = area under the curve, BID = twice daily, C_{max} = maximum plasma concentration, C_{min} = minimum plasma concentration, CYP = cytochrome P, DLV = delavirdine, DRV = darunavir, DRV/r = darunavir/ritonavir, EFV = efavirenz, ETR = etravirine, FDA = Food and Drug Administration, FPV = fosamprenavir, IDV = indinavir, LPV = lopinavir, LPV/r = lopinavir/ritonavir, MVC = maraviroc, NFV = nelfinavir, NVP = nevirapine, PI = protease inhibitor, PK = pharmacokinetic, RAL = raltegravir, RPV = rilpivirine, RTV = ritonavir, SQV = saquinavir, SQV/r = saquinarir/ritonavir, TID = three times a day, TPV = tipranavir

Preventing Secondary Transmission of HIV (Last updated March 27, 2012; last reviewed March 27, 2012)

Despite substantial advances in prevention and treatment of HIV infection in the United States, the rate of new infections has remained stable.[1-2] Although earlier prevention interventions mainly were behavioral, recent data demonstrate the strong impact of antiretroviral therapy (ART) on secondary HIV transmission. The most effective strategy to stem the spread of HIV will probably be a combination of behavioral, biological, and pharmacological interventions.[3]

Prevention Counseling

Counseling and related behavioral interventions for those living with HIV infection can reduce behaviors associated with secondary transmission of HIV. Each patient encounter offers the clinician an opportunity to reinforce HIV prevention messages, but multiple studies show that prevention counseling is frequently neglected in clinical practice.[4-5] Although delivering effective prevention interventions in a busy practice setting may be challenging, clinicians should be aware that patients often look to their providers for messages about HIV prevention. Multiple approaches to prevention counseling are available, including formal guidance from the Centers for Disease Control and Prevention (CDC) for incorporating HIV prevention into medical care settings. Such interventions have been demonstrated to be effective in changing sexual risk behavior[6-8] and can reinforce self-directed behavior change early after diagnosis.[9]

CDC has identified several prevention interventions for individuals infected with HIV that meet stringent criteria for efficacy and scientific rigor (http://www.cdc.gov/hiv/topics/research/prs/index.htm). The following three interventions have proven effective in treatment settings and can be delivered by providers as brief messages during clinic visits:

- Partnership for Health (http://effectiveinterventions.org/en/Interventions/PfH.aspx),
- Options (http://www.cdc.gov/hiv/topics/research/prs/resources/factsheets/options.htm),
- Positive Choice (http://www.cdc.gov/hiv/topics/research/prs/resources/factsheets/positive-choice.htm).

In addition, CDC's "Prevention Is Care" campaign (http://www.actagainstaids.org/provider/pic/index.html) helps providers (and members of a multidisciplinary care team) integrate simple methods to prevent transmission by HIV-infected individuals into routine care. These prevention interventions are designed to reduce the risk of secondary HIV transmission through sexual contact. The interventions are designed generally for implementation at the community or group level, but some can be adapted and administered in clinical settings by a multidisciplinary care team.

Need for Screening for High-Risk Behaviors

The primary care visit provides an opportunity to screen patients for ongoing high-risk drug and sexual behaviors for transmitting HIV infection. Routine screening and symptom-directed testing for and treatment of sexually transmitted diseases (STDs), as recommended by CDC,[10] remain essential adjuncts to prevention counseling. Genital ulcers may facilitate HIV transmission and STDs may increase HIV viral load in plasma and genital secretions.[7, 11-13] They also provide objective evidence of unprotected sexual activity, which should prompt prevention counseling.

The contribution of substance and alcohol use to HIV risk behaviors and transmission has been well established in multiple populations;[14-18] therefore, effective counseling for injection and noninjection drug users is essential to prevent HIV transmission. Identifying the substance(s) of use is important because HIV

prevalence, transmission risk, risk behaviors, transmission rates, and potential for pharmacologic intervention all vary according to the type of substance used.[19-21] Risk-reduction strategies for injection drug users (IDUs), in addition to condom use, include needle exchange and instructions on cleaning drug paraphernalia. Evidence supporting the efficacy of interventions to reduce injection drug use risk behavior also exists. Interventions include both behavioral strategies[14-15, 22] and opiate substitution treatment with methadone or buprenorphine.[23-24] No successful pharmacologic interventions have been found for cocaine and methamphetamine users; cognitive and behavioral interventions demonstrate the greatest effect on reducing the risk behaviors of these users.[25-27] Given the significant impact of cocaine and methamphetamine on sexual risk behavior, reinforcement of sexual risk-reduction strategies is important.[14-18, 28]

Antiretroviral Therapy as Prevention

ART can play an important role in preventing HIV transmission. Lower levels of plasma HIV RNA have been associated with decreases in the concentration of virus in genital secretions.[29-32] Observational studies have demonstrated the association between low serum or genital HIV RNA and a decreased rate of HIV transmission among serodiscordant heterosexual couples.[29, 33-34] Ecological studies of communities with relatively high concentrations of men who have sex with men (MSM) and IDUs suggest increased use of ART is associated with decreased community viral load and reduced rates of new HIV diagnoses.[35-37] These data suggest that the risk of HIV transmission is low when an individual's viral load is below 400 copies/mL,[35, 38] but the threshold below which transmission of the virus becomes impossible is unknown. Furthermore, to be effective at preventing transmission it is assumed that: (1) ART is capable of durably and continuously suppressing viremia; (2) adherence to an effective ARV regimen is high; and (3) there is an absence of a concomitant STD. Importantly, detection of HIV RNA in genital secretions has been documented in individuals with controlled plasma HIV RNA and data describing a differential in concentration of most ARV drugs in the blood and genital compartments exist.[30, 39] At least one case of HIV transmission from a patient with suppressed plasma viral load to a monogamous uninfected sexual partner has been reported.[40]

In the HPTN 052 trial in HIV-discordant couples, the HIV-infected partners who were ART naive and had CD4 counts between 350 and 550 cells/mm^3 were randomized to initiate or delay ART. In this study, those who initiated ART had a 96% reduction in HIV transmission to the uninfected partners.[3] Almost all of the participants were in heterosexual relationships, all participants received risk-reduction counseling, and the absolute number of transmission events was low: 1 among ART initiators and 27 among ART delayers. Over the course of the study virologic failure rates were less than 5%, a value much lower than generally seen in individuals taking ART for their own health. These low virologic failure rates suggest high levels of adherence to ART in the study, which may have been facilitated by the frequency of study follow-up (study visits were monthly) and by participants' sense of obligation to protect their uninfected partners. Therefore, caution is indicated when interpreting the extent to which ART for the HIV-infected partner protects seronegative partners in contexts where adherence and, thus, rates of continuous viral suppression, may be lower. Furthermore, for HIV-infected MSM and IDUs, biological and observational data suggest suppressive ART also should protect against transmission, but the actual extent of protection has not been established.

Rates of HIV risk behaviors can increase coincidently with the availability of potent combination ART, in some cases almost doubling compared with rates in the era prior to highly effective therapy.[9] A meta-analysis demonstrated that the prevalence of unprotected sex acts was increased in HIV-infected individuals who believed that receiving ART or having a suppressed viral load protected against transmitting HIV.[41] Attitudinal shifts away from safer sexual practices since the availability of potent ART underscore the role of provider-initiated HIV prevention counseling. With wider recognition that effective treatment decreases the risk of HIV 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

HIV in the genital and blood compartments and, hence, the inability to transmit HIV to others.[41-42]

Maximal suppression of viremia not only depends on the potency of the ARV regimen used but also on the patient's adherence to prescribed therapy. Suboptimal adherence can lead to viremia that not only harms the patient but also increases his/her risk of transmitting HIV (including drug-resistant strains) via sex or needle sharing. Screening for and treating behavioral conditions that can impact adherence, such as depression and alcohol and substance use, improve overall health and reduce the risk of secondary transmission.

Summary

Consistent and effective use of ART resulting in a sustained reduction in viral load in conjunction with consistent condom usage, safer sex and drug use practices, and detection and treatment of STDs 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 sex- and drug-related risk behaviors, diagnose and treat intercurrent STDs, review the importance of medication adherence, and foster open communication between provider and patient.

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Conclusion (Last updated January 10, 2011; last reviewed January 10, 2011)

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 (Last updated March 27, 2012; last reviewed March 27, 2012)

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
AUC	area under the curve
AV	atrioventricular
AWP	average wholesale price
AZT	zidovudine
bDNA	branched DNA
BID	twice a day
BMD	bone mineral density
BMI	body mass index
BUN	blood urea nitrogen
cap	capsule
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 plasma concentration
CME	continuing medical education
C_{min}	minimum plasma concentration
CMV	cytomegalovirus

CNICS	Centers for AIDS Research Network of Integrated Clinical Systems
CNS	central nervous system
COC	combined oral contraceptive
CPK	creatine phosphokinase
CrCl	creatinine clearance
CSF	cerebrospinal fluid
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 acetate
DOT	directly observed therapy
DR	delayed release
DRV	darunavir
DRV/r	darunavir/ritonavir
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
EI	entry inhibitor
EIA	enzyme immunoassay
ETR	etravirine
FDA	Food and Drug Administration
FI	fusion inhibitor
FPV	fosamprenavir
FPV/r	fosamprenavir/ritonavir
FTC	emtricitabine

FTC/TDF	emtricitabine + tenofovir disoproxil fumarate
GAZT	azidothymidine glucuronide
GHB	gamma-hydroxybutyrate
GI	gastrointestinal
HAD	HIV-associated dementia
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
HLA	human leukocyte antigen
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	injection drug user
IDV	indinavir
IDV/r	indinavir/ritonavir
IFN-γ	interferon-gamma
IGRA	interferon-gamma release assay

IL	interleukin
IL-2	interleukin-2
IL-6	interleukin-6
IL-7	interleukin-7
IND	investigational new drug
INH	isoniazid
inj	injection
INR	international normalized ratio
INSTI	integrase strand transfer inhibitor
IQ	inhibitory quotient
IRB	Institutional Review Board
IRIS	immune reconstitution inflammatory syndrome
IUD	intrauterine device
LDL	low-density lipoprotein
LPV	lopinavir
LPV/r	lopinavir/ritonavir
LTBI	latent tuberculosis infection
MAC	*Mycobacterium avium* complex
MDMA	methylenedioxymethamphetamine
mDOT	modified directly observed therapy
MDR	multidrug-resistant
MDRD	modification of diet in renal disease (equation)
MHC	major histocompatability complex
MI	myocardial infarction
msec	millisecond
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
OI	opportunistic infection
PAH	pulmonary arterial hypertension
PCP	*Pneumocystis jirocevi* pneumonia or *Pneumocystis* pneumonia
PDE5	phosphodiesterase type 5
PegIFN	peginterferon
p-gp	p-glycoprotein
PI	protease inhibitor
PK	pharmacokinetic
PMTCT	prevention of mother-to-child transmission
PNS	peripheral nervous system
PO	by mouth
PPI	proton pump inhibitor
PR	protease (gene)
PT	prothrombin time
QTc	QT corrected for heart rate
RAL	raltegravir
RBV	ribavirin
RPV	rilpivirine
RT	reverse transcriptase (gene)
RT-PCR	reverse transcriptase-polymerase chain reaction
RTV	ritonavir
SJS	Stevens-Johnson syndrome
soln	solution
SPT	skin patch test
SQV	saquinavir
SQV/r	saquinavir/ritonavir
STD	sexually transmitted disease
SVR	sustained virologic response
$t_{1/2}$	half-life
T20	enfuvirtide
tab	tablet
TAM	thymidine analogue mutation
TB	tuberculosis

TCA	tricyclic antidepressant
TDF	tenofovir disoproxil fumarate
TDF/FTC	tenofovir/emtricitabine
TDM	therapeutic drug monitoring
TEN	toxic epidermal necrosis
TG	triglyceride
TID	three times daily
TPV	tipranavir
TPV/r	tipranavir/ritonavir
TST	tuberculin skin test
UDP	uridine diphosphate
UGT	uridine diphosphate gluconyltransferase
UGT1A1	uridine diphosphate glucuronosyltransferase 1A1
ULN	upper limit of normal
VPA	valproic acid
WBC	white blood cell
WHO	World Health Organization
WITS	Women and Infants Transmission Study
XDR	extensively drug-resistant
XR	extended release
ZDV	zidovudine

Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (NRTIs) (Last updated March 27, 2012; last reviewed March 27, 2012) (page 1 of 3)

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 **Also available as component of fixed-dose combinations:**	Ziagen • 300-mg tablets • 120-mg/mL oral solution	Ziagen 300 mg BID or 600 mg once daily Take without regard to meals	Metabolized by alcohol dehydrogenase and glucuronyl transferase Renal excretion of metabolites 82% Dosage adjustment for ABC recommended in patients with hepatic insufficiency (See Appendix B, Table 7.)	1.5 hrs/ 12–26 hrs	• HSRs: Patients who test positive for HLA-B*5701 are at highest risk. HLA screening should be done before initiation of ABC. Rechallenge is not recommended. • 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. • Some cohort studies suggest increased risk of MI with recent or current use of ABC, but this risk is not substantiated in other studies.
Trizivir ABC with ZDV+3TC	Trizivir (ABC 300 mg + ZDV 300 mg + 3TC 150 mg) tablet	Trizivir 1 tablet BID			
Epzicom ABC with 3TC	Epzicom (ABC 600 mg + 3TC 300 mg) tablet	Epzicom 1 tablet once daily			
Didanosine (ddI)/ Videx EC (generic available; dose same as Videx EC)	Videx EC 125-, 200-, 250-, 400-mg capsules Videx 10-mg/mL oral solution	**Body weight ≥60kg:** 400 mg once daily *With TDF:* 250 mg once daily **Body weight <60kg:** 250 mg once daily *With TDF:* 200 mg once daily Take 1/2 hour before or 2 hours after a meal Note: Preferred dosing with oral solution is BID (total daily dose divided into 2 doses)	Renal excretion 50% Dosage adjustment in patients with renal insufficiency recommended (See Appendix B, Table 7.)	1.5 hrs/ >20 hrs	• Pancreatitis • Peripheral neuropathy • Retinal changes, optic neuritis • Lactic acidosis with hepatic steatosis +/- pancreatitis (rare but potentially life-threatening toxicity) • Nausea, vomiting • Potential association with noncirrhotic portal hypertension, in some cases, patients presented with esophageal varices • One cohort study suggested increased risk of MI with recent or current use of ddI, but this risk is not substantiated in other studies. • Insulin resistance/diabetes mellitus

Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (NRTIs) (Last updated March 27, 2012; last reviewed March 27, 2012) (page 2 of 3)

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)
Emtricitabine (FTC)/Emtriva **Also available as component of fixed-dose combinations:**	Emtriva • 200-mg hard gelatin capsule • 10-mg/mL oral solution	Emtriva *Capsule:* 200 mg once daily *Oral solution:* 240 mg (24 mL) once daily Take without regard to meals	Renal excretion 86% Dosage adjustment in patients with renal insufficiency recommended (See Appendix B, Table 7.)	10 hrs/ >20 hrs	• Minimal toxicity • Hyperpigmentation/skin discoloration • Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue FTC.
Atripla FTC with EFV+TDF	Atripla (FTC 200 mg + EFV 600 mg + TDF 300 mg) tablet	Atripla 1 tablet at or before bedtime Take on an empty stomach to reduce side effects			
Complera FTC with RPV+TDF	Complera (FTC 200 mg + RPV 25 mg + TDF 300 mg) tablet	Complera 1 tablet once daily with a meal			
Truvada FTC with TDF	Truvada FTC 200 mg + TDF 300 mg tablet	Truvada 1 tablet once daily			
Lamivudine (3TC)/ Epivir (generic available) **Also available as component of fixed-dose combinations:**	Epivir • 150-, 300-mg tablets • 10-mg/mL oral solution	Epivir 150 mg BID or 300 mg once daily Take without regard to meals	Renal excretion 70% Dosage adjustment in patients with renal insufficiency recommended (See Appendix B, Table 7.)	5–7 hrs/ 18–22 hrs	• Minimal toxicity • Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue 3TC.
Combivir (generic available) 3TC with ZDV	Combivir (3TC 150 mg + ZDV 300 mg) tablet	Combivir 1 tablet BID			
Epzicom 3TC with ABC	Epzicom (3TC 300 mg + ABC 600 mg) tablet	Epzicom 1 tablet once daily			
Trizivir 3TC with ZDV+ABC	Trizivir (3TC 150 mg + ZDV 300 mg + ABC 300 mg) tablet	Trizivir 1 tablet BID			
Stavudine (d4T)/ Zerit (generic available)	Zerit • 15-, 20-, 30-, 40-mg capsules • 1-mg/mL oral solution	**Body weight ≥60 kg:** 40 mg BID **Body weight <60 kg:** 30 mg BID Take without regard to meals Note: WHO recommends 30 mg BID dosing regardless of body weight.	Renal excretion 50% Dosage adjustment in patients with renal insufficiency recommended (See Appendix B, Table 7.)	1 hr/ 7.5 hrs	• Peripheral neuropathy • Lipoatrophy • Pancreatitis • Lactic acidosis/severe hepatomegaly with hepatic steatosis (rare but potentially life-threatening toxicity) • Hyperlipidemia • Insulin resistance/diabetes mellitus • Rapidly progressive ascending neuromuscular weakness (rare)

Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (NRTIs) (Last updated March 27, 2012; last reviewed March 27, 2012) (page 3 of 3)

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)
Tenofovir Disoproxil Fumarate (TDF)/Viread **Also available as component of fixed-dose combinations:**	Viread • 150-, 200-, 250-, 300-mg tablets • 40-mg/g oral powder	Viread 300 mg once daily 7.5 scoops once daily Take without regard to meals Mix oral powder with 2–4 ounces of food not requiring chewing (e.g., applesauce, yogurt). **Do not mix oral powder with liquid.**	Renal excretion 86% Dosage adjustment in patients with renal insufficiency recommended (See Appendix B, Table 7.)	17 hrs/ >60 hrs	• Renal insufficiency, Fanconi syndrome • Osteomalacia, decrease in bone mineral density • Potential decrease in bone mineral density • Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue TDF. • Asthenia, headache, diarrhea, nausea, vomiting, and flatulence
Atripla TDF with EFV+FTC	Atripla (TDF 300 mg + EFV 600 mg + FTC 200 mg) tablet	Atripla 1 tablet at or before bedtime Take on an empty stomach to reduce side effects			
Complera TDF with RPV+FTC	Complera (TDF 300 mg + RPV 25 mg + FTC 200 mg) tablet	Complera 1 tablet once daily Take with a meal			
Truvada TDF with FTC	Truvada (TDF 300 mg + FTC 200 mg) tablet	Truvada 1 tablet once daily Take without regard to meals			
Zidovudine (ZDV)/ Retrovir (generic available) **Also available as component of fixed-dose combinations:**	Retrovir • 100-mg capsule • 300-mg tablet • 10-mg/mL intravenous solution • 10-mg/mL oral solution	Retrovir 300 mg BID or 200 mg TID Take without regard to meals	Metabolized to GAZT Renal excretion of GAZT Dosage adjustment in patients with renal insufficiency recommended (See Appendix B, Table 7.)	1.1 hrs/ 7 hrs	• Bone marrow suppression: macrocytic anemia or neutropenia • Nausea, vomiting, headache, insomnia, asthenia • Nail pigmentation • Lactic acidosis/severe hepatomegaly with hepatic steatosis (rare but potentially life-threatening toxicity) • Hyperlipidemia • Insulin resistance/diabetes mellitus • Lipoatrophy • Myopathy
Combivir (generic available) ZDV with 3TC	Combivir (ZDV 300 mg + 3TC 150 mg) tablet	Combivir 1 tablet BID			
Trizivir ZDV with 3TC+ABC	Trizivir (ZDV 300 mg + 3TC 150 mg + ABC 300 mg) tablet	Trizivir 1 tablet BID			

Key to Abbreviations: 3TC = lamivudine, ABC = abacavir, BID = twice daily, d4T = stavudine, ddI = didanosine, EC = enteric coated, EFV = efavirenz, FTC = emtricitabine, GAZT = azidothymidine glucuronide, HBV = hepatitis B virus, HLA = human leukocyte antigen, HSR = hypersensitivity reaction, MI = myocardial infarction, RPV = rilpivirine, TDF = tenofovir disoproxil fumarate, TID = three times a day, WHO = World Health Organization, ZDV = zidovudine

Appendix B, Table 2. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors* (NNRTIs) (Last updated October 14, 2011; last reviewed March 27, 2012) (page 1 of 2)

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

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)
Efavirenz (EFV)/ Sustiva **Also available as component of fixed-dose combination:**	• 50-, 200-mg capsules • 600-mg tablet	600 mg once daily at or before bedtime Take on an empty stomach to reduce side effects.	Metabolized by CYPs 2B6 and 3A4 CYP3A4 mixed inducer/inhibitor (more an inducer than an inhibitor)	40–55 hrs	• Rash[a] • Neuropsychiatric symptoms[b] • Increased transaminase levels • Hyperlipidemia • False-positive results with some cannabinoid and benzodiazepine screening assays reported. • Teratogenic in nonhuman primates and potentially teratogenic in humans
Atripla EFV with TDF + FTC	(EFV 600 mg + FTC 200 mg + TDF 300 mg) tablet	1 tablet once daily at or before bedtime.			
Etravirine (ETR)/ Intelence	• 100-, 200-mg tablets	200 mg BID Take following a meal.	CYP3A4, 2C9, and 2C19 substrate 3A4 inducer; 2C9 and 2C19 inhibitor	41 hrs	• Rash, including Stevens-Johnson syndrome[a] • HSRs, characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure, have been reported. • Nausea
Nevirapine (NVP)/ Viramune or Viramine XR	• 200-mg tablet • 400-mg XR tablet • 50-mg/5-mL oral suspension	200 mg once daily for 14 days (lead-in period); thereafter, 200 mg BID or 400 mg (Viramune XR tablet) once daily Take without regard to meals. Repeat lead-in period if therapy is discontinued for more than 7 days. In patients who develop mild-to-moderate rash without constitutional symptoms, continue lead-in period until rash resolves but not 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[a] • Symptomatic hepatitis, including fatal hepatic necrosis, has been reported: - rash reported in approximately 50% of cases; - occurs at significantly higher frequency in ARV-naive female patients with pre-NVP CD4 counts >250 cells/mm^3 and in ARV-naive 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.

Appendix B, Table 2. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors* (NNRTIs) (Last updated October 14, 2011; last reviewed March 27, 2012) (page 2 of 2)

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

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)
Rilpivirine (RPV)/ Edurant **Also available as component of fixed-dose combination:**	• 25-mg tablet	25 mg once daily Take with a meal.	CYP3A4 substrate	50 hrs	• Rash[a] • Depression, insomnia, headache
Complera RPV with TDF + FTC	Complera (RPV 25 mg + TDF 300 mg + FTC 200 mg) tablet	1 tablet once daily with a meal			

Key to Abbreviations: ARV = antiretroviral, BID = twice daily, CYP = cytochrome P, DLV = delavirdine, EFV = efavirenz, ETR = etravirine, FDA = Food and Drug Administration, FTC = emtricitabine, HSR = hypersensitivity reaction, NNRTI = non-nucleoside reverse transcriptase inhibitor, NVP = nevirapine, RPV = rilpivirine, TDF = tenofovir disoproxil fumarate, XR = extended release

[a] Rare cases of Stevens-Johnson syndrome have been reported with most NNRTIs; the highest incidence of rash was seen with NVP.

[b] 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 to 4 weeks but may necessitate discontinuation of EFV in a small percentage of patients.

Appendix B, Table 3. Characteristics of Protease Inhibitors (PIs) (Last updated October 14, 2011; last reviewed March 27, 2012) (page 1 of 5)

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	Storage	Adverse Events (Also see Table 13)
Atazanavir (ATV)/ Reyataz	100-, 150-, 200-, 300-mg capsules	ARV-naive patients: 400 mg once daily or (ATV 300 mg + RTV 100 mg) once daily With TDF or in ARV-experienced patients: (ATV 300 mg + RTV 100 mg) once daily With EFV in ARV-naive patients: (ATV 400 mg + RTV 100 mg) once daily (For recommendations on dosing with H2 antagonists and PPIs, refer to Table 16a.) Take with food	CYP3A4 inhibitor and substrate Dosage adjustment in patients with hepatic insufficiency recommended (See Appendix B, Table 7.)	7 hrs	Room temperature (up to 25ºC or 77ºF)	• Indirect hyperbilirubinemia • PR interval prolongation: First degree symptomatic AV block reported. Use with caution in patients with underlying conduction defects or on concomitant medications that can cause PR prolongation. • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia • Nephrolithiasis • Skin rash (20%) • Serum transaminase elevations • Hyperlipidemia (especially with RTV boosting)
Darunavir (DRV)/ Prezista	75-, 150-, 300-, 400-, 600-mg tablets	ARV-naive patients or ARV-experienced patients with no DRV mutations: (DRV 800 mg + RTV 100 mg) once daily ARV-experienced patients with at least one DRV mutation: (DRV 600 mg + RTV 100 mg) BID **Unboosted DRV is not recommended** Take with food	CYP3A4 inhibitor and substrate	15 hrs (when combined with RTV)	Room temperature (up to 25ºC or 77ºF)	• Skin rash (10%): DRV has a sulfonamide moiety; Stevens-Johnson syndrome and erythrema multiforme have been reported. • Hepatotoxicity • Diarrhea, nausea • Headache • Hyperlipidemia • Serum transaminase elevation • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia

Appendix B, Table 3. Characteristics of Protease Inhibitors (PIs) (Last updated October 14, 2011; last reviewed March 27, 2012) (page 2 of 5)

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	Storage	Adverse Events (Also see Table 13)
Fosamprenavir (FPV)/ Lexiva (a prodrug of amprenavir [APV])	• 700-mg tablet • 50-mg/mL oral suspension	ARV-naive patients: • FPV 1400 mg BID or • (FPV 1400 mg + RTV 100–200 mg) once daily or • (FPV 700 mg + RTV 100 mg) BID PI-experienced patients (once-daily dosing not recommended): • (FPV 700 mg + RTV 100 mg) BID With EFV: • (FPV 700 mg + RTV 100 mg) BID or • (FPV 1400 mg + RTV 300 mg) once daily *Tablet*: Take without regard to meals (if not boosted with RTV tablet) *Suspension*: Take without food *FPV with RTV tablet*: Take with meals	APV is a CYP3A4 substrate, inhibitor, and inducer Dosage adjustment in patients with 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 • Diarrhea, nausea, vomiting • Headache • Hyperlipidemia • Serum transaminase elevation • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia • Nephrolithiasis
Indinavir (IDV)/ Crixivan	100-, 200-, 400-mg capsules	800 mg every 8 hrs Take 1 hour before or 2 hours after meals; may take with skim milk or low-fat meal With RTV: (IDV 800 mg + RTV 100–200 mg) BID Take without regard to meals	CYP3A4 inhibitor and substrate Dosage adjustment in patients with hepatic insufficiency recommended (See Appendix B, Table 7.)	1.5–2 hrs	Room temperature (15º–30ºC/ 59º–86ºF) Protect from moisture	• Nephrolithiasis • GI intolerance, nausea • Hepatitis • Indirect hyperbilirubinemia • Hyperlipidemia • Headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, alopecia, and hemolytic anemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia

Appendix B, Table 3. Characteristics of Protease Inhibitors (PIs) (Last updated October 14, 2011; last reviewed March 27, 2012) (page 3 of 5)

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	Storage	Adverse Events (Also see Table 13)
Lopinavir + Ritonavir (LPV/r)/ Kaletra	Tablets: (LPV 200 mg + RTV 50 mg) or (LPV 100 mg + RTV 25 mg) Oral solution: Each 5 mL contains (LPV 400 mg + RTV 100 mg) Oral solution contains 42% alcohol	LPV/r 400 mg/100 mg BID or LPV/r 800 mg/200 mg once daily 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. With EFV or NVP (PI-naive or PI-experienced patients): 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.) or LPV/r 533-mg/133-mg oral solution BID *Tablet:* Take without regard to meals *Oral solution:* Take with food	CYP3A4 inhibitor and substrate	5–6 hrs	Oral tablet is stable at room temperature. Oral solution is stable at 2°–8°C (36°–46°F) until date on label and is stable for up to 2 months when stored at room temperature (up to 25°C or 77°F).	• GI intolerance, nausea, vomiting, diarrhea • Pancreatitis • Asthenia • Hyperlipidemia (especially hypertriglyceridemia) • Serum transaminase elevation • Hyperglycemia • Insulin resistance/diabetes mellitus • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia • PR interval prolongation • QT interval prolongation and torsades de pointes have been reported; however, causality could not be established.
Nelfinavir (NFV)/ Viracept	• 250-, 625-mg tablets • 50-mg/g oral powder	1250 mg BID or 750 mg TID Dissolve tablets in a small amount of water, mix admixture well, and consume immediately. Take with food	CYP2C19 and 3A4 substrate—metabolized to active M8 metabolite; CYP 3A4 inhibitor	3.5–5 hrs	Room temperature (15°–30°C/ 59°–86°F)	• Diarrhea • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia • Serum transaminase elevation

Appendix B, Table 3. Characteristics of Protease Inhibitors (PIs) (Last updated October 14, 2011; last reviewed March 27, 2012) (page 4 of 5)

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	Storage	Adverse Events (Also see Table 13)
Ritonavir (RTV)/ Norvir	• 100-mg soft gel capsule • 100-mg tablet • 80-mg/mL oral solution 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) *Tablet:* Take with food *Capsule and oral solution:* To improve tolerability, take with food if possible.	CYP3A4 >2D6 substrate; potent 3A4, 2D6 inhibitor	3–5 hrs	Refrigerate capsules. Capsules can be left at room temperature (up to 25ºC or 77ºF) for up to 30 days. Tablets do not require refrigeration. Oral solution should not be refrigerated; store at room temperature 20º–25ºC (68º–77ºF).	• GI intolerance, nausea, vomiting, diarrhea • Paresthesias (circumoral and extremities) • Hyperlipidemia (especially hypertriglyceridemia) • Hepatitis • Asthenia • Taste perversion • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia
Saquinavir (SQV)/ Invirase	• 500-mg tablet • 200-mg hard gel capsule	(SQV 1000 mg + RTV 100 mg) BID Unboosted SQV is **not** recommended. 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 • Headache • Serum transaminase elevation • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia • PR interval prolongation • QT interval prolongation, torsades de pointes have been reported. Patients with pre-SQV QT interval >450 msec should not receive SQV (see Table 5b).

Appendix B, Table 3. Characteristics of Protease Inhibitors (PIs) (Last updated October 14, 2011; last reviewed March 27, 2012) (page 5 of 5)

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	Storage	Adverse Events (Also see Table 13)
Tipranavir (TPV)/ Aptivus	• 250-mg capsule • 100-mg/mL oral solution	(TPV 500 mg + RTV 200 mg) BID Unboosted TPV is **not** recommended. *TPV taken with RTV **tablets**:* Take with meals. *TPV taken with RTV **capsules** or **solution**:* Take without regard to meals.	CYP P450 3A4 inducer and substrate Net effect when combined with RTV (CYP 3A4, 2D6 inhibitor)	6 hrs after single dose of TPV/r	Refrigerate capsules. Capsules can be stored at room temperature (25ºC or 77ºF) for up to 60 days. Oral solution should **not** be refrigerated or frozen and should be used within 60 days after bottle is opened.	• Hepatotoxicity: Clinical hepatitis (including hepatic decompensation and hepatitis-associated fatalities) has been reported; monitor closely, especially in patients with underlying liver diseases. • Skin rash (3%–21%): TPV has a sulfonamide moiety; use with caution in patients with known sulfonamide allergy. • Rare cases of fatal and nonfatal intracranial hemorrhages have been reported. Risks include brain lesion, head trauma, recent neurosurgery, coagulopathy, hypertension, alcoholism, use of anti-coagulant or anti-platelet agents including vitamin E. • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia

Key to Abbreviations: APV = amprenavir, ARV = antiretroviral, ATV = atazanavir, AV = atrioventricular, BID = twice daily, CYP = cytochrome P, DRV = darunavir, EFV = efavirenz, FPV = fosamprenavir, GI = gastrointestinal, IDV = indinavir, LPV = lopinavir, LPV/r = lopinavir + ritonavir, msec = millisecond, NFV = nelfinavir, NVP = nevirapine, PI = protease inhibitor, PPI = proton pump inhibitor, RTV = ritonavir, SQV = saquinavir, TDF = tenofovir disoproxil fumarate, TID = three times a day, TPV = tipranavir

Appendix B, Table 4. Characteristics of Integrase Inhibitor (Last updated March 27, 2012; last reviewed March 27, 2012)

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 tablet • 25-, 100-mg chewable tablets	400 mg BID **With rifampin:** 800 mg BID Take without regard to meals.	~9 hrs	UGT1A1-mediated glucuronidation	• Rash, including Stevens-Johnson syndrome, HSR, and toxic epidermal necrolysis • Nausea • Headache • Diarrhea • Pyrexia • CPK elevation, muscle weakness, and rhabdomyolysis

Key to Abbreviations: BID = twice daily, CPK = creatine phosphokinase, HSR = hypersensitivity reaction, RAL = raltegravir, UGT = uridine diphosphate gluconyltransferase

Appendix B, Table 5. Characteristics of Fusion Inhibitor (Last updated January 29, 2008; last reviewed March 27, 2012)

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 • Each vial contains 108 mg of T20; reconstitute with 1.1mL of sterile water for injection for delivery of approximately 90 mg/1 mL.	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). Reconstituted solution should be refrigerated at 2ºC–8ºC (36ºF–46Fº) and used within 24 hours.	• Local injection site reactions (pain, erythema, induration, nodules and cysts, pruritus, ecchymosis) in almost 100% of patients • Increased incidence of bacterial pneumonia • HSR (<1% of patients): Symptoms may include rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases. Rechallenge is not recommended.

Key to Abbreviations: BID = twice daily, HSR = hypersensitivity reaction, T20 = enfuvirtide

Appendix B, Table 6. Characteristics of CCR5 Antagonist (Last updated March 27, 2012; last reviewed March 27, 2012)

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 drugs that are strong CYP3A inhibitors (with or without CYP3A inducers) including PIs (except TPV/r) • **300 mg BID** when given with NRTIs, T20, TPV/r, NVP, RAL, and other drugs that are not strong CYP3A inhibitors or inducers • **600 mg BID** when given with drugs that are CYP3A inducers, including EFV, ETR, etc. (without a CYP3A inhibitor) Take without regard to meals	14–18 hrs	CYP3A4 substrate	• Abdominal pain • Cough • Dizziness • Musculoskeletal symptoms • Pyrexia • Rash • Upper respiratory tract infections • Hepatotoxicity which may be preceded by severe rash or other signs of systemic allergic reactions • Orthostatic hypotension especially in patients with severe renal insufficiency

Key to Abbreviations: BID = twice daily; CYP = cytochrome P; EFV = efavirenz; ETR = etravirine; MVC = maraviroc; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; T20 = enfuvirtide; TPV/r = tipranavir + ritonavir

Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated March 27, 2012; last reviewed March 27, 2012) (page 1 of 4)

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

Antiretrovirals Generic Name (abbreviation)/ Trade Name	Usual Daily Dose (Refer to Appendix B, Tables 1–6 for additional dosing information.)	Dosing in Renal Insufficiency (Including with chronic ambulatory peritoneal dialysis and hemodialysis)	Dosing in Hepatic Impairment
Nucleoside Reverse Transcriptase Inhibitors **Use of fixed-dose combination NRTI (+/- NNRTI) of Atripla, Combivir, Complera, Trizivir, or Epzicom is not recommended in patients with CrCl <50 mL/min. Use of Truvada is not recommended in patients with CrCl <30 mL/min.**			
Abacavir (ABC)/ Ziagen	300 mg PO BID	No dosage adjustment necessary	**Child-Pugh Score** / **Dose** 5–6 / 200 mg BID (use oral solution) >6 / Contraindicated
Didanosine EC (ddI)/ Videx EC	**Body weight ≥60 kg:** 400 mg PO once daily **Body weight <60 kg**: 250 mg PO once daily	**CrCl (mL/min)** / **Dose (once daily) ≥60 kg** / **<60 kg** 30–59 / 200 mg / 125 mg 10–29 / 125 mg / 125 mg <10, HD, CAPD / 125 mg / use oral solution	No dosage adjustment necessary
Didanosine oral solution (ddI)/ Videx	**Body weight ≥60 kg:** 200 mg PO BID or 400 mg PO once daily **Body weight <60 kg:** 250 mg PO once daily or 125 mg PO BID	**CrCl (mL/min)** / **Dose (once daily) ≥60 kg** / **<60 kg** 30–59 / 200 mg / 150 mg 10–29 / 150 mg / 100 mg <10, HD, CAPD / 100 mg / 75 mg	No dosage adjustment necessary
Emtricitabine (FTC)/ Emtriva	200-mg oral capsule once daily; or 240-mg (24-mL) oral solution once daily	**Dose** **CrCl (mL/min)** / **Capsule** / **Solution** 30–49 / 200 mg q48h / 120 mg q24h 15–29 / 200 mg q72h / 80 mg q24h <15 or HD / 200 mg q96h / 60 mg q24h On dialysis days, take dose after HD session.	No dosage recommendation
Lamivudine (3TC)/ Epivir	300 mg PO once daily; or 150 mg PO BID	**CrCl (mL/min)** / **Dose** 30–49 / 150 mg q24h 15–29 / 1 x 150 mg, then 100 mg q24h 5–14 / 1 x 150 mg, then 50 mg q24h <5 or HD / 1 x 50 mg, then 25 mg q24h On dialysis days, take dose after HD session.	No dosage adjustment necessary

Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated March 27, 2012; last reviewed March 27, 2012) (page 2 of 4)

Antiretrovirals Generic Name (abbreviation)/ Trade Name	Usual Daily Dose (Refer to Appendix B, Tables 1–6 for additional dosing information.)	Dosing in Renal Insufficiency (Including with chronic ambulatory peritoneal dialysis and hemodialysis)	Dosing in Hepatic Impairment
Stavudine (d4T)/ Zerit	**Body weight ≥60 kg:** 40 mg PO BID **Body weight <60 kg:** 30 mg PO BID	**Dose** **CrCl (mL/min)** / **≥60 kg** / **<60 kg** 26–50 / 20 mg q12h / 15 mg q12h 10–25 or HD / 20 mg q24h / 15 mg q24h On dialysis days, take dose after HD session.	No dosage recommendation
Tenofovir (TDF)/ Viread	300 mg PO once daily	**CrCl (mL/min)** / **Dose** 30–49 / 300 mg q48h 10–29 / 300 mg twice weekly (every 72–96 hr) <10 not on HD / no recommendation HD / 300 mg q7d On dialysis days, take dose after HD session.	No dosage adjustment necessary
Emtricitabine (FTC) + **Tenofovir** (TDF)/ Truvada	1 tablet PO once daily	**CrCl (mL/min)** / **Dose** 30–49 / 1 tablet q48h <30 or HD / not recommended	No dosage recommendation
Zidovudine (AZT, ZDV)/ Retrovir	300 mg PO BID	**CrCl (mL/min)** / **Dose** <15 or HD / 100 mg TID or 300 mg once daily On dialysis days, take dose after HD session.	No dosage recommendation
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 once daily at or before bedtime	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment.
Efavirenz (EFV) + **Tenofovir** (TDF) + **Emtricitabine** (FTC) Atripla	1 tablet PO once daily	Not recommended for use in patients with CrCl <50 mL/min. Instead use individual drug components of the fixed-dose combination and adjust TDF and FTC doses according to CrCl level.	
Etravirine (ETR)/ Intelence	200 mg PO BID	No dosage adjustment necessary	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no dosage recommendation
Nevirapine (NVP)/ Viramune or Viramune XR	200 mg PO BID or 400 mg PO once daily (using Viramune XR formulation)	Patients on HD: limited data; no dosage recommendation	Child-Pugh Class A: no dosage adjustment Child-Pugh Class B or C: contraindicated

Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated March 27, 2012; last reviewed March 27, 2012) (page 3 of 4)

Antiretrovirals Generic Name (abbreviation)/ Trade Name	Usual Daily Dose (Refer to Appendix B, Tables 1–6 for additional dosing information.)	Dosing in Renal Insufficiency (Including with chronic ambulatory peritoneal dialysis and hemodialysis)	Dosing in Hepatic Impairment
Rilpivirine (RPV)/ Edurant	25 mg PO once daily	No dosage adjustment necessary	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no dosage recommendation
Rilpivirine (RPV) + **Tenofovir** (TDF) + **Emtricitabine** (FTC)/ Complera	1 tablet PO once daily	Not recommended for use in patients with CrCl <50 mL/min. Instead use individual drug components of the fixed-dose combination and adjust TDF and FTC doses levels according to CrCl level.	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no dosage recommendation
Protease Inhibitors			
Atazanavir (ATV)/ Reyataz	400 mg PO once daily or (ATV 300 mg + RTV 100 mg) PO once daily	No dosage adjustment for patients with renal dysfunction not requiring HD ARV-naive patients on HD: (ATV 300 mg + RTV 100 mg) once daily ARV-experienced patients on HD: ATV or RTV-boosted ATV not recommended	**Child-Pugh Class** / **Dose** B: 300 mg once daily C: not recommended RTV boosting is **not** recommended in patients with hepatic impairment (Child-Pugh Class B or C).
Darunavir (DRV)/ Prezista	(DRV 800 mg + RTV 100 mg) PO once daily (ARV-naive patients only) or (DRV 600 mg + RTV 100 mg) PO BID	No dosage adjustment necessary	Mild-to-moderate hepatic impairment: no dosage adjustment Severe hepatic impairment: not recommended
Fosamprenavir (FPV)/ Lexiva	1400 mg PO BID or (FPV 1400 mg + RTV 100–200 mg) PO once daily or (FPV 700 mg + RTV 100 mg) PO BID	No dosage adjustment necessary	**Child-Pugh Score** / **Dose** PI-naive patients only: 5–9: 700 mg BID 10–15: 350 mg BID PI-naive or PI-experienced patients: 5–6: 700 mg BID + RTV 100 mg once daily 7–9: 450 mg BID + RTV 100 mg once daily 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

Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Last updated March 27, 2012; last reviewed March 27, 2012) (page 4 of 4)

Antiretrovirals Generic Name (abbreviation)/ Trade Name	Usual Daily Dose (Refer to Appendix B, Tables 1–6 for additional dosing information.)	Dosing in Renal Insufficiency (Including with chronic ambulatory peritoneal dialysis and hemodialysis)	Dosing in Hepatic Impairment
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	1250 mg PO BID	No dosage adjustment necessary	Mild hepatic impairment: no dosage adjustment Moderate-to-severe hepatic impairment: do not use
Ritonavir (RTV)/ Norvir	As a PI-boosting agent: 100–400 mg per day	No dosage adjustment necessary	Refer to recommendations for the primary PI.
Saquinavir (SQV)/ Invirase	(SQV 1000 mg + RTV 100 mg) PO BID	No dosage adjustment necessary	Mild-to-moderate hepatic impairment: use with caution 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 Child-Pugh Class B or C: contraindicated
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 and potential for drug-drug interactions. See Appendix B, Table 6 for detailed dosing information.	**CrCl <30 mL/min or HD** Without potent CYP3A inhibitors or inducers: 300 mg BID; reduce to 150 mg BID if postural hypotension occurs 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 Severe hepatic insufficiency: no recommendation

Key to Abbreviations: 3TC = lamivudine, ABC = abacavir, ARV = antiretroviral, ATV = atazanavir, AZT = zidovudine, BID = twice daily, CAPD = chronic ambulatory peritoneal dialysis, CrCl = creatinine clearance, CYP = cytochrome P, d4T = stavudine, ddI = didanosine, DLV = delavirdine, DRV = darunavir, EC = enteric coated, EFV = efavirenz, ETR = etravirine, FPV = fosamprenavir, FTC = emtricitabine, hr = hour, HD = hemodialysis, IDV = indinavir, LPV/r = lopinavir/ritonavir, MVC = maraviroc, NFV = nelfinavir, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, PO = orally, RAL = raltegravir, RPV = rilpivirine, RTV = ritonavir, SQV = saquinavir, T20 = enfuvirtide, TDF = tenofovir, TID = three times daily, TPV = tipranavir, XR = extended release, ZVD = zidovudine

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[a]	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[b]	<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

[a] 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

[b] Modified total bilirubin used for patients who have Gilbert's syndrome or who are taking indinavir or atazanavir

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

[c] Sum of points for each component

Appendix C, Table 1. Monthly Average Wholesale Price[a] of Antiretroviral Drugs (Last updated March 27, 2012; last reviewed March 27, 2012) (page 1 of 2)

Antiretroviral Drug Generic (Brand) Name	Strength	Dosing	Tabs/Capsules/ mLs per Month	AWP[a] (Monthly)
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)				
abacavir (Ziagen)	300-mg tab 20-mg/mL soln	2 tabs daily 30 mLs daily	60 tabs 900 mL	$641.50 $674.60
didanosine DR (generic product) (Videx EC)	400-mg cap 400-mg cap	1 cap daily 1 cap daily	30 caps (≥ 60 kg) 30 caps (≥ 60 kg)	$368.72 $460.14
emtricitabine (Emtriva)	200-mg cap	1 cap daily	30 tabs	$504.37
lamivudine (generic) (Epivir) (Epivir)	300-mg tab 300-mg tab 10-mg/mL soln	1 tab daily 1 tab daily 30 mL daily	30 tabs 30 tabs 900 mL	$429.66 $477.41 $509.28
stavudine (generic) (Zerit)	40-mg cap 40-mg cap	1 cap twice daily 1 cap twice daily	60 caps 60 caps	$411.16 $493.38
tenofovir (Viread)	300-mg tab	1 tab daily	30 tabs	$873.28
zidovudine (generic) (Retrovir)	300-mg tab 300-mg tab	1 tab twice daily 1 tab twice daily	60 tabs 60 tabs	$360.97 $557.83
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)				
delavirdine (Rescriptor)	200-mg tab	2 tabs three times daily	180 tabs	$365.45
efavirenz (Sustiva)	200-mg cap 600-mg tab	3 caps daily 1 tab daily	90 caps 30 tabs	$689.52 $689.52
etravirine (Intelence)	100-mg tab 200-mg tab	2 tabs twice daily 1 tab twice daily	120 tabs 60 tabs	$978.64 $978.64
nevirapine (Viramune) nevirapine XR (Viramune XR)	200-mg tab 400-mg tab	1 tab twice daily 1 tab daily	60 tabs 30 tabs	$723.08 $632.68
rilpivirine (Edurant)	25-mg tab	1 tab daily	30 tabs	$804.38
Protease Inhibitors (PIs)				
atazanavir (Reyataz)	150-mg cap[b] 200-mg cap 300-mg cap[b]	2 caps daily 2 caps daily 1 cap daily	60 caps 60 caps 30 caps	$1,176.23 $1,176.23 $1,165.12
darunavir (Prezista)	400-mg tab[b] 600-mg tab[b]	2 tabs daily 1 tab twice daily	60 tabs 60 tabs	$1,230.20 $1,230.20
fosamprenavir (Lexiva)	700-mg tab	2 tabs twice daily 1 tab twice daily[b] 2 tabs once daily[b]	120 tabs 60 tabs 60 tabs	$1,812.68 $906.34 $906.34
indinavir (Crixivan)	400-mg cap	2 caps three times daily 2 caps twice daily[b]	180 caps 120 caps	$548.12 $365.41
nelfinavir (Viracept)	625-mg tab	2 tabs twice daily	120 tabs	$879.84
ritonavir (Norvir)	100-mg tab	1 tab once daily 1 tab twice daily 2 tabs twice daily	30 tabs 60 tabs 120 tabs	$308.60 $617.20 $1,234.40

Appendix C, Table 1. Monthly Average Wholesale Price[a] of Antiretroviral Drugs (Last updated March 27, 2012; last reviewed March 27, 2012) (page 2 of 2)

Antiretroviral Drug Generic (Brand) Name	Strength	Dosing	Tabs/Capsules/ mLs per Month	AWP[a] (Monthly)
saquinavir (Invirase)	500-mg tab[b]	2 tabs twice daily	120 tabs	$1,088.84
tipranavir (Aptivus)	250-mg cap[b]	2 caps twice daily	120 caps	$1,335.14
Integrase Strand Transfer Inhibitor (INSTI)				
raltegravir (Isentress)	400-mg tab	1 tab twice daily	60 tabs	$1,171.30
Fusion Inhibitor				
enfuviritide (Fuzeon)	90-mg inj kit	1 inj twice daily	60 doses (1 kit)	$3,248.72
CCR5 Antagonist				
maraviroc (Selzentry)	150-mg tab 300-mg tab	1 tab twice daily 1 tab twice daily	60 tabs 60 tabs	$1,148.16 $1,148.16
Coformulated Combination Antiretroviral Drugs				
abacavir/lamivudine (Epzicom)	600/300-mg tab	1 tab daily	30 tabs	$1,118.90
tenofovir/emtricitabine (Truvada)	300/150-mg tab	1 tab daily	30 tabs	$1,391.45
zidovudine/lamivudine (generic) (Combivir)	300/150-mg tab 300/150-mg tab	1 tab twice daily 1 tab twice daily	60 tabs 60 tabs	$931.61 $1,035.12
abacavir/lamivudine/zidovudine (Trizivir)	600/150/300-mg tab	1 tab twice daily	60 tabs	$1,676.62
lopinavir/ritonavir (Kaletra)	200 mg/50-mg tab 400 mg/100 mg per 5-mL soln	2 tabs twice daily or 4 tabs once daily 5 mL twice daily	120 tabs 300 mL	$871.36 $871.34
rilpivirine/tenofovir/emtricitabine (Complera)	200/25/300 mg	1 tab daily	30 tabs	$2,195.83
efavirenz/tenofovir/emtricitabine (Atripla)	300/200/600 mg	1 tab daily	30 tabs	$2,080.97

[a] AWP = Average Wholesale Price in 2012 (source: First DataBank Blue Book AWP, accessed January 2012) Note that this price may not represent the pharmacy acquisition price or the price paid by consumers.

[b] Should be used in combination with ritonavir. Please refer to Appendix B, Table 3 for ritonavir doses.

Key to Abbreviations: AWP = average wholesale price; cap = capsule, DR = delayed release, EC = enteric coated, inj = injection, soln = solution, tab = tablet, XR = extended release