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

December 1, 2007

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

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

What's New in the Document?

The following changes have been made to several sections of the October 10, 2006 version of the guidelines. Additional revisions to other sections of these guidelines will be released in 2008.

Laboratory Assessment

- Drug Resistance Testing – The Panel recommends performing genotypic drug resistance testing for all treatment-naïve patients entering into clinical care, regardless of whether antiretroviral therapy is to be initiated **(AIII)**. This recommendation is based on the fact that transmitted resistance mutation may be detected at a time point more proximal to the time of infection than later. Repeat testing may be considered at the time when therapy is to be initiated **(CIII)**.

- Tropism Assay – The Panel recommends tropism testing prior to the initiation of a CCR5 antagonist, such as maraviroc **(AII)**. Coreceptor tropism testing might also be considered for patients exhibiting virologic failure on maraviroc (or any CCR5 inhibitor) **(BIII)**.

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

When to Start Antiretroviral Therapy

1. The Panel recommends that antiretroviral therapy should be initiated in patients with history of an AIDS-defining illness or with a CD4 T-cell count <350 cells/mm^3; the data supporting this recommendation are stronger for those with a CD4 T-cell count <200 cells/mm^3 and with a history of AIDS **(AI)** than for those with CD4 T-cell counts between 200 and 350 cells/mm^3 **(AII)**.
2. The Panel also recommends treatment for the following groups regardless of CD4 T-cell count:
    1. pregnant patients **(AI)**;
    2. patients with HIV-associated nephropathy **(AI)**;
    3. patients coinfected with hepatitis B when treatment for hepatitis B virus is indicated **(BIII)**.
3. The optimal time to initiate therapy in asymptomatic patients with CD4 T-cell count >350 cells/mm^3 is not well defined. The decision of whether or not to start therapy in these patients should take into account the potential benefits and risks associated with therapy, comorbidities, and patient readiness and willingness to adhere to long-term treatment.

Management of Treatment-Experienced Patients

This section was revised to include (1) a review of the newer classes of antiretroviral agents (CCR5 antagonists and integrase inhibitors) and their roles in the management of treatment-experienced patients with virologic failure and (2) a discussion of immunologic failure.

Tables Update

Various tables have been updated to reflect new recommendations and new information on specific antiretroviral drugs.

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DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents Panel Roster

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Introduction

Antiretroviral therapy (ART) for treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection has improved steadily since the advent of combination therapy in 1996. More recently, new drugs have been approved that offer new mechanisms of action, added potency, dosing convenience, and improved safety profiles, whereas some previously popular drugs are being used less often as their drawbacks become better defined. Resistance testing is used more commonly in clinical practice, and interactions among antiretroviral agents and other drugs have become more complex.

The Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel), a working group of the Office of AIDS Research Advisory Council, develops these guidelines, which outline current understanding of how clinicians should use antiretroviral drugs to treat adults and adolescents with HIV infection in the United States. The Panel considers new evidence and adjusts recommendations accordingly. The primary areas of attention and revision have included when to initiate therapy, which drug combinations are preferred and which drugs or combinations should be avoided, and means to continue clinical benefit in the face of antiretroviral drug resistance. In contrast, some aspects of therapy, such as medication adherence, although important, have seen less rapid data evolution and thus fewer changes. Yet other topics, such as the treatment of HIV during pregnancy, have warranted more in-depth attention by separate guidelines groups.

KEY CLINICAL QUESTIONS ADDRESSED BY GUIDELINES

For ease of use, these guidelines are organized so as to answer the following series of clinical questions clinicians are most likely to face in making treatment decisions:

- ***What are some key clinical and laboratory parameters to assess and monitor before and after initiation of antiretroviral therapy?***
- ***What is the role of resistance testing in guiding therapy decisions?***
- ***When should therapy be started in patients with established HIV infection?***
- ***Which drugs are preferred for initial therapy? What are some alternative options? What drugs or drug combinations should not be used?***
- ***What are some limitations to the safety and efficacy of antiretroviral therapy?***
- ***What are the goals and how should therapy be optimized in treatment-experienced patients with virologic failure?***
- ***What are specific considerations when using antiretroviral therapy in certain special patient populations (e.g., acute HIV infection, HIV-infected adolescents, illicit drug users, HIV-infected females [including pregnant women], and patients with coinfections such as hepatitis B or C or tuberculosis)?***

GUIDELINES PROCESS

These guidelines outline the current understanding of how clinicians should use antiretroviral agents to treat adults and adolescents infected with HIV-1.

Basis for Recommendations

Recommendations are based upon expert opinion and scientific evidence. Each recommendation has a letter/Roman numeral rating (**Table 1**). The letter indicates the strength of the recommendation based on the expert opinion of the Panel. The Roman numeral indicates the quality of the scientific evidence to support the recommendation. When appropriate data are unavailable, inconclusive, or contradictory, the recommendation is based on expert opinion. These recommendations are not intended to supersede the judgment of clinicians who are knowledgeable in the care of HIV infection.

Updating of Guidelines

These guidelines generally represent the state of knowledge regarding the use of antiretroviral agents. However, as the science rapidly evolves, the availability of new agents and new clinical data may rapidly change therapeutic options and preferences. The guidelines are therefore updated frequently by the Panel, which meets monthly by teleconferencing to make ongoing revisions as necessary. All revisions are

summarized and highlighted on the AIDS*info* Web site. Proposed revisions are posted for a public comment period, generally for 2 weeks, after which comments are reviewed by the Panel prior to finalization. Comments can be sent to **aidsinfowebmaster@aidsinfo.nih.gov**.

Other Guidelines

These guidelines focus on treatment for adults and adolescents. Separate guidelines outline how to use antiretroviral therapy for such populations as pregnant women, pediatric patients and health care workers with possible occupational exposure to HIV. (See **http://aidsinfo.nih.gov/guidelines.**) There is a brief discussion of the management of women of reproductive age and pregnant women in this document. However, for more detailed and up-to-date discussion on this and other special populations, the Panel defers to the designated expertise outlined by panels that have developed these guidelines.

Importance of HIV Expertise in Clinical Care

Multiple studies have demonstrated that better outcomes are achieved in patients cared for by a clinician with expertise *[1-6]*. This has been shown in terms of mortality, rate of hospitalizations, compliance with guidelines, cost of care, and adherence to medications. The definition of expertise in these studies has varied, but most rely on the number of patients actively managed. Based on this observation, the Panel recommends HIV primary care by a clinician with at least 20, and preferably at least 50, HIV-infected patients. Many authoritative groups have combined the recommendation based on active patients, along with fulfilling ongoing continuing medical education (CME) requirements on HIV-related topics.

Baseline Evaluation

Each patient initially entering care should have a complete medical history, physical examination, and laboratory evaluation. The purpose is to confirm the presence of HIV infection, determine if HIV infection is acute (See **Acute HIV Infection.**), determine the presence of coinfections, and assess overall health condition as recommended by the primary care guidelines for the management of HIV-infected patients *[7]*.

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

- HIV antibody testing (if laboratory confirmation not available) **(AI)**;
- CD4 T-cell count **(AI)**;
- Plasma HIV RNA **(AI)**;
- Complete blood count, chemistry profile, transaminase levels, BUN and creatinine, urinalysis, RPR or VDRL, tuberculin skin test (unless a history of prior tuberculosis or positive skin test), *Toxoplasma gondii* IgG, Hepatitis A, B, and C serologies, and PAP smear in women **(AIII)**;
- Fasting blood glucose and serum lipids if considered at risk for cardiovascular disease and for baseline evaluation prior to initiation of combination antiretroviral therapy **(AIII)**; and
- For patients with pretreatment HIV RNA >1,000 copies/mL, genotypic resistance testing is recommended when the patients enter into care, regardless of whether therapy will be initiated immediately **(AIII)**. If therapy is to be deferred, repeat testing at the time of antiretroviral initiation should be considered **(CIII).** (See **Drug Resistance Testing** section.)

In addition:

1. An optional test for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in order to identify high-risk behavior and the need for sexually transmitted disease (STD) therapy **(BII)**; and
2. Chest x-ray if clinically indicated **(BIII)**.

Patients living with HIV infection must often cope with multiple social, psychiatric, and medical issues. Thus, the evaluation should also include assessment of substance abuse, economic factors, social support, mental illness, comorbidities, and other factors that are known to impair the ability to adhere to treatment and to alter outcomes. Once evaluated, these factors should be managed accordingly.

Laboratory Testing for Initial Assessment and Monitoring for Therapeutic Response

Two surrogate markers are routinely used to determine indications for treatment and to monitor the efficacy of therapy: CD4 T-cell count and plasma HIV RNA (viral load). In addition, resistance testing should be used to guide selection of antiretroviral regimen in both treatment-naïve and -experienced patients; viral tropism assay should be performed prior to initiation of a CCR5 antagonist; and HLA-B*5701 testing should be performed prior to initiation of abacavir. The rationale and utility of these laboratory tests are discussed below.

CD4 T-CELL COUNT

The CD4 T-cell count (or CD4 count) serves as the major clinical indicator of immunocompetence in patients with HIV infection. It is usually the most important consideration in decisions to initiate antiretroviral therapy. The most recent CD4 cell count is the strongest predictor of subsequent disease progression and survival, according to clinical trials and cohort studies data on patients receiving antiretroviral therapy. A significant change between two tests (2 standard deviations) is defined as approximately 30% change of the absolute count and 3 digit change in CD4 percentage.

- **Use of CD4 T-Cell Count for Initial Assessment**. The CD4 T-cell count is usually the most important consideration in decisions to initiate antiretroviral therapy. All patients should have a baseline CD4 cell count at entry into care **(AI)**; many authorities recommend two baseline measurements before decisions are made to initiate antiretroviral therapy because of wide variations in results **(CIII)**. The test should be repeated yet a third time if discordant results are seen **(AI)**. Recommendations for initiation of antiretroviral therapy based on CD4 T-cell count are found in the **When to Start: Indications for Antiretroviral Therapy** section**.**

- **Use of CD4 T-Cell Count for Monitoring Therapeutic Response**. Adequate viral suppression for most patients on therapy is defined as an increase in CD4 cell count that averages 100–150 cells/mm^3 per year with an accelerated response in the first 3 months. This is largely because of redistribution. Subsequent increases with good virologic control show an average increase of approximately 100 cells/mm^3 per year for the subsequent few years until a threshold is reached *[8]*.

- **Frequency of CD4 T-Cell Count Monitoring.** In general, CD4 count should be determined every 3 to 6 months to (1) determine when to start antiretroviral therapy in patients who do not meet the criteria for initiation; (2) assess immunologic response to antiretroviral therapy; and (3) assess the need for initiating chemoprophylaxis for opportunistic infections.

VIRAL LOAD TESTING

Plasma HIV RNA (viral load) may be a consideration in the decision to initiate therapy. In addition, viral load is critical for evaluating response to therapy **(AI)**. Three HIV viral load assays have been approved by the Food and Drug Administration (FDA) for clinical use:

- HIV-1 reverse transcriptase polymerase chain reaction (PCR) assay (Amplicor HIV-1 Monitor Test, version 1.5, Roche Diagnostic);
- Nucleic acid amplification test for HIV RNA (NucliSens HIV-1 QT, bioMerieux); and
- Signal amplification nucleic acid probe assay (VERSANT HIV-1RNA 3.0 assay, Bayer).

Analysis of 18 trials including more than 5,000 participants with viral load monitoring showed a significant association between a decrease in plasma viremia and improved clinical outcome. Thus, viral load testing serves as a surrogate marker for treatment response and may be useful in predicting clinical progression. The minimal change in viral load considered to be statistically significant (2 standard deviations) is a threefold or a 0.5 $\log_{10}$ copies/mL change. One key goal of therapy is a viral load below the limits of detection (at <50 copies/mL for the Amplicor assay, <75 copies/mL for the VERSANT assay, and <80 copies/mL for the NucliSens assay). This goal should be achieved by 16–24 weeks **(AI)**. Recommendations for the frequency of viral load monitoring are summarized below and in **Table 2**.

- **At Initiation or Change in Therapy**. Plasma viral load should be measured immediately before treatment and at 2–8 weeks after treatment initiation or treatment changes because of suboptimal viral suppression. In the latter measure, there should be a decrease of at least a 1.0 $\log_{10}$ copies/mL **(BI)**.
- **In Patients With Viral Suppression Where Changes are Motivated by Drug Toxicity or Regimen Simplification**. Some experts also recommend repeating viral load measurement within 2–8 weeks after changing therapy. The purpose of viral load monitoring at this point is to confirm potency of the new regimen **(BII)**.
- **In Patients on a Stable Antiretroviral Regimen** The viral load testing should be repeated every 3–4 months thereafter or if clinically indicated **(BII)**. The testing should be repeated every 3–4 months thereafter or if clinically indicated (Table 2).

Monitoring in Patients With Suboptimal Response. In addition to viral load monitoring, a number of additional factors should be assessed, such as nonadherence, altered pharmacology, or drug interactions. Resistance testing may be helpful in identifying the presence of resistance mutations that may necessitate a change in therapy **(AII)**.

DRUG RESISTANCE TESTING

Panel's Recommendations:

- ***HIV drug resistance testing is recommended for persons with HIV infection when they enter into care regardless of whether therapy will be initiated immediately (AIII). If therapy is deferred, repeat testing at the time of antiretroviral therapy initiation should be considered (CIII).***
- ***A genotypic assay is generally preferred for antiretroviral-naïve persons (AIII).***
- ***HIV drug resistance testing should be performed to assist in selecting active drugs when changing antiretroviral regimens in cases of virologic failure (AII).***
- ***Drug resistance testing should also be performed when managing suboptimal viral load reduction (AII).***
- ***Drug resistance testing in the setting of virologic failure should be performed while the patient is taking his/her antiretroviral drugs, or immediately (i.e., within 4 weeks) after discontinuing therapy (AII).***
- ***Genotypic resistance testing is recommended for all pregnant women prior to initiation of therapy (AIII) and for those entering pregnancy with detectable HIV RNA levels while on therapy (AII).***
- ***Drug resistance testing is not advised for persons with viral load <1,000 copies/mL, because amplification of the virus is unreliable (DIII).***

GENOTYPIC AND PHENOTYPIC RESISTANCE ASSAYS

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

Genotypic Assays

Genotypic assays detect drug resistance mutations present in relevant viral genes. Certain genotypic assays involve sequencing of the entire reverse transcriptase and protease genes, whereas others use probes to detect selected mutations that are known to confer drug resistance. Genotypic assays can be performed rapidly, and results can be reported within 1–2 weeks of sample collection. Interpretation of test results requires knowledge of the mutations that different antiretroviral drugs select for and of the potential for cross resistance to other drugs conferred by certain mutations. The International AIDS Society-USA (IAS-USA) maintains a list of significant resistance-associated mutations in the reverse transcriptase, protease, and envelope genes. (See **http://www.iasusa.org/resistance_mutations.**) Various techniques are now available to assist the provider in interpreting genotypic test results *[9-12]*. Clinical trials have demonstrated the benefit of consultation with specialists in HIV drug resistance in improving virologic outcomes *[13]*. Clinicians are thus encouraged to consult a specialist to facilitate interpretation of genotypic results and design of an optimal new regimen.

Phenotypic Assays

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

ratio of the IC_{50} of test and reference viruses is reported as the fold increase in IC_{50} (i.e., fold resistance).

Automated, recombinant phenotypic assays are commercially available with results available in 2–3 weeks. However, phenotypic assays cost more to perform than genotypic assays. In addition, interpretation of phenotypic assay results is complicated by incomplete information regarding the specific resistance level (i.e., fold increase in IC_{50}) that is associated with drug failure, although clinically significant fold increase cutoffs are now available for some drugs *[14-18]*. Again, consultation with a specialist can be helpful for interpreting test results.

Further limitations of both genotypic and phenotypic assays include lack of uniform quality assurance for all available assays, relatively high cost, and insensitivity for minor viral species. If drug-resistant viruses are present but constitute <10%–20% of the circulating virus population, they probably will not be detected by available assays. This limitation is important because, after drugs exerting selective pressure on drug-resistant populations are discontinued, a re-emergence of wild-type virus as the predominant plasma population often occurs, resulting in a decrease of the proportion of virus with resistance mutations to below these thresholds *[19-21]*. This reversion to predominantly wild-type virus often occurs in the first 4–6 weeks after drugs are stopped. Prospective clinical studies have shown that, despite this plasma reversion, reinstitution of the same antiretroviral agents (or those sharing similar resistance pathways) is usually associated with early drug failure, and the virus present at failure is derived from previously archived resistant virus *[22]*. 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 4–6 weeks after discontinuation may still reveal mutations. Yet, the absence of detectable resistance in such patients must be interpreted with caution in designing subsequent antiretroviral regimens.

USE OF RESISTANCE ASSAYS IN CLINICAL PRACTICE (TABLE 3)

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

Drug resistance testing is not advised for persons with viral load <1,000 copies/mL, because amplification of the virus is unreliable, and unnecessary charges may be incurred for testing **(DIII)**.

Use of Resistance Assays in Determining Initial Treatment

Transmission of drug-resistant HIV strains has been well documented and has been associated with suboptimal virologic response to initial antiretroviral therapy *[23-26]*. The likelihood that a patient will acquire drug-resistant virus is related to the prevalence of drug resistance in persons engaging in high-risk behaviors in the community. In the United States and Europe, recent studies suggest the risk that transmitted virus will be resistant to at least one antiretroviral drug is in the range of 6%–16% *[27-32]*, with 3%–5% of transmitted viruses exhibiting reduced susceptibility to drugs from more than one class *[23, 31]*. If the decision is made to initiate therapy in a person with acute HIV infection, resistance testing at baseline will likely optimize virologic response. Therefore, resistance testing in this situation is recommended **(AIII)**, and a genotypic assay is generally preferred because of its more rapid turnaround time **(AIII)**. In the absence of therapy, resistant viruses may decline over time to less than the detection limit of standard resistance tests but may still increase the risk of treatment failure when therapy is eventually initiated. Therefore, if the decision is made to defer therapy, resistance testing during acute HIV infection should still be performed **(AIII)**. In this situation, the genotypic resistance test result might be kept on record for several years before it becomes clinically useful. Because of the possibility of acquisition of drug-resistant virus during this period of time, repeat resistance testing at the time ART is initiated should be considered **(CIII)**.

Performing drug resistance testing before initiation of antiretroviral therapy in patients with chronic HIV infection is less straightforward. The rate at which transmitted resistance-associated mutations revert to wild-type virus has not been completely delineated, but mutations present at the time of HIV transmission are more stable than those selected under drug pressure, and it is often possible to detect resistance-associated mutations in viruses that were transmitted several years earlier *[33, 34]*. No prospective trial has

addressed whether drug resistance testing prior to initiation of therapy confers benefit in this population. However, limited data from several, but not all, studies suggest suboptimal virologic responses in persons with baseline mutations *[23-26, 35-37]*. In addition, a cost-effectiveness analysis of early genotypic resistance testing suggests that baseline testing in this population should be performed *[38]*. Therefore, resistance testing in chronically infected persons at the time of entry into HIV care is recommended **(AIII)**. Genotypic testing is generally preferred in this situation **(AIII)**. Repeat testing at the time ART is initiated should be considered because of the possibility that the patient may have acquired drug-resistant virus **(CIII)**.

Use of Resistance Assays in the Event of Virologic Failure

Resistance assays are useful in guiding decisions for patients experiencing virologic failure while on antiretroviral therapy. Prospective data supporting drug-resistance testing in clinical practice at this time are derived from trials in which test utility was assessed for cases of virologic failure. These studies involved genotypic assays, phenotypic assays, or both *[13, 39-45]*. In general, these studies indicated that early virologic response to salvage regimens was improved when results of resistance testing were available to guide changes in therapy, compared with responses observed when changes in therapy were guided only by clinical judgment. Thus, resistance testing appears to be a useful tool in selecting active drugs when changing antiretroviral regimens in cases of virologic failure **(AII)**. (See **Management of the Treatment-Experienced Patient**.)

Resistance testing also can help guide treatment decisions for patients with suboptimal viral load reduction **(AII)**. Virologic failure in the setting of combination antiretroviral therapy is, for certain patients, associated with resistance to only one component of the regimen *[46-48]*. In that situation, substituting individual drugs in a failing regimen might be possible, although this concept will require clinical validation. (See **Management of the Treatment-Experienced Patient**.)

Use of Resistance Assays in Pregnant Patients

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

HLA-B*5701 SCREENING

Panel's Recommendations:

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

The abacavir hypersensitivity reaction (ABC HSR) is a multiorgan clinical syndrome typically seen within the initial 6 weeks of abacavir treatment. This reaction has been reported in 5%–8% of patients participating in clinical trials when using clinical criteria for the diagnosis, and it is the major reason for early discontinuation of abacavir. (See **Table 17a**.) Discontinuing abacavir usually promptly reverses HSR, whereas subsequent rechallenge can cause a rapid, severe, and even life-threatening recurrence.

Studies that evaluated demographic risk factors for ABC HSR have shown racial background as a risk factor, with white patients generally having a higher risk (5%–8%) than black patients (2%–3%). Several groups reported a highly significant association between ABC HSR and the presence of the MHC class I allele HLA-B*5701 *[49, 50]*. An abacavir skin patch test (ABC SPT) was developed as a research tool to immunologically confirm ABC HSR, because the clinical criteria used for ABC HSR are overly sensitive and may lead to false-positive ABC HSR diagnoses *[51]*. A positive ABC SPT is an abacavir-specific delayed hypersensitivity reaction that results in redness and swelling at the skin site. All ABC SPT positive patients studied were also positive for the

HLA-B*5701 allele *[52]*. The ABC SPT could be falsely negative for some patients with ABC HSR. It is not recommended as a clinical tool at this point. The PREDICT-1 study randomized patients before starting abacavir either to be prospectively screened for HLA-B*5701 (in which HLA-B*5701–positive patients were not offered abacavir) or to standard of care (no screening, with all patients receiving abacavir) *[53]*. The overall HLA-B*5701 prevalence in this predominately white population was 5.6%. In this cohort, screening for HLA-B*5701 eliminated immunologic ABC HSR (defined as ABC SPT positive) compared with standard of care (0% vs. 2.7%), yielding a 100% negative predictive value with respect to SPT as well as significantly decreasing the rate of clinically suspected ABC HSR (3.4% vs. 7.8%). The SHAPE study corroborated the low rate of immunologically validated ABC HSR in black patients and confirmed the utility of HLA-B*5701 screening for the risk for ABC HSR (100% sensitivity in black and white populations) *[54]*.

On the basis of the results of these studies, the Panel recommends screening for HLA-B*5701 before starting patients on an abacavir-containing regimen **(AI)**. HLA-B*5701–positive patients should not be prescribed abacavir **(AI)**, and the positive status should be recorded as an abacavir allergy in the patient's medical record **(AII)**. HLA-B*5701 testing needs to be performed only once in a patient's lifetime, so efforts to carefully record and maintain the result and to educate the patient about its implications are important. The specificity of the HLA-B*5701 test 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)**.

CORECEPTOR TROPISM ASSAYS

Panel's Recommendations:

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

HIV enters cells by a complex process that involves the sequential attachment to the CD4 receptor, followed by binding to either the CCR5 or CXCR4 molecules and fusion of the viral and cellular membranes *[55]*. The CCR5 inhibitors (i.e., maraviroc, vicriviroc) prevent HIV entry into target cells by binding to the CCR5 receptor *[56]*. Phenotypic and, to a lesser degree, genotypic assays have been developed that can determine the coreceptor tropism (CCR5, CXCR4, or both) of the patient's dominant virus population. One assay (*Trofile*, Monogram Biosciences, Inc., South San Francisco, CA) was used to screen patients who were participating in studies that formed the basis of approval for maraviroc, the only CCR5 inhibitor currently available. Other assays are under development and are currently used primarily for research purposes or in clinical situations in which the *Trofile* assay is not readily available.

Background

The vast majority of patients harbor a CCR5-utilizing virus (R5 virus) during acute/recent infection, suggesting that the R5 variant is preferentially transmitted compared with CXCR4 (X4) variants. Viruses in the majority of untreated patients eventually exhibit a shift in coreceptor tropism from CCR5 to either CXCR4 or both CCR5 and CXCR4 (dual- or mixed-tropic; D/M-tropic). This shift is temporally associated with a more rapid decline in CD4 T-cell counts *[57, 58]*, although whether this shift is a cause or a consequence of progressive immunodeficiency remains undetermined *[55]*. Antiretroviral-treated patients with extensive drug-resistance are more likely to harbor detectable X4- or D/M-tropic variants than untreated patients with comparable CD4 T-cell counts *[59]*. The prevalence of X4- or D/M-tropic variants increases to more than 50% in treated patients with CD4 T-cell counts less than 100 cells/mm^3 *[60, 61]*.

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 (gp120 and gp41). These pseudoviruses are either replication-competent (*Phenoscript* assay, VIRalliance, Paris, France) or replication-defective (*Trofile* assay, Monogram

Biosciences, Inc.) *[62, 63]*. These pseudoviruses can then be used to infect target cell lines that express CD4 and 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 viral load of at least 1,000 copies/mL. *In vitro* mixing experiments of R5 and X4 variants indicate that the assay can detect a minor variant with 100% sensitivity when that variant is present at a frequency of 10%, whereas the assay has 83% sensitivity when the variant is present at a frequency of 5% *[62]*. This sensitivity may not be sufficient to rule out the presence of clinically meaningful levels of X4- or D/M-tropic virus in patients who are initiating a CCR5 inhibitor-based regimen *[64]*. For unclear reasons, a minority of samples cannot be successfully phenotyped with this assay. A more sensitive assay that has improved detection of minor viral populations is under development *[65]*.

Genotypic Assays

These assays are under investigation *[66-68]* but are not commercially available.

Use of Coreceptor Tropism Assays in Clinical Practice

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

Other potential clinical uses for the tropism assay are for prognostic purposes *[57, 58, 69]* or for assessment of tropism prior to starting ART, in case a CCR5 inhibitor is required later (e.g., in a regimen change for toxicity). Currently, there are not sufficient data to support these uses.

Treatment Goals

Eradication of HIV infection cannot be achieved with available antiretroviral regimens. This is chiefly because the pool of latently infected CD4 T-cells is established during the earliest stages of acute HIV infection *[70]* and persists with a long half-life, even with prolonged suppression of plasma viremia *[71-74]*. The primary goals driving the decision to initiate antiretroviral therapy therefore are to:

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

Adoption of treatment strategies recommended in these guidelines has resulted in substantial reductions in HIV-related morbidity and mortality *[75-77]* and has reduced vertical transmission *[78, 79]*. Higher plasma HIV RNA levels (viral load) are associated with more rapid disease progression *[80]*, although other factors likely contribute as well to the rate of CD4 T-cell decline *[81]*. Maximal suppression of plasma viremia for as long as possible to delay the selection of drug resistance mutations, to preserve CD4 T-cell numbers, and to confer substantial clinical benefits are the most important goals of antiretroviral therapy *[82]*. (See **Baseline Evaluation.**)

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

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

- high potency of antiretroviral regimen,
- excellent adherence to treatment regimen *[83, 84]*,
- low baseline viremia,
- higher baseline CD4 T-cell count *[83, 84]*, and
- rapid (i.e., $\geq$1 log $_{10}$ in 1–4 months) reduction of viremia in response to treatment *[84]*.

Successful outcomes are not always observed. Viral suppression rates in clinical practice may be lower than the 80%–90% seen in clinical trials, although the use of current compact, potent, and well-tolerated regimens has probably decreased this difference in outcomes between clinical trials and clinical practice *[85]*. (See also **Management of the Treatment-Experienced Patient: Assessment of Antiretroviral Treatment Failure and Changing Therapy**.)

STRATEGIES TO ACHIEVE TREATMENT GOALS

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

Selection of Initial Combination Regimen

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

Pretreatment Drug Resistance Testing

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

antiretroviral regimen. (See **Drug Resistance Testing** section.)

Improving Adherence

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

When to Start: Indications for Initiation of Antiretroviral Therapy

Panel's Recommendations:

- ***Antiretroviral therapy should be initiated in patients with a history of an AIDS-defining illness or with a CD4 T-cell count <350 cells/mm^3. The data supporting this recommendation are stronger for those with a CD4 T-cell count <200 cells/mm^3 and with a history of AIDS (AI) than for those with CD4 T-cell counts between 200 and 350 cells/mm^3 (AII).***

- ***Antiretroviral therapy should also be initiated in the following groups of patients regardless of CD4 T-cell count:***
  a. ***Pregnant women (AI);***
  b. ***Patients with HIV-associated nephropathy (AI); and***
  c. ***Patients coinfected with HBV when treatment for HBV infection is indicated (BIII).***

- ***Antiretroviral therapy may be considered in some patients with CD4 T-cell counts >350cells/mm^3. (See text for further discussion.)***

- ***The necessity for patient adherence to a long-term drug regimen should be discussed in depth by the patient and clinician (AIII). Barriers to adherence should be addressed before therapy is initiated.***

The primary goals of antiretroviral therapy are to improve and/or preserve immune function and reduce HIV-associated morbidity and mortality. A potential secondary benefit is the theoretical likelihood of reducing HIV transmission because of continued high-risk behaviors *[86]*.

Large observational cohort studies and prognostic models provide some guidance based on the prognosis for disease-free survival as determined by baseline CD4 T-cell count (**Figure A** and **Tables 4a**, **4b)** *[87-89]* Potent combination antiretroviral therapy can increase and potentially normalize CD4 T-cell count in the majority of patients with maximal viral suppression regardless of baseline CD4 T-cell count *[90, 91]*.

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

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

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

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

Randomized controlled trials strongly support initiation of therapy in patients with CD4 T-cell count <200 cells/mm^3. A prospective, controlled study provided strong evidence that treating symptomatic patients and patients with CD4 T-cell counts <200 cells/mm^3 improved survival and reduced disease progression *[92]*.

Subsequent long-term data from multiple observational cohort studies have provided strong support for the recommendation that therapy should always be initiated before the CD4 T-cell counts decline to <200 cells/mm^3 (**Figure A** and **Table 4a)** *[75, 76, 88, 89, 93-95]*.

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

Data from the ART Cohort Collaboration, which included 61,798 patient-years of follow-up, showed that, at 3 to 5 years after starting therapy, the risk for AIDS/death was significantly less in those who started therapy with a CD4 T-cell count between 200 and 350 compared with those who initiated ART at a CD4 threshold of 200 cells/mm^3 *[96]*. This study also demonstrated that baseline viral load was not significantly associated with risk of AIDS or death. However, patients with high viral loads 6-months posttreatment were found to have higher rates of disease progression, which indicates that virologic response to antiretroviral therapy remains a critical factor in monitoring ART.

In the era of combination antiretroviral therapy, several large observational studies have indicated that the risk of several non-AIDS-defining conditions, including cardiovascular diseases, liver-related events, renal disease, and certain non-AIDS malignancies *[97-102]* is greater than the risk for AIDS in persons with CD4 T-cell counts >200 cells/mm^3; the risk for these events increases progressively as the CD4 T-cell count decreases from 350 to 200 cells/mm^3.

The SMART study, a prospective, randomized, multicenter, cohort study, compared treatment involving CD4 count–guided treatment interruption (i.e., therapy was discontinued when the CD4 T-cell count exceeded 350 cells/mm^3 and reinitiated when the CD4 T-cell count declined to <250 cells/mm^3) with continuous antiretroviral therapy. The risks for all-cause mortality, which was largely attributed to causes other than AIDS, and several non-AIDS defining conditions (including hepatic failure, renal disease, cardiovascular disease, and non-AIDS malignancy) were greater in participants randomized to CD4 count–guided treatment interruption than in those who received continuous therapy *[103, 104]*.

In a subgroup analysis of the SMART study, in which treatment-naïve patients with CD4 T-cell counts >350 cells/mm^3 were randomized to receive antiretroviral therapy either immediately or after the CD4 T-cell count dropped to <250 cells/mm^3, the risk of opportunistic diseases and serious non-AIDS events was higher in the deferred-therapy arm than in the treatment arm (absolute risk of 4.9% vs. 1.0%, respectively). These data for this small subgroup suggest that delaying therapy until the CD4 T-cell count decreases to <250 cells/mm^3 should be avoided *[105]*.

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

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

Pregnant Women – All HIV-infected pregnant women should be started on antiretroviral therapy to manage maternal HIV infection and to maximize viral suppression, in order to reduce the risk for perinatal HIV transmission **(AI)**. For women who do not require antiretroviral therapy for their own health, postpartum discontinuation of antiretroviral drugs can be considered. For more detailed discussion, please refer to the ***Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women and Interventions to Reduce Perinatal HIV-1 Transmission in the United States*** *[106]* and the **HIV-Infected Women of Reproductive Age and Pregnant Women** section.

HIV-Associated Nephropathy (HIVAN) – HIVAN is the most frequent cause of chronic renal failure in persons living with HIV infection. This entity, which is more common in black than in white patients, is not clearly related to CD4 T-cell depletion. Ongoing viral replication appears to be directly involved in renal injury. Antiretroviral therapy for individuals with HIVAN has been associated with both preserved renal function and prolonged survival, and therefore should be initiated for patients with a diagnosis of HIVAN regardless of CD4 T-cell count **(AII)** *[107, 108]*. When prescribing antiretroviral drugs, clinicians should note that most nucleoside reverse transcriptase inhibitors (NRTIs), except for abacavir, are renally excreted. Dosage adjustment for these agents may be necessary based on renal function; prescribers can refer to **Table 15** for dosing recommendations based on calculated creatinine clearance.

Hepatitis B virus (HBV) coinfection requiring treatment of HBV – HIV-infected patients may also be coinfected with HBV. The two-NRTI combination of tenofovir plus either lamivudine or emtricitabine is a

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

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

Existing data are inadequate to recommend initiation of antiretroviral therapy in all patients with CD4 T-cell counts >350 cells/mm^3. Any theoretical potential benefits could be outweighed by unknown risks or by patient-specific preferences.

The short-term risk for AIDS or death at CD4 T-cell counts 350 cells/mm^3 is low (Table 4b). Thus, the potential absolute risk reductions associated with treatment in such patients are small (Table 4a). Within the ART Cohort Collaboration, the absolute 3-year risk differences between those with CD4 T-cell counts 200 to 349 cells/mm^3 and those with CD4 T-cell counts ≥350 cells/mm^3 were only 1.3% (for those with HIV-RNA <100,000 copies/mL) and 1.7% (for those with HIV-RNA ≥100,000 copies/mL) *[88]*. These differences were similar through 5 years of observation *[96]*. The cost-effectiveness of early initiation of antiretroviral therapy in these patients is unknown.

Data from the AIDS Therapy Evaluation Project, Netherlands (ATHENA), have demonstrated that patients who started therapy at CD4 T-cell counts >350 cells/mm^3 were significantly more likely to achieve CD4 T-cell counts >800 cells/mm^3 after 7 years of therapy than those who initiated therapy at lower CD4 T-cell counts *[91]*. A long-term study based on the Johns Hopkins Clinical Cohort demonstrated that patients who initiated ART with a CD4 T-cell count <350 cells/mm^3 were significantly less likely to achieve a CD4 T-cell count >500 cells/mm^3 after 6 years of highly active antiretroviral therapy (HAART) compared with those who started therapy at CD4 T-cell counts >350 cells/mm^3 *[109]*.

Earlier treatment of HIV infection may also have positive public health implications, as it may reduce HIV transmission *[86]*. This may have significant implication in individuals in discordant relationships (i.e., HIV-infected individuals with HIV-negative sexual partners) or in individuals who continue to engage in risky behaviors.

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

The level of HIV RNA in a patient with a higher CD4 T-cell count is not strongly associated with short-term risk of AIDS/death and is a less important criterion for initiation of therapy than the CD4 T-cell count. Nevertheless, a high viral load is a predictor of more rapid progression to AIDS overall. Some experts may take viral load into consideration when deciding whether or not to start therapy in patients with CD4 T-cell counts >350 cells/mm^3 *[87, 110]*.

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

Special considerations in patients presenting with an opportunistic disease. The timing of when to start therapy in patients presenting with an opportunistic disease is controversial and is covered in detail in the **Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Patients *[in preparation]***. The optimal time to start therapy varies, depending on the clinical scenarios. In patients with conditions for which there is no effective therapy

except for improvement of immune function as a result of antiretroviral therapy (e.g., cryptosporidiosis, microsporidiosis, progressive multifocal leukoencephalopathy, and HIV-associated dementia), the early benefits of potent antiretroviral therapy outweigh any increased risk, and therefore therapy should be started as soon as possible **(AIII)**. In the setting of *Mycobacterium avium* complex infection, *Pneumocysitis jiroveci* pneumonia (PCP), and cryptococcoccal meningitis, in which immediate therapy may increase the risk of immune reconstitution inflammatory syndrome (IRIS), a short delay may be warranted before initiating antiretroviral treatment **(CIII)**. With concomitant *M.tuberculosis* infection, delay of ART for 2 to 8 weeks after initiation of tuberculosis (TB) treatment is recommended in order to avoid confusion in the event of adverse drug reactions and to prevent or minimize IRIS **(BIII)**. (See **TB/HIV Coinfection** section.)

Adherence Considerations. Concern about adherence to therapy is a major determinant for timing of initiation of therapy, with patient readiness to start treatment being a key factor in future adherence *[111]*. Depression and substance abuse may negatively affect adherence and response to therapy and should therefore be addressed, whenever possible, before therapy is initiated. However, no patient should automatically be excluded from consideration for antiretroviral therapy simply because the clinician judges that the patient exhibits behaviors or characteristics affecting adherence. Instead, the necessity for patient adherence to a long-term drug regimen should be discussed in detail by the patient and clinician before therapy is initiated. To achieve the level of adherence necessary for effective therapy, providers are encouraged to use strategies for assessing and assisting adherence. (See **Adherence** section.)

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

Much progress has been made since zidovudine monotherapy demonstrated survival benefits as initial antiretroviral therapy in advanced HIV patients in the 1980s *[112]*. As of August 2006, there are more than 20 approved antiretroviral drugs, belonging to 5 mechanistic classes, with which to design combination regimens. These 5 classes include the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), entry inhibitors (EIs), and integrase inhibitors.

Summary of Recommended Regimens

Since the introduction of potent combination antiretroviral therapy (sometimes referred to as "highly active antiretroviral therapy" or "HAART"), a substantial body of clinical trial data has been amassed to guide the selection of initial therapy for the previously untreated patient. To date, most clinical experience with combination therapy in treatment-naïve individuals is based on two different types of combination regimens, namely: NNRTI-based (1 NNRTI + 2 NRTI) and PI-based (1–2 PI + 2 NRTI) regimens. Recommendations are, accordingly, organized by these categories.

A list of Panel-recommended components for initial therapy in treatment-naïve patients can be found in **Table 6a**. Column A lists the preferred and alternative NNRTI and PI components, and Column B lists the preferred and alterative dual-NRTI components. To construct a complete three- or four-drug antiretroviral regimen, one component should be selected from Column A and one from Column B. **Table 6b** lists other antiretroviral components that are inferior to preferred or alternative components but may be used as initial therapy under special circumstances.
A list of agents or components not recommended for initial treatment can be found in **Table 7**. Some agents or components not generally recommended for use because of lack of potency or potential serious safety concerns are listed in **Table 8**.

Potential advantages and disadvantages of the components recommended as initial therapy for treatment-naïve patients are listed in **Table 9** to guide prescribers in choosing the regimen best suited for an individual patient.

CRITERIA FOR RECOMMENDED COMBINATION ANTIRETROVIRAL REGIMENS

Data Used for Making Recommendations

In its deliberations for the guidelines, the Panel reviews clinical trial data published in peer-reviewed journals and data prepared by manufacturers for FDA review. In selected cases, data presented in abstract format in major scientific meetings are also reviewed. The first criteria for selection are data from a randomized, prospective clinical trial with an adequate sample size, demonstrating potency as measured by durable viral suppression and immunologic enhancement (as evidenced by increased 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 are mostly based on surrogate marker endpoints. A summary of selected prospective comparative trials for initial therapy with at least 48-week data can be seen in **Table 10**.

The Panel reviewed data across numerous clinical trials in arriving at preferred versus alternative ratings in **Table 6a** and the other possible options in **Table 6b**. Components are designated as preferred for use in treatment-naïve patients when clinical trial data have demonstrated optimal efficacy and durability with acceptable tolerability and ease of use. Alternative components refer to those for which clinical trial data show efficacy but also show disadvantages compared with preferred components in terms of antiviral activity, durability, tolerability, or ease of use. In some cases, based on individual patient characteristics and needs, a regimen listed as an alternative regimen may actually be the preferred regimen in that patient. Other possible options are components that have inferior virologic efficacy or greater or more serious toxicities than the preferred and alternative regimens.

With improved choices of more effective and more convenient regimens, some of the agents or

combinations previously recommended by the Panel as alternative regimens have been removed from the list or placed as other possible options.

Factors to Consider When Selecting an Initial Regimen

The Panel affirms that regimen selection should be individualized, taking into consideration a number of factors including:

- comorbidity or conditions such as TB, liver disease, psychiatric disease, cardiovascular disease, chemical dependency, or pregnancy;
- adherence potential;
- dosing convenience regarding pill burden, dosing frequency, and food and fluid considerations;
- potential adverse drug effects;
- potential drug interactions with other medications;
- pregnancy potential;
- results of genotypic drug resistance testing; and
- gender and pretreatment CD4 count if considering nevirapine.

Considerations for Therapies

A listing of characteristics (dosing, pharmacokinetics, and common adverse effects) of individual antiretroviral agents can be found in **Tables 9** and **Tables 11–14**. Additionally, **Table 15** provides clinicians with dosing recommendations of these agents in patients with renal or hepatic insufficiency.

Insufficient Data for Recommendation

Current data are insufficient to recommend a number of other combinations that are under investigation, such as NRTI-sparing regimens (e.g., NNRTI + PI or ritonavir-boosted PI monotherapy), quadruple-class regimens (e.g., NRTI + NNRTI + PI + EI combinations); regimens containing EI as part of initial therapy; quadruple-NRTI regimens; regimens containing five or more active agents; or other novel strategies in treatment-naïve patients.

Not Recommended Strategies

Triple-class (e.g., NRTI + NNRTI + PI) regimens *[113, 114]* and a triple-NRTI + NNRTI regimen *[115]* have shown no benefit over standard regimens.

NNRTI–BASED REGIMENS (1 NNRTI + 2 NRTIs)

Panel's Recommendations:

Preferred NNRTI (AII):

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

Alternative NNRTI (BII):

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

**** Women with high pregnancy potential are those who are trying to conceive or who are not using effective and consistent contraception.***

Summary: NNRTI-Based Regimens

Three NNRTIs (namely, delavirdine, efavirenz, and nevirapine) are currently marketed for use.

NNRTI-based regimens are commonly prescribed as initial therapy for treatment-naïve patients. In general, these regimens have the advantage of lower pill burden compared with most of the PI-based regimens. Use of NNRTI-based regimens as initial therapy can preserve the PIs for later use, reducing or delaying patient exposure to some of the adverse effects more commonly associated with PIs. The major disadvantages of currently available NNRTIs are the prevalence of NNRTI-resistant viral strains in treatment-naïve patients *[27, 28, 34]* and the low genetic barrier of NNRTIs for development of resistance. Resistance testing is now recommended for treatment-naïve patients prior to starting therapy. (See **Drug Resistance Testing** section.) NNRTIs only require a single mutation to confer resistance, and cross resistance often develops across the three approved NNRTIs. As a result, patients who fail this initial regimen may lose the utility of other NNRTIs and may transmit NNRTI-resistant virus to others.

Based on clinical trial results and safety data, the Panel recommends the use of efavirenz as the preferred NNRTI as part of initial antiretroviral therapy **(AII)**. The exception is during pregnancy (especially during the first trimester), in women who are planning to conceive, or in women who are not using effective and consistent contraception.

Nevirapine may be used as an alternative to efavirenz for the initial NNRTI-based regimen in adult females with pretreatment CD4 counts ≤250 cells/mm^3 or in adult males with pretreatment CD4 counts ≤400 cells/mm^3 **(BII)**. Symptomatic, sometimes serious or

life-threatening hepatic events were observed with much greater frequency in women with pretreatment CD4 counts >250/mm^3 and in men with pretreatment CD4 counts >400/mm^3; nevirapine should be used in these patients only if the benefit clearly outweighs the risk. Close monitoring for elevated liver enzymes and skin rash should be undertaken for all patients during the first 18 weeks of nevirapine therapy.

Among these three agents, delavirdine appears to have the least potent antiviral activity. As such, it is not recommended as part of an initial regimen **(DII)**.

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

Efavirenz as Preferred NNRTI (AII)

Large randomized, controlled trials and cohort studies of treatment-naïve patients have demonstrated potent viral suppression in efavirenz-treated patients with a substantial proportion having HIV RNA <50 copies/mL during up to 3 years of follow-up *[115, 116]*. Efavirenz-based regimens also have been compared head-to-head with other regimens. Specifically, these studies demonstrated that regimens containing efavirenz + 2 NRTIs were superior virologically to some PI-based regimens, including indinavir *[117]*, lopinavir/ritonavir *[118]*, and nelfinavir *[119]* and to triple-NRTI-based regimens *[120, 121]* and had comparable activities to nevirapine- *[122, 123]* and atazanavir-based regimens *[124]*.

The ACTG 5142 study randomized patients to receive two NRTIs together with either efavirenz or lopinavir/ritonavir (or an NRTI-sparing regimen of efavirenz + lopinavir/ritonavir) *[118]*. In this study, the dual-NRTI + efavirenz regimen had significantly better virologic responses than the dual-NRTI + lopinavir/ritonavir regimen (89% vs. 77% with HIV RNA <50 copies/mL at 96 weeks), whereas the dual-NRTI + lopinavir/ritonavir regimen had significantly better CD4 count responses (+268 cells/mm^3 vs. +241 cells/mm^3 at 96 weeks) and less drug resistance following virologic failure.

The 2NN trial was the first randomized, controlled trial comparing efavirenz and nevirapine, both given with stavudine and lamivudine, in treatment-naïve patients. Although not statistically significant, the results showed less treatment failure (as defined by virologic failure, disease progression or death, or therapy change) in the efavirenz arm compared with the nevirapine arm *[122]*.

Two major limitations of efavirenz are its common central nervous system side effects (which usually resolve over a few weeks) and its potential teratogenic effect on the unborn fetus. In animal reproductive studies, efavirenz was found to cause major central nervous system congenital anomalies in nonhuman primates at drug exposure levels similar to those achieved in humans *[125]*. Several cases of neural tube defects in human newborns, when mothers were exposed to efavirenz during first trimester of pregnancy, have been identified *[126, 127]*. The relative risk of teratogenicity of efavirenz in humans is unclear.

Studies using efavirenz + dual-NRTI combinations (abacavir, didanosine, stavudine, tenofovir, or zidovudine together with emtricitabine or lamivudine) show durable virologic activity. A single pill coformulated with tenofovir, emtricitabine, and efavirenz now allows one-pill, once-daily dosing.

Nevirapine as Alternative NNRTI (BII)

In the 2NN trial, the proportion of patients with virologic suppression (defined as HIV RNA <50 copies/mL) was not significantly different between the efavirenz and nevirapine twice-daily arms (70% and 65.4%, respectively) *[122]*. However, two deaths were attributed to nevirapine use. One resulted from fulminant hepatitis and one from staphylococcal sepsis as a complication of Stevens-Johnson syndrome.

Symptomatic, serious, and even fatal hepatic events have been observed when nevirapine was initiated in treatment-naïve patients. These events generally occur within the first few weeks of treatment. In addition to elevated serum transaminases, approximately half of the patients also develop skin rash, with or without fever or flu-like symptoms. Women with higher CD4 counts appear to be at highest risk *[128, 129]*. In a recent analysis, a 12-fold higher incidence of symptomatic hepatic events was seen in women (including pregnant women) with CD4 counts >250 cells/mm^3 at the time of nevirapine initiation when compared with women with CD4 counts $\leq$250 cells/mm^3 (11.0% vs. 0.9%). An increased risk was also seen in men with pre-nevirapine CD4 counts >400 cells/mm^3 when compared with men with pre-nevirapine CD4 counts $\leq$400 cells/mm^3 (6.3% vs. 1.2%). Most of these patients had no identifiable underlying hepatic abnormalities. In some cases, hepatic injuries continued to progress despite discontinuation of nevirapine *[128, 130]*. Symptomatic hepatic events have not been reported with single doses of nevirapine given to mothers or infants for prevention of perinatal HIV infection.

Based on the safety data described, the Panel recommends that nevirapine may be used as an alternative to efavirenz in adult female patients with pretreatment CD4 counts ≤250 cells/mm^3 or in adult male patients with CD4 counts ≤400 cells/mm^3 **(BII)**. In female patients with CD4 counts >250 cells/mm^3 or in male patients with CD4 counts >400 cells/mm^3, nevirapine should not be initiated unless the benefit clearly outweighs the risk **(DI)**.

When starting nevirapine, a 14-day lead-in period at a dosage of 200mg once daily should be prescribed before increasing to the maintenance dosage of 200mg twice daily. Serum transaminases should be obtained at baseline, prior to and 2 weeks after dose escalation, then monthly for the first 18 weeks. Clinical and laboratory parameters should be assessed at each visit. More detailed recommendations on the management of nevirapine-associated hepatic events can be found in **Table 17a**.

PI-BASED REGIMENS (1 OR 2 PIs + 2 NRTIs)

Panel's Recommendations:

Preferred PIs:

- ***atazanavir + ritonavir* (AIII)***
- ***fosamprenavir + ritonavir* twice daily (AII)***
- ***lopinavir/ritonavir (coformulated) twice daily (AII)***

Alternative PIs (BII):

- ***atazanavir*****
- ***fosamprenavir***
- ***fosamprenavir + ritonavir* once daily***
- ***lopinavir/ritonavir (coformulated) once daily***

Other Possible Options (CII):

- ***nelfinavir***
- ***saquinavir + ritonavir****

**** Ritonavir at daily doses of 100–400mg used as a pharmacokinetic booster***

***** Ritonavir 100mg per day is recommended when tenofovir is used with atazanavir.***

Summary: PI-Based Regimens

PI-based regimens (1or 2 PIs + 2 NRTIs) revolutionized the treatment of HIV infection, leading to sustained viral suppression, improved immunologic function, and prolonged patient survival. Since their inception in the mid-1990s, much has been learned about their efficacy as well as some short-term and long-term adverse effects.

To date, 10 PIs have been approved for use in the United States. Each agent has its own unique characteristics based on its clinical efficacy, adverse effect profile, and pharmacokinetic properties. The characteristics, advantages, and disadvantages of each PI can be found in **Tables 9** and **13**. In selecting a PI-based regimen for a treatment-naïve patient, factors such as dosing frequency, food and fluid requirements, pill burden, drug interaction potential, baseline hepatic function, and toxicity profile should be taken into consideration. A number of metabolic abnormalities, including dyslipidemia, fat maldistribution, and insulin resistance, have been associated with PI use. The 10 PIs differ in their propensity to cause these metabolic complications. At this time, the extent to which these complications may result in adverse long-term consequences, such as increased cardiac events, is unknown.

The potent inhibitory effect of ritonavir on the cytochrome P450 (CYP) 3A4 isoenzyme has allowed the addition of low-dose ritonavir to other PIs (with the exception of nelfinavir) as a pharmacokinetic booster to increase drug exposure and prolong plasma half-lives of the active PIs. This allows for reduced dosing frequency and pill burden; in the case of indinavir, the addition of low-dose ritonavir also eliminates the need for food restrictions. All of these advantages may improve overall adherence to the regimen. The increased trough concentration (C_{min}) may improve the antiretroviral activity of the active PIs, which is most beneficial in cases where the patient harbors HIV-1 strains with reduced susceptibility to the PI *[131-133]*. The major drawbacks associated with this strategy are the potential for increased risk of hyperlipidemia and a greater potential of drug-drug interactions from the addition of ritonavir.

The list of Panel-recommended PIs can be found in **Table 6a**. The Panel considers atazanavir + ritonavir **(AIII)**, fosamprenavir + ritonavir (given twice daily, **AII**), and lopinavir/ritonavir (coformulated, given twice daily, **AII**) as preferred PIs for the treatment-naïve patient. As discussed below, this recommendation is based on clinical trial data for virologic potency, the barrier for virologic resistance, convenience, and tolerability. Alternative PIs include atazanavir **(BII)**, fosamprenavir **(BII)**, once-daily fosamprenavir + ritonavir **(BII),** or once-daily lopinavir/ritonavir **(BII)**. Other possible options discussed below include nelfinavir

(CII) or saquinavir + ritonavir **(CII)**. PIs not recommended in initial treatment regimens **(DIII)** include darunavir + ritonavir, indinavir (with or without ritonavir), ritonavir alone, saquinavir (without ritonavir), or tipranavir + ritonavir.

Preferred PI Components (in alphabetical order)

Ritonavir-boosted Atazanavir (AIII). Atazanavir is an azapeptide PI with the advantages of once-daily dosing. Ritonavir-boosting of atazanavir enhances the concentrations of atazanavir and demonstrates similar efficacy as unboosted atazanavir in combination with two NRTIs in treatment-naïve patients *[134]*. The comparative virologic efficacy to unboosted atazanavir in treatment-naïve patients, the improved pharmacokinetics with ritonavir-boosting, and the experience of atazanavir + ritonavir in treatment-experienced patients *[135]* supports its designation as a preferred regimen. The main adverse effect associated with atazanavir + ritonavir use is indirect hyperbilirubinemia, with or without jaundice or scleral icterus, but without concomitant hepatic transaminase elevations. The lipid effects associated with atazanavir + ritonavir are uncertain. Patients who receive concomitant therapy with tenofovir or efavirenz should use ritonavir-boosted ataznavir to overcome the pharmacokinetic interactions between unboosted atazanavir and these two agents. Atazanavir + ritonavir requires acidic gastric pH for dissolution. Thus, concomitant use of drugs that raise gastric pH, such as antacids, H2 antagonists, and particularly proton pump inhibitors, may significantly impair absorption of atazanavir + ritonavir. (See **Tables 20 and 21a.**)

Ritonavir-boosted Fosamprenavir (twice daily) (AII). Fosamprenavir is a prodrug of the PI amprenavir. A head-to-head, randomized trial compared twice-daily ritonavir-boosted fosamprenavir with lopinavir/ritonavir, each in combination with abacavir and lamivudine in antiretroviral-naïve patients. At week 48, 73% of the patients in the ritonavir-boosted fosamprenavir arm and 71% of those in the lopinavir/ritonavir arm achieved viral loads of <400 copies/mL (95% confidence interval [CI] around treatment difference: -4.84 to 7.05). Clinical and laboratory adverse events did not differ between the regimens. In this study of treatment-naïve subjects, twice-daily ritonavir-boosted fosamprenavir was non-inferior to twice-daily lopinavir/ritonavir, and this supports the recommendation of twice-daily ritonavir-boosted fosamprenavir as a preferred PI component *[136]*.

Lopinavir/ritonavir (coformulated; twice daily) (AII). In several clinical trials, regimens containing twice-daily lopinavir/ritonavir with two NRTIs have shown potent virologic activity in treatment-naïve patients. In a randomized, placebo-controlled trial comparing lopinavir/ritonavir with nelfinavir (each with stavudine and lamivudine) in 653 patients, lopinavir/ritonavir was superior to nelfinavir in maintaining a viral load <400 copies/mL through 48 weeks (84% versus 66% with persistent virologic response through 48 weeks; hazard ratio = 2.0; 95% CI: 1.5 to 2.7) *[137]*. Overall adverse event rates and study discontinuation rates because of adverse events were similar in the two groups. No evidence of genotypic or phenotypic resistance to PIs was detected in the 51 lopinavir/ritonavir-treated patients with >400 copies/mL at up to 48 weeks follow-up. In contrast, D30N and/or L90M mutations were detected in 43 of 96 (45%) of nelfinavir-treated patients *[138]*. A 7-year follow-up study of lopinavir/ritonavir and two NRTIs showed sustained virologic suppression in patients who were maintained on the originally assigned regimen *[139]*. The major adverse effects of lopinavir/ritonavir are gastrointestinal intolerance (particularly diarrhea) and hyperlipidemia, especially hypertriglyceridemia, necessitating pharmacologic management in some patients. The tablet formulation reduces the pill count to two pills twice daily, allows administration without food restriction, and eliminates the need for refrigeration.

In a pharmacokinetic study of standard dosing using capsule formulation, lopinavir plasma concentrations were significantly reduced during the third trimester of pregnancy *[140]*. The implication of this pharmacokinetic change on virologic outcome in the mother and the risk of perinatal HIV transmission remain unknown. Further studies are under way to examine the pharmacologic and clinical efficacy of increased dosing of lopinavir/ritonavir in this population and with the new tablet formulation.

Alternative PI-based regimens (in alphabetical order)

Atazanavir (BII). Unboosted atazanavir is given once daily and has fewer adverse effects on lipid profiles than other available PIs. Three studies compared atazanavir-based combination regimens to either nelfinavir- or efavirenz-based regimens. These studies established similar virologic efficacy among atazanavir 400mg once daily and both comparator treatment groups in antiretroviral-naïve patients after 48 weeks of therapy *[124, 141, 142]*. Atazanavir may be chosen as initial therapy for patients when a once-

daily regimen (without ritonavir) is desired and in patients with underlying risk factors when hyperlipidemia may be particularly undesirable. Patients who receive concomitant therapy with tenofovir or efavirenz should use ritonavir-boosted atazanavir to overcome the adverse pharmacokinetic interactions between unboosted atazanavir and these two agents. Atazanavir requires acidic gastric pH for dissolution. Thus, concomitant use of drugs that raise gastric pH, such as antacids, H2 antagonists, and proton pump inhibitors, may significantly impair its absorption (See **Tables 20 and 21a.**)

Fosamprenavir (BII) and Ritonavir-Boosted Fosamprenavir (once daily) (BII). Fosamprenavir can be given without ritonavir (twice daily) or as a once-daily ritonavir-boosted regimen. Two studies compared twice-daily fosamprenavir and once-daily ritonavir-boosted fosamprenavir to nelfinavir *[143, 144]*. In the first trial, more patients randomized to fosamprenavir achieved viral suppression at 48 weeks than those assigned to nelfinavir, with greater differences seen in those patients with pretreatment viral load >100,000 copies/mL *[143]*. Once-daily ritonavir-boosted fosamprenavir had similar virologic activity to nelfinavir in the second trial *[144]*.

Lopinavir/ritonavir (once daily) (BII). Lopinavir/ritonavir can be given once daily in treatment-naïve patients. When compared with the traditional twice-daily dosing, giving the same total dose once daily results in a similar mean area under the concentration-time curve but a lower mean trough concentration. In a randomized trial comparing once-daily and twice-daily lopinavir/ritonavir in combination with tenofovir and emtricitabine, a similar proportion of patients achieved viral suppression to <50 copies/mL at 48 weeks *[145]*. However, a greater incidence of moderate to severe diarrhea was reported in the patients randomized to the once-daily arm (16% vs. 5%). A lower trough concentration is expected with the once-daily dosing, so this dosing strategy is not recommended in PI-experienced patients, especially in those who may have HIV-1 strains with reduced susceptibility to lopinavir.

Other PI Options - Inferior to Preferred or Alternative PI Components

Nelfinavir (CII). Nelfinavir is generally well tolerated except for diarrhea, which occurs in up to 30%–40% of patients. Clinical trials have shown a virologic effect of nelfinavir similar to atazanavir *[141]* and to once-daily ritonavir-boosted fosamprenavir *[146]* but inferior to twice-daily lopinavir/ritonavir *[137]*, unboosted fosamprenavir *[143]*, and efavirenz *[119]* in terms of virologic suppression at 48 weeks. In contrast to other PIs (particularly ritonavir-boosted PIs), genotypic resistance is often seen in patients with virologic rebound on nelfinavir *[138, 147]*. Most commonly a D30N mutation is selected, although the presence of the D30N mutation alone does not confer resistance to other PIs. A smaller percentage of patients may select the multiple-PI-resistant L90M mutation upon virologic rebound, which may limit the choice of PIs as future options *[138, 147]*. Because of suboptimal virologic responses and more drug resistance following virologic failure compared with other regimens, nelfinavir is recommended only when preferred or alternative regimens cannot or should not be used.

Among the currently marketed PIs, nelfinavir has the most safety and pharmacokinetic data in pregnant women. The approved dosage of 1,250mg twice daily produces similar pharmacokinetic profiles during the third trimester of pregnancy compared with a nonpregnant state *[148]*. Thus, no dosage adjustment is deemed necessary when nelfinavir is used during pregnancy.

Ritonavir-boosted Saquinavir (CII). The low oral bioavailability of saquinavir hard-gel capsules makes this drug suboptimal when used as the only PI. Ritonavir inhibits CYP 3A4 isoenzymes in both the intestine and the liver. The addition of low-dose ritonavir to saquinavir results in a significant increase in oral bioavailability and a delay in saquinavir clearance. This leads to a higher peak saquinavir concentration, a longer elimination half-life, and a higher predose concentration. In a comparative study in which a substantial number of patients were PI-naïve, low-dose (100mg twice daily) ritonavir-boosted saquinavir (1,000mg twice daily) had a similar virologic response but better tolerability than the ritonavir + indinavir combination *[132]*. However, a similarly designed study demonstrated decreased virologic responses with ritonavir-boosted saquinavir compared with lopinavir/ritonavir *[133]*.

DUAL-NUCLEOSIDE OPTIONS AS PART OF INITIAL COMBINATION THERAPY

Panel's Recommendations:

Preferred dual-NRTI (AII):

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

Alternative dual-NRTI (BII):

- ***abacavir/lamivudine*(coformulated)***
- ***didanosine + (lamivudine or emtricitabine)***

Other possible option (CII):

- ***stavudine + lamivudine****

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

Eight nucleoside/nucleotide HIV-1 reverse transcriptase inhibitors are currently approved in the United States. Dual-NRTI combinations are commonly utilized components of combination antiretroviral regimens upon which the addition of an NNRTI or a PI (often boosted with ritonavir) confers potency for long-term efficacy.

Most dual-NRTI combinations used in clinical practice consist of a primary NRTI in combination with lamivudine or emtricitabine. Both lamivudine and emtricitabine have negligible side effects, and each selects for the M184V mutation that can confer improved susceptibility to zidovudine or tenofovir *[149]*.

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

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

The following sections list the Panel-recommended dual-NRTI combinations and discuss the rationale behind each recommendation.

Preferred Dual-NRTI Components

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

Tenofovir, when used with either lamivudine or emtricitabine as part of an efavirenz-based regimen in treatment-naïve patients, demonstrated potent virologic suppression through 144 weeks *[116]* and was not inferior to zidovudine/lamivudine in virologic efficacy at 48 and 96 weeks *[150, 151]*. In the Gilead 934 study, more subjects in the zidovudine/lamivudine arm developed lower limb fat on DEXA scans and anemia at 96 weeks compared with the tenofovir/emtricitabine arm *[150]*. A tenofovir-based dual-NRTI combination has not been compared head-to-head with another dual-NRTI combination in a PI-based regimen. In a study comparing once- and twice-daily lopinavir/ritonavir using tenofovir/emtricitabine as the dual-NRTI backbone, the 48-week virologic efficacy was similar to other trials in treatment-naïve subjects *[145]*.

Renal impairment, manifested by increases in serum creatinine, glycosuria, hypophosphatemia, and acute tubular necrosis, has been reported with tenofovir use *[152, 153]*. The extent of this toxicity is still undefined. Renal function, urinalysis, and electrolytes should be monitored in patients while on tenofovir. In patients with some degree of pre-existing renal insufficiency, tenofovir dosage adjustment is required; however, no safety data using the dosage adjustment guidelines for renal dysfunction are available.

Zidovudine/lamivudine (coformulated) (AII). The dual-NRTI combination of zidovudine/lamivudine has been the main dual-NRTI component in multiple clinical trials examining the potency of various NNRTI- and PI-based regimens *[117, 119, 120, 124, 154-156]*. This combination has extensive experience in durability, safety, and tolerability. A fixed-dose combination of zidovudine/lamivudine is available for one-tablet, twice-daily dosing. Bone marrow suppression, manifested by macrocytic anemia and/or neutropenia, may be seen in some patients. Selection of the lamivudine-associated M184V mutation has been associated with increased susceptibility to zidovudine or tenofovir.

Alternative Dual-NRTI Components

Abacavir/lamivudine (coformulated) (BII). In a comparative trial of abacavir/lamivudine and zidovudine/lamivudine (both given twice daily and combined with efavirenz), subjects from both arms achieved similar virologic responses. The abacavir-treated subjects experienced a greater CD4 T-cell increase at 48 weeks (+209/mm^3 in the abacavir arm vs. +155/mm^3 in the zidovudine arm, p = 0.005) *[157]*. However, the potential for serious abacavir-associated HSRs in 5%–8% of patients warrants placement of abacavir/lamivudine as an alternative dual-NRTI option at this time. The risk of this reaction can be substantially decreased with pretreatment HLA B*5701 testing *[53, 54]*. Abacavir should not be given to patients who test positive for HLA-B*5701. The fixed-dose combination of abacavir/lamivudine allows for one-pill, once-daily dosing.

Didanosine + (emtricitabine or lamivudine) (BII). To date, the clinical trial experience with didanosine + emtricitabine or lamivudine is limited. The FTC-301A trial tested didanosine + emtricitabine with efavirenz and demonstrated potent virologic suppression (78% <50 copies/mL at 48 weeks) *[35]*. In a small, single-arm study of didanosine + lamivudine + efavirenz as once-daily therapy, 77% of the patients achieved HIV RNA <50 copies/mL at 48 weeks *[158]*. Because of the limited data, didanosine together with either emtricitabine or lamivudine can only be recommended as an alternative dual-NRTI component.

Acceptable Alternative Dual-NRTI Option but Inferior to Preferred or Alternative Components

Stavudine + Lamivudine (CII). Despite durable virologic efficacy in some studies *[116, 159]*, long-term use of stavudine has been associated with irreversible and sometimes serious toxicities, such as peripheral neuropathy, lipoatrophy, serious and life-threatening lactic acidosis with hepatic steatosis with or without pancreatitis, and rapidly progressive neuromuscular weakness *[160-162]*. Because there are a number of less toxic NRTI options at this time, the Panel recommends a dual-NRTI component consisting of stavudine + lamivudine (or emtricitabine) only when the preferred or alternative dual-NRTI options listed above cannot be used.

NRTIs and Hepatitis B. Three of the current NRTIs, emtricitabine, lamivudine, and tenofovir, all have activity against HBV. Lamivudine is currently approved as a treatment for hepatitis B infection. It is important to note that patients with hepatitis B and HIV coinfection may be at risk of acute exacerbation of hepatitis after initiation or upon discontinuation of these drugs *[163-165]*. Thus, these patients should be monitored closely for clinical or chemical hepatitis if these drugs are to be initiated or discontinued. (See **Hepatitis B (HBV)/HIV CoInfection** section.)

TRIPLE-NRTI REGIMENS

A triple-NRTI combination regimen has multiple advantages: fewer drug-drug interactions, low pill burden, availability of a fixed-dose combination (zidovudine/lamivudine/abacavir combined as Trizivir), and the ability to spare patients from potential side effects seen with PIs and NNRTIs. However, several clinical trials that studied triple-NRTI regimens have shown suboptimal virologic activity *[120, 121, 166-170]*.

The Panel recommends that a triple-NRTI regimen consisting of abacavir/lamivudine/zidovudine should only be used when a preferred or an alternative NNRTI-based or a PI-based regimen may be less desirable because of concerns over toxicities, drug interactions, or regimen complexity **(CII)**.

Abacavir/lamivudine/zidovudine (coformulated) (CII). Abacavir/lamivudine/zidovudine is the only triple-NRTI combination for which randomized, controlled trials are available. Abacavir/lamivudine/zidovudine demonstrated comparable antiretroviral activity to indinavir *[154, 155]* and to nelfinavir *[171]* but was inferior virologically to an efavirenz-based regimen *[120]*.

Zidovudine/lamivudine + tenofovir (DII). The DART study demonstrated virologic responses in patients taking zidovudine/lamivudine + tenofovir *[172]*; however, comparative data with standard regimens are not available.

What Not To Use: (Table 8)

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

ANTIRETROVIRAL REGIMENS NOT RECOMMENDED

Monotherapy (EII). Single NRTI therapy does not demonstrate potent and sustained antiviral activity and should not be used.

Single-drug treatment regimens with a ritonavir-boosted PI, either lopinavir *[173]* or atazanavir *[174]*, are under investigation but cannot be recommended outside of a clinical trial at this time.

A rare, though controversial, exception is the use of zidovudine monotherapy to prevent perinatal HIV-1 transmission in a woman who does not meet clinical, immunologic, or virologic criteria for initiation of therapy and who has an HIV RNA <1,000 copies/mL *[106, 175]* **(DIII)**. Most clinicians, however, prefer to use a combination regimen in the pregnant woman for both the management of the mother's HIV infection and for the prevention of perinatal transmission.

The efficacy of zidovudine monotherapy during pregnancy to reduce perinatal transmission was identified in the PACTG 076 study. The goal of therapy in this case is solely to prevent perinatal HIV-1 transmission. Zidovudine monotherapy should be discontinued immediately after delivery. Combination antiretroviral therapy should be initiated postpartum if indicated. More information regarding management of the pregnant HIV patients can be found in "**Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States**" at **http://aidsinfo.nih.gov**.

Dual-nucleoside regimens (EII). These regimens are not recommended, because they have not demonstrated potent and sustained antiviral activity as compared with three-drug combination regimens *[176]*.

Triple-NRTI regimens (EII). Except for abacavir/lamivudine/zidovudine (CII) and possibly zidovudine/lamivudine + tenofovir (DII), triple-NRTI regimens should NOT be used routinely, because of suboptimal virologic activity *[121, 166-170]* or lack of data.

NRTI-sparing regimens (DII). Because of pharmacokinetic interactions, drug toxicities, and drug resistance issues, these regimens (e.g., efavirenz together with indinavir or lopinavir/ritonavir) are not recommended routinely.

ANTIRETROVIRAL COMPONENTS NOT RECOMMENDED *(in alphabetical order)*

Atazanavir + indinavir (EIII). Both of these PIs can cause grade 3 to 4 hyperbilirubinemia and jaundice. Additive or worsening of these adverse effects may be possible when these agents are used concomitantly.

Didanosine + stavudine (EII). The combined use of didanosine and stavudine as a dual-NRTI backbone can result in a high incidence of toxicities, particularly peripheral neuropathy, pancreatitis, and lactic acidosis *[119, 160, 161]*. This combination has been implicated in several deaths of HIV-1-infected pregnant women secondary to severe lactic acidosis with or without hepatic steatosis and pancreatitis *[177]*.

Efavirenz in first trimester of pregnancy and in women with significant childbearing potential (EIII). Efavirenz use was associated with significant teratogenic effects in primates at drug exposures similar to those representing human exposure. Several cases of congenital anomalies have been reported after early human gestational exposure to efavirenz *[126, 127]* Efavirenz should be avoided in pregnancy, particularly during the first trimester, and in women who are trying to conceive or who are not using effective and consistent contraception. If no other antiretroviral options are available in the woman who is pregnant or at risk for becoming pregnant, consultation should be obtained with a clinician who has expertise in both HIV infection and pregnancy.

Emtricitabine + lamivudine (EIII). 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 *[178]*.

Nelfinavir in pregnant women (EIII). In September 2007, the FDA and the manufacturer of nelfinavir issued a warning regarding the presence of small amounts of a byproduct (ethyl methanesulfonate or EMS), during the manufacturer process, in the final product of nelfinavir. EMS is an animal carcinogen, mutagen, and teratogen. Because of the unknown risk of EMS to the unborn fetus, nelfinavir should not be used in pregnant women or in women anticipating conception until further notice. Women who become pregnant while on nelfinavir should switch to an alternative antiretroviral agent.

Nevirapine initiated in treatment-naïve women with CD4 counts >250 cells/mm^3 or in treatment-naïve men with CD4 counts >400 cells/mm^3 (DI). Greater risk of symptomatic, including serious and life-threatening, hepatic events have been observed in these patient groups. Nevirapine should be initiated only if the benefit clearly outweighs the risk *[128-130]*.

Saquinavir as a single PI (i.e., unboosted) (EII). Saquinavir mesylate is contraindicated as a single PI because of poor bioavailability that averages only 4%, even with a concurrent high-fat meal.

Stavudine + zidovudine (EII). These two NRTIs should not be used in combination because of the demonstration of antagonism *in vitro [179]* and *in vivo [180]*.

Limitations to Treatment Safety and Efficacy

A number of factors may influence the safety and efficacy of antiretroviral therapy in individual patients. Examples include but are not limited to nonadherence to therapy, adverse drug reactions, drug-drug interactions, and development of drug resistance. Each is discussed below. Drug resistance, which has become a major reason for treatment failure, is discussed in greater detail in the section, **Management of the Treatment-Experienced Patient**.

ADHERENCE TO ANTIRETROVIRAL THERAPY

HIV viral suppression, reduced rates of resistance *[181, 182],* and improved survival *[183]* have been correlated with high rates of adherence to antiretroviral therapy. According to recommendations in these guidelines, many patients will be initiating, or have initiated, therapy when asymptomatic. This treatment must be maintained for a lifetime, which is an even greater challenge given that the efficacy of therapy has increased life expectancy for people living with HIV. A commitment to lifelong therapy requires a commitment of both the patient and the health care team.

Measurement of adherence is imperfect and currently lacks established standards. Although patient self-reporting of complete adherence has been an unreliable predictor of adherence, a patient's estimate of suboptimal adherence is a strong predictor and should be taken seriously *[184, 185]*. The clinician's estimate of the likelihood of a patient's adherence has also been proven to be an unreliable predictor of patient adherence *[186]*.

Regimen complexity and pill burden were the most common reasons for nonadherence when combination therapy was first introduced. A number of advances over the past several years have dramatically simplified many of the regimens. These guidelines note regimen simplicity as well as potency in their recommendations.

Adherence to HIV medications has been well studied. However, the determinants, measurements, and interventions to improve adherence to antiretroviral therapies are insufficiently characterized and understood. Additional research on this topic continues to be needed. Various strategies can be used and have been associated with improvements in adherence. These strategies are listed in **Table 16**.

Clinicians seeking additional information are referred to the **http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL_AdherenceSup.pdf** Web site.

Assessing and Monitoring Adherence

The first principle to success is to negotiate an understandable treatment plan to which the patient can commit *[187, 188]*. Trusting relationships among the patient, clinician, and health care team (including case managers, social workers, pharmacists, and others) are essential for optimal adherence. Therefore, establishing a trusting relationship over time is critical to good communication that will facilitate quality treatment outcomes. This often requires several office visits and the patience of clinicians, before therapy can be started.

Prior to writing the first prescriptions, clinicians need to assess the patient's readiness to take medication.

Patients need to understand that the first regimen is the best chance for long-term success *[189]*. Resources need to be identified to assist in success. Interventions can also assist with identifying adherence education needs and strategies for each patient. Examples include adherence support groups, adherence counselors, behavioral interventions *[190]*, and using community-based case managers and peer educators.

Lastly, and most importantly, adherence counseling and assessment should be done at each clinical encounter. Early detection of nonadherence and prompt intervention can greatly reduce the chance of virologic failure and development of viral resistance.

ADVERSE EFFECTS OF ANTIRETROVIRAL AGENTS

Adverse effects have been reported with virtually all antiretroviral drugs and are among the most common reasons for switching or discontinuation of therapy and for medication nonadherence *[191]*. In a review of more

than 1,000 patients in a Swiss HIV cohort that received combination antiretroviral therapy, 47% and 27% of the patients were reported to have clinical and laboratory adverse events, respectively *[192]*. Whereas some common adverse effects were identified during pre-marketing clinical trials, some less frequent toxicities (such as lactic acidosis with hepatic steatosis and progressive ascending neuromuscular weakness syndrome) and some long-term complications (such as dyslipidemia and fat maldistribution) were not recognized until after the drugs had been used in a larger population for a longer duration. In rare cases, some events may result in significant morbidity and even mortality.

Several factors may predispose individuals to certain antiretroviral-associated adverse events. For example, female patients seem to have a higher propensity of developing Stevens-Johnson syndrome and symptomatic hepatic events from nevirapine *[128, 193, 194]* or lactic acidosis from NRTIs *[195]*. Other factors may also contribute to the development of adverse events, such as use of concomitant medications with overlapping and additive toxicities; comorbid conditions that may increase risk of or exacerbate adverse effects (e.g., alcoholism *[196]* or coinfection with hepatitis B or C may increase risk of hepatotoxicity *[197-199]*); or drug-drug interactions that may lead to an increase in dose-related toxicities (e.g., concomitant use of hydroxyurea *[200, 201]* or ribavirin *[202-204]* with didanosine may increase didanosine-associated toxicities).

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

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

- **Tables 11–14** summarize common adverse effects of individual antiretroviral agents;
- **Tables 17a–c** provide clinicians with a list of antiretroviral-associated adverse events, along with their common causative agents, estimated frequency of occurrence, symptom onset and clinical manifestations, potential preventive measures, and suggested management strategies. Adverse events of antiretroviral drugs are classified in these tables in the following categories, based on the acuity and severity of the presenting signs and symptoms:
  - Potentially life-threatening and serious toxicities;
  - Adverse effects that may lead to long-term consequences; and
  - Adverse effects presenting as clinical symptoms that may affect overall quality of life or may impact overall medication adherence.
- **Table 18** includes a list of overlapping toxicities of antiretroviral agents and other drugs commonly used in HIV patients.
- **Table 19** lists Black Box Warnings found in the product labeling of antiretroviral drugs.

Drug Interactions

Potential drug-drug and/or drug-food interactions should be taken into consideration when selecting an antiretroviral regimen. A thorough review of current medications can help in designing a regimen that minimizes undesirable interactions. Moreover, review of drug interaction potential should be undertaken when any new drug, including over-the-counter agents, is added to an existing antiretroviral combination. **Tables 20–22b** list significant drug interactions with different antiretroviral agents and suggested recommendations on contraindication, dose modification, and alternative agents.

PI and NNRTI Drug Interactions

Most drug interactions with antiretrovirals are mediated through inhibition or induction of hepatic drug metabolism *[205]*. All PIs and NNRTIs are metabolized in the liver by the CYP system, particularly by the CYP3A4 isoenzyme. The list of drugs that may have significant interactions with PIs or NNRTIs is extensive and continuously expanding. Some examples of these drugs include medications that are commonly prescribed in HIV patients for non-HIV medical conditions, such as lipid-lowering agents (statins), benzodiazepines, calcium channel blockers, immunosuppressants (such as cyclosporine and tacrolimus), anticonvulsants, rifamycins, erectile dysfunction agents (such as sildenafil), ergot derivatives, azole antifungals, macrolides, oral contraceptives, and methadone. Unapproved therapies, such as St. John's Wort, can also cause negative interactions.

All PIs are substrates of CYP3A4, so their metabolic rate 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. Tipranavir, for example, is a potent inducer of P-glycoprotein. The net effect of tipranavir/ritonavir on CYP3A *in vivo*

appears to be enzyme inhibition. Thus, concentrations of drugs that are substrates for only CYP3A are likely to be increased if given with tipranavir/ritonavir. The net effect of tipranavir/ritonavir on a drug that is a substrate for both CYP3A and P-glycoprotein cannot be confidently predicted; significant decreases in saquinavir, amprenavir, and lopinavir concentrations have been observed *in vivo* when given with tipranavir/ritonavir.

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

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

The inhibitory effect of ritonavir (or delavirdine), however, can be beneficial when added to a PI, such as amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, or saquinavir *[206]*. Lower than therapeutic doses of ritonavir are commonly used in clinical practice as a pharmacokinetic enhancer to increase the trough concentration (C_{min}) and prolong the half-life of the active PIs *[207]*. The higher C_{min} allows for a greater C_{min}: IC_{50} ratio, reducing the chance for development of drug resistance as a result of suboptimal drug exposure; the longer half-life allows for less frequent dosing, which may enhance medication adherence.

Coadministration of PIs or NNRTIs with a potent CYP3A4 inducer, on the other hand, may lead to suboptimal drug concentrations and reduced therapeutic effects of the antiretroviral agents. These drug combinations should be avoided. If this is not possible, close monitoring of plasma HIV RNA, with or without antiretroviral dosage adjustment and therapeutic drug monitoring (TDM), may be warranted. For example, the rifamycins (rifampin, and, to a lesser extent, rifabutin) are CYP3A4 inducers that can significantly reduce plasma concentrations of most PIs and NNRTIs *[208, 209]*. As rifabutin is a less potent inducer, it is generally considered a reasonable alternative to rifampin for the treatment of TB when it is used with a PI- or NNRTI-based regimen, despite wider experience with rifampin use *[210]*. **Table 21** lists dosage recommendations for concomitant use of rifamycins and other CYP3A4 inducers and PIs and NNRTIs.

NRTI Drug Interactions

Unlike PIs and NNRTIs, NRTIs do not undergo hepatic transformation through the CYP metabolic pathway. Some, however, do have other routes of hepatic metabolism. Significant pharmacodynamic interactions of NRTIs and other drugs have been reported. They include increases in intracellular drug levels and toxicities when didanosine is used in combination with hydroxyurea *[211, 212]* or ribavirin *[204]*; additive bone marrow suppressive effects of zidovudine and ganciclovir *[213]*; and antagonism of intracellular phosphorylation with the combination of zidovudine and stavudine *[179]*. Pharmacokinetic interactions have also been reported. However, the mechanisms of some of these interactions are still unclear. Some such interactions include increases of didanosine concentrations in the presence of oral ganciclovir or tenofovir *[214, 215]* and decreases in atazanavir concentration when it is coadministered with tenofovir *[216, 217]*. **Table 21** lists significant interactions with NRTIs.

CCR5 Antagonist Drug Interaction

Maraviroc, the first FDA-approved CCR5 antagonist, is a substrate of CYP3A enzymes. As a consequence, the concentrations of maraviroc can be significantly increased in the presence of strong CYP3A inhibitors (such as ritonavir and other PIs, except for ritonavir-boosted tipranavir) and are reduced when used with CYP3A inducers, such as efavirenz or rifampin. Dose adjustment is necessary when used in combination with these agents. (See **Table 14a** for dosage recommendations) Maraviroc is neither an inducer nor an inhibitor of CYP3A system. It does not alter the pharmacokinetic of the drugs evaluated in interaction studies to date.

Fusion Inhibitor Drug Interaction

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

Integrase Inhibitor Drug Interaction

Raltegravir, an HIV integrase strand transfer inhibitor, is primarily eliminated by glucuronidation mediated

by the enzyme UDP-glucuronosyltransferases (UGT1A1). Strong inducers of UGT1A1 enzymes (such as rifampin) can significantly reduce the concentration of raltegravir. The significance of this interaction is unknown; thus this combination should be used with caution or an alternative therapy should be considered. Other inducers of UGT1A1, such as efavirenz, tipranavir/ritonavir, or rifabutin, can also reduce raltegravir concentration. A pharmacokinetic interaction should be considered if optimal virologic response is not achieved when these drugs are used in combination.

Management of the Treatment-Experienced Patient

Panel's Recommendations:

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

THE TREATMENT-EXPERIENCED PATIENT

Most patients benefit from antiretroviral therapy regimens. In clinical trials of effective combination regimens, a majority of study participants maintained virologic suppression for 3–7 years *[116, 139, 218, 219]*.

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

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

DEFINITIONS AND CAUSES OF ANTIRETROVIRAL TREATMENT FAILURE

Antiretroviral treatment failure can be defined as a suboptimal response to therapy. Treatment failure is often associated with virologic failure, immunologic failure, and/or clinical progression.

Many factors are associated with an increased risk of treatment failure, including:

- Baseline patient factors, such as:
  - earlier calendar year of starting therapy, in which less potent regimens or less well-tolerated antiretroviral drugs were used,

  - higher pretreatment or baseline HIV RNA level (depending on the specific regimen used),
  - lower pretreatment or nadir CD4 T-cell count,
  - prior AIDS diagnosis,
  - comorbidities (e.g., depression, active substance use),
  - presence of drug-resistant virus, and
  - prior treatment failure, with development of drug resistance or cross resistance;
- incomplete medication adherence and missed clinic appointments;
- drug side effects and toxicity;
- suboptimal pharmacokinetics (variable absorption, metabolism, and/or penetration into reservoirs, food/fasting requirements, adverse drug-drug interactions with concomitant medications);
- suboptimal potency of the antiretroviral regimen; and/or
- other, unknown reasons.

Data from some patient cohorts suggest that suboptimal adherence and toxicity accounted for 28%–40% of treatment failure and regimen discontinuations *[220, 221]*. Multiple reasons for treatment failure can occur in one patient. Some factors that have not been associated with treatment failure include gender, pregnancy, and history of past substance use.

ASSESSMENT OF ANTIRETROVIRAL TREATMENT FAILURE AND CHANGING THERAPY

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

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

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

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

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

Further Assessment of Treatment Failure. When adherence, tolerability, and pharmacokinetic causes of treatment failure have been considered and addressed, make further assessments for virologic failure, immunologic failure, and clinical progression. **Virologic suppression** can be defined as a sustained reduction in HIV RNA level below the assay limit of detection (e.g., 50 copies/mL). Virologic failure is best understood in the context of virologic success; that is, virologic failure is defined as the inability to achieve or maintain suppression of viral replication to levels below the limit of detection (<50 copies/mL) and may manifest as any of the following:

- ***Incomplete virologic response***: Two consecutive HIV RNA >400 copies/mL after 24 weeks or >50 copies/mL by 48 weeks in a treatment-naïve patient who is initiating therapy. Baseline HIV RNA may affect the time course of response, and some patients will take longer than others to suppress HIV RNA levels. The timing, pattern, and/or slope of HIV RNA decrease may predict ultimate virologic response *[222]*. For example, most patients with an adequate virologic response at 24 weeks had at least a 1 $\log_{10}$ decrease in HIV RNA copies/mL at 1–4 weeks after starting therapy *[223-225]*.
- ***Virologic rebound***: After virologic suppression, repeated detection of HIV RNA above the assay limit of detection (e.g., 50 copies/mL).

Assessment of Virologic Failure. There is no consensus on the optimal time to change therapy for virologic failure. The most aggressive approach would be to change for any repeated, detectable viremia (e.g., two consecutive HIV RNA >50 copies/mL after suppression to <50 copies/mL in a patient taking the regimen). Other approaches allow detectable viremia up to an arbitrary level (e.g., 1,000–5,000 copies/mL). However, ongoing viral replication in the presence of antiretroviral drugs promotes the selection of drug resistance mutations *[226]* and may limit future treatment options. Isolated episodes of viremia ("blips," e.g., single levels of 51–1,000 copies/mL) may simply represent laboratory variation *[227]* and usually are not associated with subsequent virologic failure, but rebound to higher viral load levels or more frequent episodes of viremia increase the risk of failure *[228, 229]*.

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

Management of Virologic Failure:
General Approach. Ideally, one should design a regimen with at least two, and preferably three, fully active drugs on the basis of drug history, resistance testing, or new mechanistic class **(BII)** *[41, 230-237]*. Some antiretroviral drugs (e.g., NRTIs) may contribute partial antiretroviral activity to an antiretroviral regimen, despite drug resistance. Because of the potential for drug-class cross resistance that reduces drug activity, using a "new" drug that a patient has not yet taken may not mean that the drug is fully active. Drug potency and viral susceptibility are more important than the number of drugs prescribed.

Several clinical trials illustrate effective therapeutic strategies for treatment-experienced patients *[231, 232, 236-239]*. In these studies, patients received an antiretroviral regimen optimized based on drug treatment history and resistance testing and then were randomized to receive a new active antiretroviral agent or placebo. Patients who received more active drugs (e.g., a ritonavir-boosted PI and a drug with activity against resistance viral strains with or without a new mechanism of action) had a better and more prolonged virologic response than those with fewer active drugs in the regimen. These studies illustrate and support the strategy of conducting resistance testing while a treatment-experienced patient is taking a failing regimen, designing a new regimen based on the treatment history and resistance testing results, and selecting active antiretroviral drugs for the new treatment regimen.

Early studies of treatment-experienced patients identified factors associated with better virologic responses to subsequent regimens *[240, 241]*.They included lower HIV RNA at the time of therapy change, using a new (i.e., not yet taken) class of drugs (e.g., NNRTI, EI, integrase inhibitor), and using ritonavir-boosted PIs in PI-experienced patients. More recent studies show that higher CD4 T-cell counts and higher genotypic and/or phenotypic susceptibility scores (indicating a greater number of active agents) are associated with better virologic responses *[233-237]*.

In general, adding a single, fully active antiretroviral drug in a new regimen is not recommended because of the risk of development of rapid resistance **(DII)**. However, in patients with a high likelihood of clinical progression (e.g., CD4 T-cell count <100/mm^3) and limited drug options, adding a single drug may reduce

the risk of immediate clinical progression, because even transient decreases in HIV RNA and or transient increases in CD4 T-cell counts have been associated with clinical benefits **(CI)** *[242]*. Weighing the risks (e.g., selection of drug resistance) and benefits (e.g., antiretroviral activity) of using a single active drug in the heavily treatment experienced patient is complicated, and consultation with an expert is advised.

Discontinuing or briefly interrupting therapy (even with ongoing viremia) may lead to a rapid increase in HIV RNA and a decrease in the CD4 T-cell count, and it increases the risk for clinical progression *[243, 244]*. Therefore, it is not recommended **(DIII)**.

Sequencing and Cross Resistance. The order of use of some antiretroviral agents may be important. Cross resistance among NRTIs is common but varies by drug. Most, if not all, NNRTI-associated resistance mutations confer resistance to all approved NNRTIs, although NNRTIs with activity against NNRTI-resistant strains (e.g., etravirine) are under development. Novel early mutations to some PIs (e.g., unboosted fosamprenavir, atazanavir, nelfinavir, saquinavir) that do not confer cross resistance to other PIs may occur initially, but subsequent accumulation of additional mutations confers broad cross resistance to the entire PI class. Pharmacologic boosting of PIs with ritonavir markedly reduces the likelihood of PI resistance with failure in patients without pre-existing PI mutations.

Tipranavir and darunavir are the two newest PIs approved for patients who are highly treatment-experienced or have HIV-1 strains resistant to multiple PIs based on demonstrated activity against PI-resistant viruses *[238, 239]*. However, with ongoing viremia and the accumulation of additional mutations, antiretroviral activity is time limited unless the regimen contains other active drugs (e.g., enfuvirtide, a CCR5 inhibitor, or an integrase inhibitor).

Newer Agents. Maraviroc, the first approved CCR5 inhibitor, is an antiretroviral drug that specifically binds to the CCR5 receptor of the CD4 T-cell, thereby inhibiting HIV strains that use this coreceptor for cellular entry. Phase III clinical studies enrolled triple-class, treatment-experienced patients who experienced failure on their current antiretroviral regimens with detectable viremia with only CCR5-tropic (R5) viral strains (documented using a tropism assay). In these studies, maraviroc resulted in significantly better virologic responses over 24 weeks compared with placebo when added to an antiretroviral regimen that was optimized based on treatment history and drug resistance testing *[234, 235]*. In another study, maraviroc did not demonstrate significant virologic activity in treatment-experienced patients with viremia with only X4 virus, a dual/mixed population of X4 and R5 viruses, or an indeterminate tropism result, although CD4 increases were seen *[245]*. Maraviroc was generally safe and well tolerated, although theoretical concerns about the longer-term safety of CCR5 inhibitors require additional assessment. With a unique mechanism of action and documented short-term efficacy and safety, maraviroc should be considered a fully active antiretroviral agent in treatment-experienced patients who have only R5 virus and who are naïve to CCR5 inhibitors.

Raltegravir, the first approved HIV integrase inhibitor, specifically inhibits the final step in integration, strand transfer of viral DNA to host cell DNA. Phase III clinical studies enrolled triple-class, treatment-experienced patients who experienced failure on their current antiretroviral regimens with detectable viremia. In these studies, raltegravir resulted in significantly better virologic responses over 24 weeks compared with placebo when added to an antiretroviral regimen that was optimized based on treatment history and drug resistance testing *[236, 237]*. Raltegravir was generally safe and well tolerated. With a unique mechanism of action and documented short-term efficacy and safety, raltegravir should be considered a fully active antiretroviral agent in treatment-experienced patients who are naïve to HIV integrase inhibitors.

Etravirine, an NNRTI, has activity *in vitro* against viral strains with mutations that confer resistance to efavirenz and nevirapine *[246]*. Phase III studies enrolled triple-class, treatment-experienced patients who had at least one NNRTI-associated drug resistance mutation and who were experiencing failure on their current antiretroviral regimen with detectable viremia. In these studies, etravirine resulted in significantly better virologic responses over 24 weeks compared with placebo when added to an optimized background antiretroviral regimen that included darunavir/ritonavir *[247, 248]*. Etravirine was generally safe and well tolerated. With activity against some NNRTI-resistant viral strains, etravirine may provide significant virologic activity in treatment-experienced patients, depending on the amount of NNRTI-resistance. (See **Table 27** for information regarding etravirine expanded access program.)

Other investigational drugs with newer mechanisms of action demonstrate short-term antiretroviral activity in patients with resistance to reverse transcriptase

inhibitors and PIs *[249-251]* and are also under investigation in clinical trials.
Specific clinical scenarios follow:

- ***Prior treatment with no resistance identified.*** Consider the timing of the drug resistance test (e.g., Was the patient off antiretroviral medications?) and/or nonadherence. Consider resuming the same regimen or starting a new regimen and then repeating genotypic testing early (e.g., in 2–4 weeks) to determine whether a resistant viral strain emerges **(CIII)**. Consider intensifying with one drug (e.g., tenofovir) **(BII)** *[252]* or pharmacokinetic enhancement (use of ritonavir boosting of an unboosted PI, e.g. atazanavir, fosamprenavir) **(BII)** *[131]*.

- ***Prior treatment and drug resistance.*** The goals in this situation are to resuppress HIV RNA levels maximally (e.g., to <50 copies/mL) and to prevent further selection of resistance mutations. With virologic failure, consider changing the treatment regimen sooner, rather than later, to minimize continued selection of resistance mutations. Discontinuing an NNRTI in a patient with ongoing viremia and evidence of NNRTI resistance in order to decrease the risk of selecting additional NNRTI-resistance mutations is particularly important, because newer NNRTIs with activity against some NNRTI-resistant strains are available. A new regimen should include at least two, and preferably three, fully active agents **(BII)**.

- ***Extensive prior treatment and drug resistance.*** The goal is to resuppress the HIV RNA levels maximally (e.g., to <50 copies/mL). With the availability of multiple new antiretroviral drugs, including some with new mechanisms of action, this goal is now possible in many patients, including those with extensive treatment experience and drug resistance. In some cases, however, viral suppression may be difficult to achieve. If maximal virologic suppression cannot be achieved, the goals are to preserve immunologic function and to prevent clinical progression (even with ongoing viremia). Even partial virologic suppression of HIV RNA >0.5 $\log_{10}$ copies/mL from baseline correlates with clinical benefits *[242]*; however, this must be balanced with the ongoing risk for accumulating additional resistance mutations.

- ***New regimen that contains at least two fully active agents cannot be identified.*** It is reasonable to observe a patient on the same regimen, rather than changing the regimen, depending on the stage of HIV disease **(BII)**. There is evidence from cohort studies that continuing therapy, even in the presence of viremia and the absence of CD4 T-cell count increases, decreases the risk of disease progression *[20]*. Other cohort studies suggest continued immunologic and clinical benefits if the HIV RNA level is maintained <10,000–20,000 copies/mL *[253, 254]*.

Immunologic Failure can be defined as a failure to achieve and maintain an adequate CD4 T-cell response despite virologic suppression. There is no specific definition for immunologic failure, although some studies have focused on patients who fail to increase CD4 T-cell counts above a specific threshold (e.g. >350 or 500 cells/mm^3) over a specific period of time (e.g. 4–7 years). Others have focused on an inability to increase CD4 T-cell counts above pre-therapy levels by a certain threshold (e.g. >50 or 100 cells/mm^3) over a given time period. The former approach may be preferable because of recent data linking these thresholds with the risk of non-AIDS clinical events *[101]*.

The proportion of patients experiencing immunologic failure depends on how failure is defined, the observation period, and the CD4 T-cell count when treatment was started. In the longest study conducted to date, the percentage of patients with suppressed viremia who reached a CD4 T-cell count >500 cells/mm^3 through 6 years of treatment was 42% (starting treatment with a CD4 <200 cells/mm^3), 66% (starting with CD4 200–350 cells/mm^3), and 85% (starting with CD4 >350 cells/mm^3) *[109]*; increases in CD4 T-cell counts in treatment-naïve patients with initial antiretroviral regimens are approximately 150 cells/mm^3 over the first year *[255]*. A CD4 T-cell count plateau may occur after 4–6 years of treatment with suppressed viremia *[8, 109, 256-258]*.

A persistently low CD4 T-cell count while on suppressive antiretroviral therapy is associated with a small, but appreciable, risk of AIDS- and non–AIDS-related morbidity and mortality *[259, 260]*. For example, in the FIRST study *[261]* , a low CD4 T-cell count on therapy was associated with an increased risk for AIDS-related complications (adjusted hazard ratio of 0.57 for CD4 T-cell count 100 cells/mm^3 higher). Similarly, a low CD4 T-cell count was associated with an increased risk for non-AIDS events, including cardiovascular, hepatic, renal, and cancer events. Other studies support these associations *[97, 102, 103]*.

Factors associated with immunologic failure:

- CD4 count <200/mm^3 when starting ART;
- Older age;
- Coinfection (e.g., HCV);
- Medications, both antiretrovirals (ZDV *[262]*, TDF + ddI *[263-265]*) and other medications;
- Persistent immune activation; and
- Loss of regenerative potential of the immune system.

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

Management of Immunologic Failure: There is no consensus on when or how to treat immunologic failure. Given the risk of clinical events, it is reasonable to focus on patients with CD4 T-cell counts <200/mm^3. Patients with higher CD4 T-cell counts have a low risk of clinical events.
It is not clear that immunologic failure in the setting of virologic suppression should prompt a change in the antiretroviral drug regimen. Because ongoing viral replication occurs in some patients with suppressed HIV RNA levels, some have suggested adding a drug to an existing regimen. However, this strategy does not result in clear virologic or immunologic benefit *[266]*. Others suggest changing the regimen (e.g., to a more suppressive regimen or from an NNRTI-based regimen to a PI-based regimen, based on some evidence that suggests improved CD4 T-cell count responses); however, these strategies have not been formally tested.

Immune-based therapies, such as interleukin-2, demonstrated robust and sustained CD4 T-cell count increases in some studies *[267, 268]*. However, controversy persists as to how much enhancement of immune function occurs. With this controversy, drug-associated side effects, and the need for parenteral administration, this strategy cannot be recommended unless with enrollment into a clinical trial **(DII)**. Other investigational immune-based therapies (e.g., growth hormone, cyclosporine, interleukin-7) have associated toxicity and costs and cannot be recommended routinely. Currently, immune-based therapies should only be used in the context of a clinical trial **(DII)**.

Clinical Progression can be defined as the occurrence or recurrence of HIV-related events (after at least 3 months on an antiretroviral regimen), excluding immune reconstitution syndromes *[269, 270]*. In one study, clinical progression (a new AIDS event or death) occurred in 7% of treated patients with virologic suppression, 9% of treated patients with virologic rebound, and 20% of treated patients who never achieved virologic suppression in 2.5 years *[271]*.

Management of Clinical Progression. Consider the possibility of immune reconstitution syndrome *[269, 270]*, which typically occurs within the first 3 months after starting effective antiretroviral therapy and which may respond to anti-inflammatory treatment(s) rather than changing antiretroviral therapy. Clinical progression may not warrant a change in therapy in the setting of suppressed viremia and adequate immunologic response **(BIII)**.

Relationship Among Virologic Failure, Immunologic Failure, and Clinical Progression: Some patients demonstrate discordant responses in virologic, immunologic, and clinical parameters *[272]*. In addition, virologic failure, immunologic failure, and clinical progression have distinct time courses and may occur independently or simultaneously. In general, virologic failure occurs first, followed by immunologic failure, and finally by clinical progression. These events may be separated by months to years *[273]*.

THERAPEUTIC DRUG MONITORING (TDM) FOR ANTIRETROVIRAL AGENTS

TDM is a strategy applied to certain antiarrhythmics, anticonvulsants, and antibiotics to utilize drug concentrations to design regimens that are safe and will achieve a desired therapeutic outcome. The key characteristic of a drug that is a candidate for TDM is knowledge of a therapeutic range of concentrations. The therapeutic range is a probabilistic concept. It is a range of concentrations established through clinical investigations that are associated with achieving the desired therapeutic response and reducing the frequency of drug-associated adverse reactions.

Current antiretroviral agents meet most of the characteristics of agents that can be considered candidates for a TDM strategy *[274]*. The rationale for TDM in managing antiretroviral therapy arises because of:

- data showing that considerable interpatient variability in drug concentrations among patients who take the same dose, and
- data indicating relationships between the concentration of drug in the body and anti-HIV effect—and, in some cases, toxicities.

TDM with PIs and NNRTIs. Data describing relationships between antiretroviral agents and treatment response have been reviewed in various publications *[275-278]*. Although there are limitations and unanswered questions in these data, the consensus of U.S. and European clinical pharmacologists is that the data provide a framework for the potential implementation of TDM for PIs and NNRTIs. This is because concentration-response data exist for PIs and NNRTIs. Information on relationships between concentrations and drug-associated toxicities is sparse. Clinicians using TDM as a strategy to manage these toxicities should consult the most current literature for specific concentration recommendations.

TDM with NRTIs. Relationships between plasma concentrations of NRTIs and their intracellular pharmacologically active moieties have not yet been established. Therefore, monitoring of plasma NRTI concentrations largely remains a research tool.

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

- **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;
- **in persons such as pregnant women** who may be at risk for virologic failure as a result of their pharmacokinetic characteristics that result in plasma concentrations lower than those achieved in the typical patient;
- **in treatment-experienced persons** who may have viral isolates with reduced susceptibility to antiretroviral agents;
- **use of alternative dosing regimens** in which safety and efficacy have not been established in clinical trials;
- **concentration-dependent toxicities**; and
- **lack of expected virologic response** in a treatment-naïve person.

Use of TDM to Monitor Drug Concentrations. There are several challenges and scientific gaps to the implementation of TDM in the clinical setting. (See **Limitations to Using TDM in Patient Management**.) Use of TDM to monitor drug concentration 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;
- 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 *[275]*. (See **http://www.hivpharmacology.com** *[279]*.)

Limitations to Using TDM in Patient Management. There are multiple factors that limit the use of TDM in the clinical setting. They include the following:

1. lack of prospective studies demonstrating that TDM improves clinical outcome. This is the most important limiting factor for the implementation of TDM at present;
2. lack of established therapeutic range of concentrations associated with achieving the desired

therapeutic response and/or reducing the frequency of drug-associated adverse reactions; and

3. lack of widespread availability of laboratories that perform quantitation of antiretroviral drug concentrations under rigorous quality assurance/quality control standards and the lack of experts in the interpretation of antiretroviral concentration data and application of such data to revise patients' dosing regimens.

TDM in Different Patient Populations.

- **Patients with wild-type virus**. Table 23 presents a synthesis of recommendations *[275-277, 279]* for minimum target trough PI and NNRTI concentrations in persons with wild-type virus.
- **Treatment-experienced patients**. Fewer data are available to formulate suggestions for minimum target trough concentration in treatment-experienced patients who have viral isolates with reduced susceptibility to these agents. It is likely that use of these agents in the setting of reduced viral susceptibility may require higher trough concentrations than those for wild-type virus.

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

DISCONTINUATION OR INTERRUPTION OF ANTIRETROVIRAL THERAPY

Unplanned interruption of antiretroviral therapy may become necessary because of serious drug toxicity, intervening illness, surgery that precludes oral therapy, or antiretroviral medication nonavailability. In addition, planned treatment discontinuation has been suggested as a strategy in several situations: in patients who achieve viral suppression, to reduce costs and long-term toxicities; or in patients who experience treatment failure, 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 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 of antiretroviral therapy vary and may include drug toxicity; intercurrent illnesses that preclude oral intake, such as gastroenteritis or pancreatitis; surgical procedures; or nonavailability of drugs. The general recommendation is to discontinue all antiretroviral agents simultaneously, especially if the interruption is because of serious toxicities.

However, if a short-term interruption is anticipated in the case of elective surgery, the pharmacokinetic properties and food requirements of specific drugs should be considered. Recommendations for some scenarios are listed below:

- **When all regimen components have similar half-lives and do not require food for proper absorption** – all drugs should be stopped simultaneously or may be given with a sip of water, if allowed. All discontinued regimen components should be restarted simultaneously.
- **When all regimen components have similar half-lives and require food for adequate absorption, and the patient is required to take nothing by mouth for a sustained period of time** – temporary discontinuation of all drug components is indicated. The regimen should be restarted as soon as the patient can resume oral intake.
- **When the antiretroviral regimen contains drugs with differing half-lives –** stopping all drugs simultaneously may result in functional monotherapy with the drug with the longest half-life (typically an NNRTI). Options in this circumstance are discussed below. (See **Discontinuation of efavirenz or nevirapine**.)
- **When a patient experiences a severe or life-threatening toxicity** – all components of the drug regimen should be stopped simultaneously, regardless of drug half-life.

Interruption of therapy after pregnancy

HIV-infected pregnant women who otherwise do not meet current CD4 count criteria for starting treatment may initiate antiretroviral therapy primarily for the purpose of preventing mother-to-child HIV transmission. These women may desire to stop therapy after delivery. Discontinuation recommendations are in the current guidelines for pregnant women *[137]*. (See **HIV-Infected Women of Reproductive Age and Pregnant Women**.)

Planned long-term therapy interruptions

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

- **In patients who initiated therapy during acute HIV infection and achieved virologic suppression**—the optimal duration of treatment and the consequences of treatment discontinuation are not known at this time. (See **Acute HIV Infection** section.)
- **In patients who have had exposure to multiple antiretroviral agents, have experienced antiretroviral treatment failure, and have few treatment options available because of extensive resistance mutations**—interruption is generally not recommended unless it is done in a clinical trial setting. Several clinical trials, yielding conflicting results, have been conducted to better understand the role of treatment interruption in these patients *[244, 280-282]*. The Panel notes that partial virologic suppression from combination therapy has been associated with clinical benefit; therefore, interruption of therapy should be avoided.
- **In patients on antiretroviral therapy who have maintained a CD4 count above the level currently recommended for treatment initiation and whose baseline CD4 count was either above or below that recommended threshold**—interruption is also not recommended unless it is done in a clinical trial setting. (See discussion below highlighting potential adverse outcomes seen in some treatment interruption trials.)

Temporary treatment interruption to reduce overall treatment cost, inconvenience, or potential long-term toxicity has been considered as a strategy for patients with viral suppression on antiretroviral therapy who have maintained CD4 counts above those currently recommended for initiating therapy. Several clinical trials have been designed to determine the safety of such interruptions, in which reinitiation is triggered by predetermined CD4 count thresholds. In these trials, various CD4 count levels have been set to guide both treatment interruption and reinitiation. Recently, two separate, randomized clinical trials of intentional, CD4 count-guided treatment interruption have been reported. In the SMART study, interrupting treatment with CD4 count levels >350 cells/mm^3 and reinitiating when <250 cells/mm^3 was associated with an increased risk of disease progression and death compared with the trial arm of continuous antiretroviral therapy *[283]*. In the TRIVACAN study, the same CD4 count triggers were used for stopping and restarting treatment *[284]*. This study also showed that interruption was an inferior strategy; the interventions in both trials were stopped early because of these findings. Two small randomized studies with no reported safety concerns have been published *[285-287]*. Other trials continue to collect data using other designs, including using higher CD4 count levels for reinitiation of therapy (e.g., CD4 >350/mm^3), and have not been stopped because of safety concerns. These trials may yield additional data regarding the safety and efficacy of differing designs for intentional interruptions. However, until further data from randomized controlled trials are available, treatment discontinuation in clinical practice should be avoided outside of a clinical trial setting.

Physicians and patients considering treatment interruption for any reason should be aware of the potential clinical consequences observed during some clinical and observational studies of treatment interruption strategies. The outcomes of these studies are not uniform, and there are important differences in their designs, including the study populations, duration of therapy, and thresholds for the resumption of treatment.

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, decline of CD4 count, HIV disease progression, development of minor HIV-associated manifestations such as oral thrush, development of drug resistance, and the need for chemoprophylaxis against opportunistic infections depending on the CD4 count. A timeline for restarting therapy should be discussed. Each patient should be counseled about the need to follow safe behavior guidelines to reduce the risk of HIV transmission. Data from relevant controlled trials should be shared with the patient.

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

- **Discontinuation of efavirenz or nevirapine.** The optimal interval between stopping efavirenz or nevirapine and other antiretroviral drugs is not known. The duration of detectable levels of these drugs after discontinuation ranges from less than 1 week to more than 3 weeks *[288, 289]*. Simultaneously stopping all drugs in a regimen containing these agents may result in functional monotherapy with the NNRTIs, because their half-lives are longer than other agents. This may increase the risk of selection of NNRTI-resistant mutations.

It is further complicated by evidence that certain host genetic polymorphisms may result in slower rates of clearance. Such polymorphisms may be more common among specific ethnic groups, such as African Americans and Hispanics *[290, 291]*. Some experts recommend stopping the NNRTI but continuing the other antiretroviral drugs for a period of time. The optimal time sequence for staggered component discontinuation has not been determined. A study in South Africa demonstrated that giving 4 or 7 days of zidovudine + lamivudine after a single dose of nevirapine reduced the risk of postnatal nevirapine resistance from 60% to 10%–12% *[292]*. An alternative strategy used by some experts is to substitute a PI for the NNRTI and to continue the PI with dual NRTIs for a period of time; however, no specific efficacy data supporting this have been reported. The optimal duration needed to continue the PI-based regimen after stopping the NNRTI is not known. Given the prolonged potential of 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.

- **Discontinuation and reintroduction of nevirapine**. Because nevirapine is an inducer of the drug-metabolizing hepatic enzymes, administration of full therapeutic doses of nevirapine without a 2-week, low-dose escalation phase will result in excess plasma drug levels and potentially increase the risk for toxicity. Therefore, in a patient who has interrupted treatment with nevirapine for more than 2 weeks and is to be restarted later, nevirapine should be reintroduced with a dose escalation period of 200mg once daily for 14 days followed by a 200mg twice-daily regimen **(AII)**.
- **Discontinuation of emtricitabine, lamivudine, or tenofovir in patients with hepatitis B coinfection**. Patients with hepatitis B coinfection (hepatitis B surface antigen or HBeAg positive) and receiving one or a combination of these NRTIs may experience an exacerbation of hepatitis upon drug discontinuation *[164, 165]*. If any of the above agents is discontinued, the patients should be closely monitored for exacerbation of hepatitis or for hepatic flare **(AII)**. Some experts suggest initiating adefovir or entecavir for the treatment of HBV in these patients **(CIII)**. (See **Hepatitis B and HIV Coinfection** section.)

Considerations for Antiretroviral Use in Special Patient Populations

ACUTE HIV INFECTION

Panel's Recommendations:

- ***Whether treatment of acute HIV infection results in long-term virologic, immunologic, or clinical benefit is unknown; treatment should be considered optional at this time (CIII).***
- ***Therapy should also be considered optional for patients in whom HIV seroconversion has occurred within the previous 6 months (CIII).***
- ***If the clinician and patient elect to treat acute HIV infection with antiretroviral therapy, treatment should be implemented with the goal of suppressing plasma HIV RNA levels to below detectable levels (AIII).***
- ***For patients with acute HIV infection in whom therapy is initiated, testing for plasma HIV RNA levels and CD4 count and toxicity monitoring should be performed as described for patients with established, chronic HIV infection (AII).***
- ***If the decision is made to initiate therapy in a person with acute HIV infection, genotypic resistance testing at baseline will likely optimize virologic response; this strategy is therefore recommended (BIII). If therapy is deferred, genotypic resistance testing should still be considered, because the result may be useful in optimizing the virologic response when therapy is ultimately initiated (CIII).***

An estimated 40%–90% of patients acutely infected with HIV will experience symptoms of acute retroviral syndrome (**Table 24**) *[293-296]*. However, acute HIV infection is often not recognized by primary care clinicians because of the similarity of the symptoms to those of influenza, infectious mononucleosis, or other illnesses. Additionally, acute infection can occur asymptomatically.

Diagnosis of Acute HIV Infection

Health care providers should consider a diagnosis of acute HIV infection for patients who experience a compatible clinical syndrome (**Table 24**) and who report recent high-risk behavior. In these situations, tests for plasma HIV RNA and HIV antibody should be obtained **(BII)**. Acute HIV infection is defined by detectable HIV RNA in plasma by using sensitive PCR or bDNA assays 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).

Patients with HIV infection diagnosed by HIV RNA testing should have confirmatory serologic testing performed at a subsequent time point **(AI)** (**Table 2**).

Data from the United States and Europe demonstrate that transmitted virus may be resistant to at least one antiretroviral drug in up to 16% of patients. If the decision is made to initiate therapy in a person with acute HIV infection, resistance testing at baseline will likely optimize virologic response; this strategy is therefore recommended **(BIII)**. *(*See **Drug Resistance Testing** section.)

Treatment for Acute HIV Infection

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

- **Potential Benefits of Treating Acute Infection**. Preliminary data indicate that treatment of acute HIV infection with combination antiretroviral therapy has a beneficial effect on laboratory markers of disease progression *[297-301]*.Theoretically, early intervention could decrease the severity of acute disease; alter the initial viral setpoint, which can affect disease-progression rates; reduce the rate of viral mutation as a result of suppression of viral replication; preserve immune function; and reduce the risk for viral transmission.
- **Potential Risks of Treating Acute HIV Infection**. The potential disadvantages of initiating therapy include exposure to antiretroviral therapy without a known clinical benefit, which could result in drug toxicities, development of antiretroviral drug resistance, the need for continuous therapy, and adverse effect on quality of life.

The above risk and benefit considerations are similar to those for initiating therapy in the chronically infected asymptomatic patient. 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)**.

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

Besides patients with acute HIV infection, experienced clinicians also recommend consideration of therapy for patients in whom seroconversion has occurred within the previous 6 months **(CIII)**. Although the initial burst of viremia among infected adults usually resolves in 2 months, rationale for treatment during the 2- to 6-month period after infection is based on the probability that virus replication in lymphoid tissue is still not maximally contained by the immune system during this time *[302]*.

Decisions regarding therapy for patients who test antibody positive and who believe the infection is recent, but for whom the time of infection cannot be documented, should be made as discussed in **When to Start: Indications for Initiation of Antiretroviral Therapy** **(CIII)**.

Treatment Regimen

If the clinician and patient have made the decision to use antiretroviral therapy for acute or recent HIV infection, treatment should be implemented in an attempt to suppress plasma HIV RNA levels to below detectable levels **(AIII)**. Data are insufficient to draw firm conclusions regarding specific drug recommendations to use in acute HIV infection. Potential combinations of agents should be those used in established infection (**Table 4**). Genotypic testing to detect antiretroviral drug resistance can be helpful in regimen selection and is therefore recommended **(BIII)**.

Patient Follow-up

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

Duration of Therapy for Acute HIV Infection

The optimal duration of therapy for patients with acute 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 infection should be considered when first counseling the patient regarding therapy.

HIV-INFECTED ADOLESCENTS

Older children and adolescents now make up the largest percentage of HIV-infected children cared for at U.S. sites. The CDC estimates that at least one-half of the 40,000 yearly new HIV-infected cases in the United States are in people 13 to 24 years of age *[303]*. HIV-infected adolescents represent a heterogeneous group in terms of sociodemographics, mode of HIV infection, sexual and substance abuse history, clinical and immunologic status, psychosocial development, and readiness to adhere to medications. Many of these factors may influence decisions concerning when to start and what antiretroviral medications should be used.

Most adolescents have been infected during their teenage years and are in an early stage of infection, making them ideal candidates for early intervention, such as prevention counseling. A limited but increasing number of HIV-infected adolescents are long-term survivors of HIV infection acquired perinatally or through blood products as infants. Such adolescents may have a unique clinical course that differs from that of adolescents infected later in life *[304]*.

Antiretroviral Therapy Considerations in Adolescents

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

Dosage for medications for HIV infection and opportunistic infections should be prescribed according to Tanner staging of puberty and not on the basis of age *[305, 306]*. Adolescents in early puberty (i.e., Tanner Stage I and II) should be administered doses using

pediatric schedules, whereas those in late puberty (i.e., Tanner Stage V) should follow adult dosing schedules. Because puberty may be delayed in perinatally HIV-infected children *[307]*, continued use of pediatric doses in puberty-delayed adolescents can result in medication doses that are higher than the usual adult doses. Because data are not available to predict optimal medication doses for each antiretroviral medication for this group of children, issues such as toxicity, pill or liquid volume burden, adherence, and virologic and immunologic parameters should be considered in determining when to transition from pediatric to adult doses. Youth who are in their growth spurt (i.e., Tanner Stage III in females and Tanner Stage IV in males) using adult or pediatric dosing guidelines and those adolescents whose doses have been transitioned from pediatric to adult doses should be closely monitored for medication efficacy and toxicity.

Adherence Concerns in Adolescents

HIV-infected adolescents have specific adherence problems. Comprehensive systems of care are required to serve both the medical and psychosocial needs of HIV-infected adolescents, who are frequently inexperienced with health care systems. 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; and
- lack of familial and social support.

Treatment regimens for adolescents must balance the goal of prescribing a maximally potent antiretroviral regimen with realistic assessment of existing and potential support systems to facilitate adherence. Adolescents benefit from reminder systems (beepers, timers, and pill boxes) that are stylish and do not call attention to themselves. It is important to make medication adherence as user friendly and as little stigmatizing as possible for the older child or adolescent. The concrete thought processes of adolescents make it difficult for them to take medications when they are asymptomatic, particularly if the medications have side effects. Adherence to complex regimens is particularly challenging at a time of life when adolescents do not want to be different from their peers. Direct observed therapy, although considered impractical for all adolescents, might be important for selected adolescents infected with HIV *[308, 309]*. 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** *[310]*.

Developmental issues make caring for adolescents unique. The adolescent's approach to illness is often different from that of an adult. The adolescent also faces difficulties in changing caretakers—graduating from a pediatrician to an adolescent care provider, then to an internist.

Special Considerations in Adolescent Females

Gynecological care is especially difficult to provide for the HIV-infected female adolescent but is a critical part of their care. Because many adolescents with HIV infection are sexually active, contraception and prevention of HIV transmission should be discussed with the adolescent, including the interaction of specific antiretroviral drugs on birth control pills. The potential for pregnancy may also alter choices of antiretroviral therapy. As an example, efavirenz should be used with caution in females of childbearing age and should only be prescribed after intensive counseling and education about the potential effects on the fetus, the need for close monitoring including periodic pregnancy testing, and a commitment on the part of the teen to use effective contraception. For a more detailed discussion, see **HIV-Infected Women of Reproductive Age and Pregnant Women** *[106]*.

Given the lifelong infection with HIV and the need for treatment through several stages of growth and development, HIV care programs and providers need to support this appropriate transition in care for HIV-infected infants through adolescents.

INJECTION DRUG USERS

Challenges of Treating Injection Drug Users (IDUs) Infected With HIV

Injection drug use represents the second most common route of transmission of HIV in the United States. Although treatment of HIV disease in this population can be successful, IDUs with HIV disease present special treatment challenges. These include the existence of an array of complicating comorbid conditions, limited access to HIV care, inadequate adherence to therapy, medication side effects and toxicities, need for substance abuse treatment, and the presence of treatment-complicating drug interactions *[311-313]*.

Underlying health problems among this population result in increased morbidity and mortality, either independent of or accentuated by HIV disease. Many of these problems are the consequence of prior poverty-related infectious disease exposures and the added effects of nonsterile needle and syringe use. These include TB, skin and soft tissue infections, recurrent bacterial pneumonia, endocarditis, hepatitis B and C, and neurologic and renal disease. Furthermore, the high prevalence of underlying mental illness in this population, antedating and/or exacerbated by substance use, results in both morbidity and difficulties in provision of clinical care and treatment *[311-313]*. Successful HIV therapy for IDUs often rests upon acquiring familiarity with and providing care for these comorbid conditions**.**

IDUs often have decreased access to HIV care and are less likely to receive antiretroviral therapy than other populations *[314, 315]*. Factors associated with lack of use of antiretroviral therapy among drug users have included active drug use, younger age, female gender, suboptimal health care, not being in a drug treatment program, recent incarceration, and lack of health care provider expertise *[314, 315]*. The chaotic lifestyle of many drug users, the powerful pull of addictive substances, and a series of beliefs about the dangers of antiretroviral therapy among this population impact on and blunt the benefit of antiretroviral therapy and contribute to decreased adherence to antiretroviral therapy *[316]*. The chronic and relapsing nature of substance abuse and lack of appreciation of substance abuse as a biologic and medical disease, compounded by the high rate of coexisting mental illness, further complicates the relationship between health care workers and IDUs.

Efficacy of HIV Treatment in IDUs

Although underrepresented in clinical trials of HIV therapies, available data indicate that, when not actively using drugs, efficacy of antiretroviral therapies among IDUs is similar to other populations. Further, therapeutic failure in this population is generally the degree to which drug use results in disruption of organized daily activities, rather than drug use *per se*. Whereas many drug users can control their drug use sufficiently and over sustained periods of time to engage in care successfully, treatment of substance abuse is often a prerequisite for successful antiretroviral therapy. Close collaboration with substance abuse treatment programs and proper support and attention to the special needs of this population are often critical components of successful treatment for HIV disease. Essential to this end as well are flexible, community-based HIV care sites characterized by familiarity with, and nonjudgmental expertise in, managing the wide array of needs of substance abusers and the development and use of effective strategies for promoting medication adherence *[312, 313]*. Foremost among these is the provision of substance abuse treatment. In addition, other support mechanisms for adherence are of value, and the use of drug treatment and community-based outreach sites for modified directly observed therapy (DOT) has shown promise in this population *[317]*.

IDU/HIV Drug Toxicities and Interactions

IDUs are more likely to experience an increased frequency of side effects and toxicities of antiretroviral therapies. Although not systematically studied, this is likely because of the high prevalence of underlying hepatic, renal, neurologic, psychiatric, gastrointestinal, and hematologic disease among IDUs. The selection of initial and continuing antiretroviral agents in this population should be made based upon the presence of these conditions and risks.

Methadone and Antiretroviral Therapy

Methadone, an orally administered long-acting opiate agonist, is the most common pharmacologic treatment for opiate addiction. Its use is associated with decreased heroin use, improved quality of life, and decreased needle sharing. Methadone exists in two racemic forms, R (active) and S (inactive). As a consequence of its opiate-induced effects on gastric emptying and metabolism by CYP isoenzymes 3A4 and 2D6, pharmacologic effects and interactions with antiretrovirals may commonly occur *[318]*. These may diminish the effectiveness of either or both therapies by causing opiate withdrawal, opiate overdose, or increased toxicity or decreased efficacy of antiretrovirals.

- **Methadone and NRTIs**. Most of the currently available antiretrovirals have been examined in terms of potential pharmacokinetic interactions of significance with methadone. (See **Table 21**.) Among the NRTIs, none appears to have a clinically significant effect on methadone metabolism. Conversely, important effects of methadone on NRTIs have been well documented. Methadone is known to increase the area under the curve of zidovudine by 40% *[318]*, with a possible increase in zidovudine-related side effects. Methadone decreases levels of stavudine and the buffered tablet didanosine formulation (no longer available) by 18% and 63%, respectively *[319]*. This marked reduction in didanosine levels is not observed with

the EC formulation. Recent data indicate lack of significant interaction between abacavir and tenofovir and methadone.

- **Methadone and NNRTIs**. Pharmacokinetic interactions between NNRTIs and methadone are well known and clinically problematic *[320]*. Both efavirenz and nevirapine, potent inducers of CYP isoenzymes, have been associated with significant decreases in methadone levels. Methadone levels are decreased by 43% and 46% in those receiving efavirenz and nevirapine, respectively, with corresponding clinical opiate withdrawal. It is necessary to inform patients and substance abuse treatment facilities of the likelihood of occurrence of this interaction if either drug is prescribed to those receiving methadone. The clinical effect is usually seen after 7 days of coadministration and is treated with increase in methadone dosage, usually at 5–10mg daily until the patient is comfortable. Delavirdine, an inhibitor of CYP isoenzymes, increases methadone levels moderately and without clinical significance.
- **Methadone and PIs**. Limited information indicates that PI levels are generally not affected by methadone, except for amprenavir, which appears to be reduced by 30%. However, many PIs have significant effects on methadone metabolism. Saquinavir does not affect free, unbound methadone levels. However, amprenavir, nelfinavir, and lopinavir administration each results in a significant decrease in methadone levels *[321, 322]*. Whereas fosamprenavir may result in mild opiate withdrawal, decrease in methadone concentration from nelfinavir was not associated with opiate withdrawal. This is likely because of lack of effect on free, rather than total, methadone levels. Lopinavir/ritonavir combination has been associated with significant reductions in methadone levels and opiate withdrawal symptoms. This is because of the lopinavir, not ritonavir, component *[323]*. Another study indicates a lack of pharmacokinetic interaction among atazanavir and methadone *[324]*.

Buprenorphine

Buprenorphine, a partial μ-opiate agonist, is increasingly being used for opiate abuse treatment. Its decreased risk of respiratory depression and overdose enables use in physician's offices for the treatment of opioid dependence. This flexible treatment setting could be of significant value to drug-abusing opiate-addicted HIV-infected patients requiring antiretroviral therapy, as it would enable one physician or program to provide needed medical and substance abuse services.

Only limited information is currently available about interactions between buprenorphine and antiretroviral agents. In contrast to methadone, buprenorphine does not appear to raise zidovudine levels. Pilot data indicate that buprenorphine levels do not appear to be reduced and opiate withdrawal does not occur during coadministration with efavirenz.

Summary

Provision of successful antiretroviral therapy for IDUs is possible. It is enhanced by supportive clinical care sites and provision of drug treatment, awareness of interactions with methadone and the increased risk of side effects and toxicities, and the need for simple regimens to enhance medication adherence. These are important considerations in selection of regimens and provision of appropriate patient monitoring in this population. Preference should be given to antiretroviral agents with lower risk for hepatic and neuropsychiatric side effects, simple dosing schedules, and lack of interaction with methadone.

HIV-INFECTED WOMEN OF REPRODUCTIVE AGE AND PREGNANT WOMEN

Panel's Recommendations:

- ***When initiating antiretroviral therapy for women of reproductive age, the indications for initiation of therapy and the goals of treatment are the same as for other adults and adolescents (AI).***
- ***Efavirenz should be avoided for the woman who desires to become pregnant or who does not use effective and consistent contraception (AIII).***
- ***For the woman who is pregnant, an additional goal of therapy is prevention of mother-to-child transmission (PMTCT), with a goal of viral suppression to <1,000 copies/mL to reduce the risk of transmission of HIV to the fetus and newborn (AI).***
- ***Selection of an antiretroviral combination should take into account known safety, efficacy, and pharmacokinetic data of each agent during pregnancy (AIII).***
- ***Clinicians should consult the most current Public Health Service (PHS) guidelines when designing a regimen for a pregnant patient (AIII).***

This section provides a brief discussion of some unique considerations when caring for HIV-1-infected women of reproductive age and pregnant women. For a more up-to-date and in-depth discussion regarding the management of these patients, clinicians should consult the latest guidelines of the ***Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States***, which can be found in the **http://www.aidsinfo.nih.gov** Web site *[106]*.

Women of Reproductive Age

In women of reproductive age, antiretroviral regimen selection should account for the possibility of planned or unplanned pregnancy. The most vulnerable period in fetal organogenesis is early in gestation, often before pregnancy is recognized. Sexual activity, reproductive plans, and use of effective contraception should be discussed with the patient. As part of the evaluation for initiating therapy, women should be counseled about the potential teratogenic risk of efavirenz-containing regimens, should pregnancy occur. These regimens should be avoided in women who are trying to conceive or who are not using effective and consistent contraception. Various PIs and NNRTIs are known to interact with oral contraceptives, resulting in possible decreases in ethinyl estradiol or increases in estradiol or norethindrone levels. (See **Table 21**.) These changes may decrease the effectiveness of the oral contraceptives or potentially increase risk of estrogen- or progestin-related side effects. Providers should be aware of these drug interactions and an alternative or additional contraceptive method should be considered. Amprenavir (and probably fosamprenavir) not only increases blood levels of both estrogen and progestin components, but oral contraceptives decrease amprenavir levels as well; these drugs should not be coadministered. There is minimal information about drug interactions with use of newer hormonal contraceptive methods (e.g., patch, vaginal ring). Counseling should be provided on an ongoing basis. Women who express a desire to become pregnant should be referred for preconception counseling and care, including discussion of special considerations with antiretroviral therapy use during pregnancy.

Pregnant Women

Pregnancy should not preclude the use of optimal therapeutic regimens. However, because of considerations related to PMTCT and to maternal and fetal safety, timing of initiation of treatment and selection of regimens may be different from nonpregnant adults or adolescents.

PMTCT

Antiretroviral therapy is recommended in all pregnant women, regardless of virologic, immunologic, or clinical parameters, for the purpose of PMTCT **(AI)**. Reduction of HIV RNA levels to <1,000 copies/mL and use of antiretroviral therapy appear to have an independent effect on reduction of perinatal transmission *[78, 79, 175]*.

The decision to use any antiretroviral drug during pregnancy should be made by the woman after discussion with her clinician regarding the benefits versus risks to her and her fetus. Long-term follow-up is recommended for all infants born to women who have received antiretroviral drugs during pregnancy, regardless of the infants' HIV status.

Regimen Considerations

Recommendations regarding the choice of antiretroviral drugs for treatment of infected women are subject to unique considerations including:

- potential changes in pharmacokinetics, thus dosing requirements, resulting from physiologic changes associated with pregnancy;
- potential adverse effects of antiretroviral drugs on a pregnant woman;
- effect on the risk for perinatal HIV transmission; and
- potential short- and long-term effects of the antiretroviral drug on the fetus and newborn, all of which are not known for many antiretroviral drugs. (See **Table 25**.)

Based on available data, recommendations related to drug choices have been developed by the U.S. Public Health Service Task Force and can be found in **Table 26**.

Current pharmacokinetic studies in pregnancy, although not completed for all agents, suggest no need for dosage modification of NRTIs and nevirapine. Nelfinavir 1,250mg twice daily achieves optimal blood levels, but 750mg three times daily does not; thus, the 1,250mg twice daily dosage should be used in all pregnant women *[148]*. Serum concentrations for unboosted indinavir and saquinavir may result in lower than optimal levels during pregnancy, thus ritonavir boosting will be necessary to achieve more optimal concentrations. Preliminary data suggest

lower than optimal concentration of lopinavir is seen with the currently recommended adult dose of lopinavir/ritonavir, so this agent should be used with close monitoring of virologic response *[140]*.

Some agents may cause harm to the mother and/or the fetus, and are advised to be avoided or used with extreme caution. These agents include:

- Efavirenz-containing regimens: should be avoided in pregnancy (particularly during the first trimester) because significant teratogenic effects were seen in primate studies at drug exposures similar to those achieved during human exposure. In addition, several cases of neural tube defects have now been reported after early human gestational exposure to efavirenz *[126]*
- The combination of ddI and d4T: should be avoided during pregnancy because of several reports of fatal and nonfatal but serious lactic acidosis with hepatic steatosis and/or pancreatitis after prolonged use of regimens containing these two nucleoside analogues in combination *[177]*. This combination should be used during pregnancy only when other NRTI drug combinations have failed or have caused unacceptable toxicity or side effects.
- Nevirapine: has been associated with a 12-fold increased risk of symptomatic hepatotoxicity in women with prenevirapine CD4 counts >250 cells/mm^3. A majority of the cases occurred within the first 18 weeks of therapy. Hepatic failure and death have been reported among a small number of pregnant patients *[325]*. Pregnant patients on chronic nevirapine prior to pregnancy are probably at a much lower risk for this toxicity. In nevirapine-naïve pregnant women with CD4 counts >250 cells/mm^3, nevirapine should not be initiated as a component of a combination regimen unless the benefit clearly outweighs the risk. If nevirapine is used, close clinical and laboratory monitoring, especially during the first 18 weeks of treatment, is strongly advised.
- **Nelfinavir in pregnant women (EIII).** In September 2007, the FDA and the manufacturer of nelfinavir issued a warning regarding the presence of small amounts of a byproduct (ethyl methanesulfonate or EMS), during the manufacturer process, in the final product of nelfinavir. EMS is an animal carcinogen, mutagen, and teratogen. Because of the unknown risk of EMS to the unborn fetus, nelfinavir should not be used in pregnant women or in women anticipating conception until further notice. Women who become pregnant while on nelfinavir should switch to an alternative antiretroviral agent.

Clinicians who are treating HIV-infected pregnant women are strongly encouraged to report cases of prenatal exposure to antiretroviral drugs (either administered alone or in combinations) to the **Antiretroviral Pregnancy Registry** (**Telephone: 910–251–9087** or **1–800–258–4263**). The registry collects observational, nonexperimental data regarding antiretroviral exposure during pregnancy for the purpose of assessing potential teratogenicity. For more information regarding selection and use of antiretroviral therapy during pregnancy, please refer to ***Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States*** *[106]*.

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

Discontinuation of Antiretroviral Therapy Postpartum

Pregnant women who are started on antiretroviral therapy during therapy for the sole purpose of PMTCT and who do not meet criteria for starting treatment for their own health may choose to stop antiretroviral therapy after delivery. However, if therapy includes nevirapine, stopping all regimen components simultaneously may result in functional monotherapy because of its long half-life and subsequent increased risk for resistance. Nevirapine resistance mutations have been identified postpartum in women taking nevirapine-containing combination regimens only for PMTCT. In one study, nevirapine resistance was identified in 16% of women despite continuation of the nucleoside backbone for 5 days after stopping nevirapine *[326]*. Further research is needed to assess appropriate strategies for stopping nevirapine-containing combination regimens after delivery in situations when ongoing maternal treatment is not indicated.

Antiretroviral Considerations in Patients with Coinfections

HEPATITIS B (HBV)/HIV COINFECTION

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

- Emtricitabine, lamivudine, and tenofovir have activity against both HIV and HBV. Discontinuation of these drugs may potentially cause serious hepatocellular damage resulting from reactivation of HBV *[322]*;
- Lamivudine-resistant HBV is observed in approximately 40% of patients after 2 years of lamivudine monotherapy for chronic HBV and in approximately 90% after 4 years when it is used as the only active drug for HBV in coinfected patients *[78, 79, 323, 324]*;
- Entecavir has activity against HIV, and its use in patients with dual infection has been associated with selection of the M184V mutation that confers resistance to lamivudine and emtricitabine *[327, 328]*. Therefore, entecavir should be used only with a fully suppressive antiretroviral regimen in HIV/HBV-coinfected patients.
- Immune reconstitution can be associated with elevation in transaminases, possibly because HBV is primarily an immune-mediated disease *[329]*; and
- Many antiretroviral drugs can cause increases in transaminase levels. The rate and magnitude of these increases are higher with HBV coinfection *[330, 331]*. The etiology and consequences of these changes in liver function tests are unclear, because continuation of therapy may be accompanied by resolution of the changes. Nevertheless, some experts suspend the implicated agent(s) when the ALT is increased to 5–10 times the upper limit of normal. However, in HIV/HBV-coinfected persons, increases in transaminase levels can herald HBeAg seroconversion, so the cause of the elevations should be investigated prior to the decision to discontinue medications. HBeAg seroconversion can be evaluated by checking HBeAg and anti-HBe as well as HBV DNA levels.

Treatment Recommendations for HBV/HIV Coinfected Patients

- All patients with HBV should be advised to abstain from alcohol; should receive hepatitis A vaccine if found not to be immune at baseline (i.e., absence of hepatitis A total or IgG antibody); should be advised on methods to prevent HBV transmission (which do not differ from those to prevent HIV transmission); and should be evaluated for the severity of HBV infection.
- **If neither HIV nor HBV infection requires treatment**: Monitor the progression of both infections. If treatment becomes necessary for either infection, follow the guidelines listed in the scenarios below.
- **If treatment is needed for HIV but not for HBV**: The combination of tenofovir and emtricitabine or tenofovir and lamivudine should be used as the NRTI backbone of an antiretroviral regimen, which will result in treatment of both infections. Because the preferred antiretroviral regimens all contain either lamivudine or emtricitabine, it is not possible to treat only HIV infection without using a nonpreferred regimen. To avoid development of HBV-resistant mutants, none of these agents should be used as the only agent with anti-HBV activity in an antiretroviral regimen.
- **If treatment for HBV is needed**: Patients who need treatment for HBV infection should also be started on a fully suppressive antiretroviral regimen that contains NRTIs with activity against both viruses: for example, tenofovir plus either emtricitabine or lamivudine. The use of lamivudine, emtricitabine, or tenofovir as the only active anti-HBV agent should be avoided because of the risk for resistance. If tenofovir cannot be used, another agent with anti-HBV activity should be used in combination with lamivudine or emtricitabine for treatment of HBV infection. Management of HIV should be continued with a combination regimen to provide maximal suppression.
- **Treating only HBV**: In instances when HIV treatment is not an option or is not desirable,

pegylated interferon-alpha may be used for the treatment of HBV infection, as it does not lead to the emergence of HIV or HBV resistance. Adefovir dipivoxil is active against HBV but not against HIV at the 10mg dose; however, there is a theoretical risk for development of HIV resistance, as it has anti-HIV activity at higher doses and is related to tenofovir. Because of the risk for HIV drug resistance, the use of emtricitabine, lamivudine, tenofovir, or entecavir without a full combination antiretroviral regimen should be avoided.

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

HEPATITIS C (HCV)/HIV COINFECTION

Long-term studies of patients with chronic HCV infection show that 2%–20% develop cirrhosis in 20 years *[332]*. This rate of progression increases with older age, alcoholism, and HIV infection *[332-334]*. A meta-analysis demonstrated that the rate of progression to cirrhosis with HCV/HIV coinfection was about threefold higher when compared with patients who are seronegative for HIV *[333]*. This accelerated rate is magnified in patients with low CD4 counts. Chronic HCV infection also complicates HIV treatment by the increased frequency of antiretroviral-associated hepatotoxicity *[198]*. Multiple studies show poor prognosis for HCV/HIV coinfection in the era of combination antiretroviral therapy. It is unclear if HCV adversely affects the rate of HIV progression *[335, 336]* or if this primarily reflects the impact of injection drug use (See **Injection Drug Users** section), which is strongly linked to HCV infection *[336-338]*. It is also unclear if antiretroviral therapy improves the attributable morbidity/mortality for untreated HCV.

Assessment of HCV/HIV Coinfection

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

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

Clinical trials in patients with HCV/HIV coinfection using pegylated interferon plus ribavirin for 48 weeks show sustained virologic response (SVR) rates of 60%–70% for HCV genotype 2/3 but only 15%–28% for genotype 1 *[339, 340]*. These data are based on experience almost exclusively in carefully selected patients with CD4 counts >200 cells/mm^3 *[340-342]*.

Treatment of HCV/HIV Coinfection

Based on these observations, treatment of HCV is recommended according to standard guidelines *[343]* with preference for those with higher CD4 counts (>200 cells/mm^3). For some patients with lower CD4 counts, it may be preferable to initiate antiretroviral therapy and delay HCV therapy. Concurrent treatment is feasible but may be complicated by pill burden, drug toxicities, and drug interactions.

Scenarios for Treating HCV/HIV Coinfection

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

- Ribavirin should not be given with didanosine because of the potential for drug-drug interactions leading to pancreatitis and lactic acidosis *[179]*;
- Some NRTIs and all NNRTIs and PIs are potentially hepatotoxic so that monitoring of serum transaminase levels is particularly important *[344]*;
- Zidovudine combined with ribavirin is associated with higher rates of anemia suggesting this combination be avoided when possible;
- Growth factors to manage interferon-associated neutropenia and ribavirin-associated anemia may be required.

MYCOBACTERIUM TUBERCULOSIS (TB/HIV COINFECTION)

Panel's Recommendations:

- ***The treatment of TB in patients with HIV infection should follow the same principles for persons without HIV infection (AI).***
- ***Presence of active TB requires immediate initiation of treatment (AI).***
- ***In antiretroviral-naïve patients, delay of antiretroviral therapy for 4-8 weeks after initiation of TB treatment permits a better definition of causes of adverse reactions and paradoxical reactions (BIII).***
- ***DOT is strongly recommended for HIV/TB coinfected patients (AII).***
- ***Rifampin/rifabutin-based regimens should be given at least three times weekly in patients with CD4 counts <100 cells/mm^3 (AII).***
- ***Once-weekly rifapentine is not recommended in HIV-infected patients (EI).***
- ***Despite drug interactions, rifamycin should be included in patients receiving antiretroviral therapy, with dosage adjustment as necessary (AII).***
- ***Paradoxical reaction should be treated with continuation of treatment for TB and HIV, along with use of nonsteroidal anti-inflammatory agents (BIII).***
- ***In severe cases of paradoxical reaction, some suggest use of high-dose prednisone (CIII).***

HIV infection increases the risk of progression from latent to active TB by approximately 100-fold *[345]*. The CD4 count influences both the frequency and clinical expression of active TB *[346, 347]*. TB also negatively impacts HIV disease. It is associated with a higher HIV viral load and more rapid progression of HIV disease *[345, 346]*. Important issues with respect to the use of antiretroviral drugs in patients with TB coinfection are the sequencing of treatments, potential for significant drug interactions with rifamycins, high rates of hepatotoxicity with drugs used for both infections, and development of immune reconstitution TB (paradoxical reactions).

Scenarios for Treating TB/HIV Coinfection

The treatment of TB should follow the general principles for TB in persons without HIV **(AI)**. Below are various scenarios:

- **Patients on Antiretroviral Therapy**. Patients receiving antiretroviral treatment at the time TB treatment is started will require assessment of the antiretroviral regimen with changes that will permit use of the optimal TB regimen with particular attention to rifamycins (discussed below).
- **Patients Not Currently on Antiretroviral Therapy**. For patients who have not received antiretroviral therapy, the simultaneous initiation of treatment of both conditions has been associated with a high rate of side effects and paradoxical reactions *[348, 349]*. Active TB always requires immediate initiation of treatment **(AI)**. A delay in antiretroviral therapy for 4–8 weeks permits better definition of causes of adverse drug reactions and paradoxical reactions. Thus, it is recommended that simultaneous initiation for TB and HIV should be avoided, with the possible exception of patients who have CD4 count <50 cells/mm^3. The optimal time to delay initiation of antiretroviral therapy is not known, but many authorities suggest a delay of 4–8 weeks **(BIII)**.

Treatment of TB

Treatment of drug-susceptible TB should consist of the standard regimen outlined in treatment guidelines, which consists of isoniazid (INH), rifampin or rifabutin (RIF), pyrazinamide (PZA), and ethambutol (EMB) or streptomycin (SM) given for 2 months, followed by INH + RIF for 4–7 months *[350]* **(AI)**. Special attention should be given to the potential of drug-drug interactions with rifamycin as discussed below. In the case of single- or multi–drug-resistant TB, therapy should be prescribed based on susceptibility, preferably in consultation with TB experts.

Directly Observed Therapy (DOT)

DOT is strongly recommended for patients with TB/HIV coinfection **(AII)**. Once- or twice-weekly dosing has been associated with increased rates of rifamycin resistance in patients with advanced HIV *[351, 352]*. Thus, once-weekly rifapentine is not recommended **(EI)** and rifampin/rifabutin-based TB regimens should be given at least three times weekly for those with a CD4 count <100 cells/mm^3 *[350]* **(AII)**. In general, daily DOT is recommended for the first 2 months and then three times weekly DOT for the continuation phase **(BII)**.

Anti-TB/Antiretroviral Drug Toxicities and Interactions

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

Rifamycins are essential drugs for the treatment of TB but are also associated with frequent drug interactions with PIs and NNRTIs because of their effects as inducers of the hepatic CYP enzyme system. Despite these interactions, rifamycin should be included in the TB treatment regimen in patients receiving antiretroviral agents *[353]* **(AII)**. Among the rifamycins, rifampin is the most potent inducer. Unfortunately, of all available NNRTIs and PIs, rifampin may be used only with full-dose ritonavir or with efavirenz (**Table 20**). Rifampin cannot be used safely with ritonavir-boosted PI regimens. Rifabutin is recommended when used in combination with appropriate dose adjustments, according to **Table 21** *[354]*.

Some patients treated for TB will develop a paradoxical reaction, characterized by fever, new lymphadenopathy, worsening of pulmonary infiltrates and expanding pleural effusions. These reactions may occur in the absence of HIV infection or in the absence of antiretroviral therapy, but are more common with immune reconstitution because of antiretroviral treatment. If not severe, these reactions should be managed with continuation of drugs for TB and HIV and with nonsteroidal anti-inflammatory agents **(BIII)**. Occasional severe cases have been managed with high-dose prednisone (1mg/kg for 1–2 weeks followed by tapering doses) *[348, 349]* **(CIII)**.

Prevention Counseling for the HIV-Infected Patient

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

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

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

The following link provides more information that providers can access to provide them with better understanding of the need for prevention and prevention counseling. (**http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5212a1.htm**) *[355]*.

Conclusion

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

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

As further research is conducted and reported, guidelines will be modified. The Panel expects new drugs from current and newer classes to become available soon. These may well affect choices in initial and secondary drug regimens. The Panel also anticipates continued progress in the simplicity of regimens and in reduced toxicity. The Panel hopes the guidelines are useful and is committed to their continued adjustment and improvement.

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

Table 1. Rating Scheme for Clinical Practice Recommendations

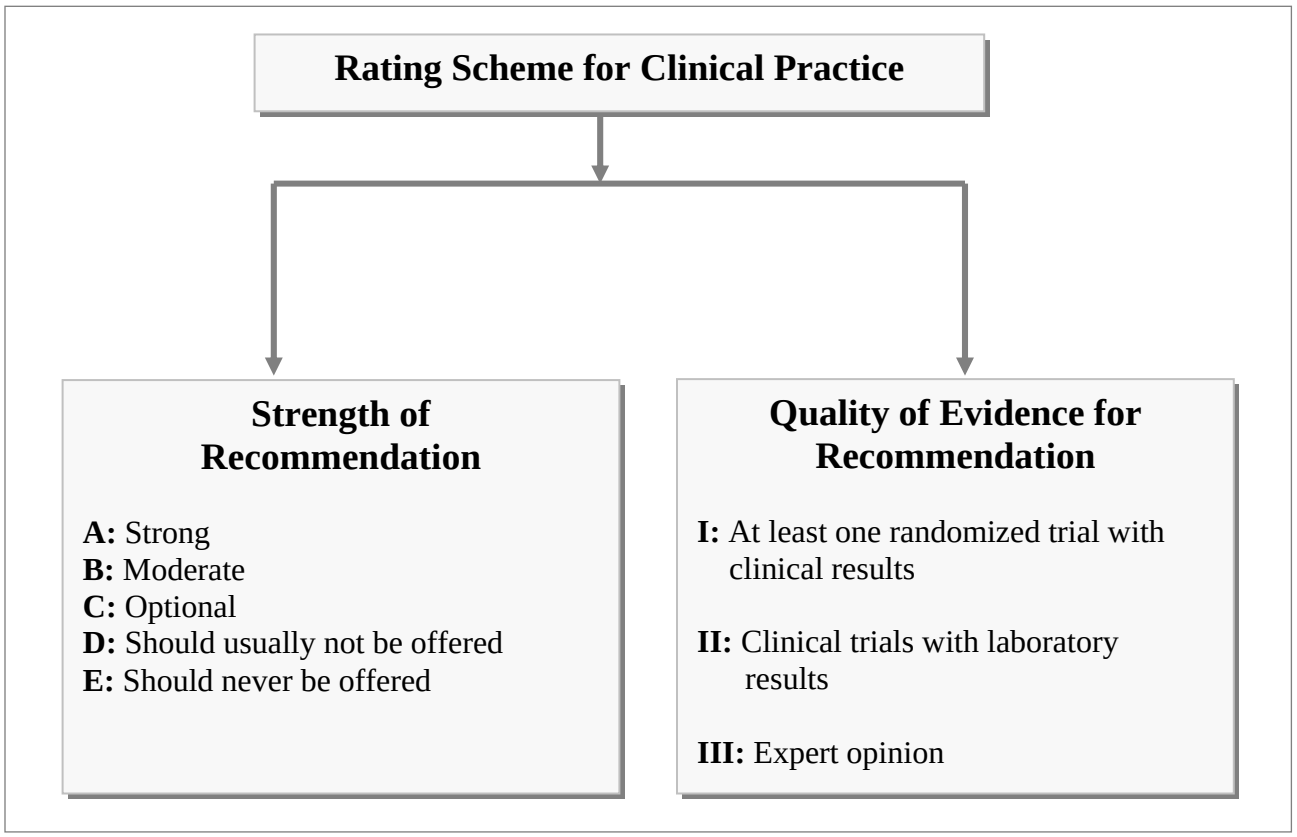

Table 2. Indications for Plasma HIV RNA Testing*

Clinical Indication	Information	Use
Syndrome consistent with acute HIV infection (See **Table 24**.)	Establishes diagnosis when HIV antibody test is negative or indeterminate	Diagnosis†
Initial evaluation of newly diagnosed HIV infection	Baseline viral load setpoint	Use in conjunction with CD4 count for decision to start or defer therapy
Every 3–4 months in patients not on therapy	Changes in viral load	Use in conjunction with CD4 count for decision to start therapy
2–8 weeks after initiation of or change in antiretroviral therapy	Initial assessment of drug efficacy	Decision to continue or change therapy
3–4 months after start of therapy	Assessment of virologic effect of therapy	Decision to continue or change therapy
Every 3–4 months in patients on therapy	Durability of antiretroviral effect	Decision to continue or change therapy
Clinical event or significant decline in CD4 T-cells	Association with changing or stable viral load	Decision to continue, initiate, or change therapy

* Acute illness (e.g., bacterial pneumonia, tuberculosis, herpes simplex virus, *Pneumocystis jiroveci* pneumonia), and vaccinations can cause an increase in plasma HIV RNA for 2–4 weeks; viral load testing should not be performed during this time. Plasma HIV RNA results should usually be verified with a repeat determination before starting or making changes in therapy.

† Diagnosis of HIV infection made by HIV RNA testing should be confirmed by standard methods (i.e., ELISA and Western blot testing) performed 2–4 months after the initial indeterminate or negative test.

Table 3. Recommendations for Using Drug Resistance Assays

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

Table 4a: Probability of Progressing to AIDS or Death According to CD4 Cell Count, Viral Load, and Sociodemographic factors

	CD4 cell count (cells/μL)									
	< 50		50–99		100–199		200–349		≥ 350	
	Viral load ≥ 5*	Viral load < 5*	Viral load ≥ 5*	Viral load < 5*	Viral load ≥ 5*	Viral load < 5*	Viral load ≥ 5*	Viral load < 5*	Viral load ≥ 5*	Viral load < 5*
CDC stage A/B and no history of IDU										
Age < 50 years										
Year 1	12 (11–14)	9.5 (8.0–11)	9.2 (7.7–11)	7.0 (5.8–8.5)	6.2 (5.2–7.3)	4.7 (4.0–5.6)	2.6 (2.1–3.2)	2.0 (1.6–2.5)	2.0 (1.6–2.5)	1.5 (1.2–1.9)
Year 2	17 (15–20)	13 (11–15)	13 (11–15)	10 (8.4–12)	9.5 (8.1–11)	7.3 (6.2–8.5)	4.5 (3.7–5.4)	3.3 (2.8–4.1)	3.3 (2.7–4.0)	2.5 (2.1–3.0)
Year 3	20 (18–23)	16 (13–19)	16 (14–19)	12 (10–15)	12 (10–14)	9.3 (7.9–11)	6.1 (5.0–7.4)	4.7 (3.9–5.6)	4.4 (3.6–5.4)	3.4 (2.8–4.1)
Age ≥ 50 years										
Year 1	17 (14–20)	13 (11–16)	12 (10–15)	9.6 (7.7–12)	8.5 (7.0–10)	6.5 (5.3–7.9)	3.6 (2.8–4.5)	2.7 (2.2–3.4)	2.8 (2.2–3.5)	2.1 (1.6–2.7)
Year 2	23 (19–27)	18 (15–21)	18 (15–21)	14 (11–17)	13 (10–15)	9.9 (8.2–12)	6.1 (5.0–7.6)	4.7 (3.8–5.8)	4.5 (3.6–5.7)	3.4 (2.8–4.3)
Year 3	27 (23–32)	21 (18–25)	22 (18–26)	17 (14–20)	16 (14–19)	13 (10–15)	8.3 (6.7–10)	6.4 (5.1–7.9)	6.0 (4.8–7.6)	4.6 (3.7–5.8)
CDC stage A/B and history of IDU										
Age < 50 years										
Year 1	17 (14–20)	13 (11–16)	12 (10–15)	9.5 (7.7–12)	8.4 (7.0–10)	6.5 (5.3–7.9)	3.6 (2.8–4.5)	2.7 (2.2–3.4)	2.7 (2.1–3.5)	2.1 (1.6–2.6)
Year 2	24 (21–28)	19 (16–23)	19 (16–22)	15 12–18)	14 (12–16)	11 (8.8–13)	6.6 (5.4–8.1)	5.0 (4.1–6.1)	4.9 (3.9–6.1)	3.7 (3.0–4.6)
Year 3	30 (26–35)	24 (20–28)	24 (20–28)	19 (15–23)	18 (15–22)	14 (12–17)	9.4 (7.6–11)	7.2 (5.8–8.8)	6.8 (5.4–8.6)	5.2 (4.2–6.5)
Age ≥ 50 years										
Year 1	22 (18–27)	17 (14–22)	17 (13–21)	13 (10–16)	11 (9.1–14)	8.8 (6.9–11)	4.9 (3.7–6.4)	3.7 (2.8–4.9)	3.8 (2.8–5.0)	2.9 (2.2–3.8)
Year 2	32 (26–38)	25 (20–31)	25 (20–31)	20 (15–25)	18 (15–23)	14 (11–18)	9.0 (7.0–11)	6.9 (5.4–8.8)	6.7 (5.1–8.7)	5.1 (3.9–6.6)
Year 3	39 (32–46)	31 (25–38)	33 (26–38)	25 (20–31)	24 (20–30)	19 (15–24)	13 (9.9–16)	9.8 (7.6–12)	9.3 (7.1–12)	7.1 (5.4–9.2)
CDC stage C and no history of IDU										
Age < 50 years										
Year 1	17 (15–19)	13 (11–15)	13 (11–15)	9.8 (8.1–12)	8.7 (7.2–10)	6.6 (5.5–8.1)	3.7 (2.9–4.7)	2.8 (2.2–3.5)	2.8 (2.2–3.6)	2.1 (1.7–2.7)
Year 2	23 (21–26)	18 (16–21)	18 (15–21)	14 (12–17)	13 (11–16)	10 (8.4–12)	6.3 (5.1–7.8)	4.8 (3.9–5.9)	4.6 (3.7–5.9)	3.5 (2.8–4.4)
Year 3	28 (25–31)	22 (19–25)	22 (19–26)	17 (14–21)	17 (14–20)	13 (11–15)	8.5 (6.9–11)	6.5 (5.2–8.1)	6.2 (4.9–7.9)	4.7 (3.7–6.0)
Age ≥ 50 years										
Year 1	23 (20–26)	18 (15–21)	17 (14–20)	13 (11–16)	12 (9.7–14)	9.1 (7.3–11)	5.1 (3.9–6.5)	3.8 (3.0–5.0)	3.9 (3.0–5.1)	3.0 (2.3–3.9)
Year 2	31 (27–35)	24 (20–28)	24 (20–28)	19 (15–23)	18 (15–21)	14 (11–17)	8.6 (6.8–11)	6.6 (5.2–8.3)	6.4 (4.9–8.2)	4.9 (3.8–6.2)
Year 3	36 (32–41)	29 (24–34)	29 (25–34)	23 (19–28)	22 (18–27)	17 (14–21)	12 (9.2–15)	8.9 (7.0–11)	8.5 (6.5–11)	6.5 (5.0–8.3)
CDC stage C and history of IDU										
Age < 50 years										
Year 1	23 (20–26)	18 (15–21)	17 (14–21)	13 (11–16)	12 (9.5–14)	9.0 (7.2–11)	5.0 (3.9–6.5)	3.8 (2.9–5.0)	3.9 (2.9–5.1)	2.9 (2.2–3.9)
Year 2	33 (29–37)	26 (22–30)	26 (22–30)	20 (16–24)	19 (15–23)	15 (12–18)	9.2 (7.3–12)	7.0 (5.6–8.9)	6.8 (5.3–8.8)	5.2 (4.1–6.7)
Year 3	40 (35–45)	32 (27–37)	32 (27–38)	25 (21–31)	25 (22–30)	19 (16–24)	13 (10–16)	10.0 (7.9–13)	9.5 (7.3–12)	7.3 (5.6–9.4)
Age ≥ 50 years										
Year 1	30 (25–36)	24 (19–29)	23 (18–28)	18 (14–23)	16 (12–20)	12 (9.5–16)	6.9 (5.1–9.2)	5.3 (3.9–7.1)	5.3 (3.9–7.2)	4.0 (3.0–5.5)
Year 2	42 (36–49)	34 (28–41)	34 (27–41)	27 (21–33)	25 (20–31)	20 (15–25)	12 (9.6–16)	9.6 (7.3–13)	9.3 (7.0–12)	7.1 (5.3–9.5)
Year 3	50 (43–58)	41 (34–49)	42 (34–50)	33 (27–41)	33 (26–40)	26 (20–32)	17 (13–23)	14 (10–18)	13 (9.6–17)	9.9 (7.4–13)

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

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Table 4b. Predicted 6-month Risk of AIDS According to Age and Current CD4 Cell Count and Viral Load, Based on a Poisson Regression Model

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

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

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

Table 5. Indications for Initiating Antiretroviral Therapy for the Chronically HIV-1 Infected Patient

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

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

Benefits and Risks of Treatment

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

Potential Benefits of Early Therapy Include:

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

Potential Risks of Early Therapy Include:

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

Table 6a. Antiretroviral Components Recommended for Treatment of HIV-1 Infection in Treatment-Naïve Patients

A combination antiretroviral regimen in treatment-naïve patients generally contains 1 NNRTI + 2 NRTIs or a single or ritonavir-boosted PI + 2 NRTIs.

Selection of a regimen for an antiretroviral-naïve patient should be individualized based on virologic efficacy, toxicities, pill burden, dosing frequency, drug-drug interaction potential, and comorbid conditions. Components listed below are designated as preferred when clinical trial data suggest optimal and durable efficacy with acceptable tolerability and ease of use. Alternative components are those that clinical trial data show efficacy but that have disadvantages, such as antiviral activity or toxicities, compared with the preferred agent. In some cases, for an individual patient, a component listed as alternative may actually be the preferred component. Clinicians initiating antiretroviral regimens in the HIV-1-infected pregnant patient should refer to "***Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States***" at **http://aidsinfo.nih.gov/guidelines/**.

To Construct an Antiretroviral Regimen, Select 1 Component from Column A + 1 from Column B

	Column A (NNRTI or PI Options – in alphabetical order)			**Column B (Dual-NRTI Options – in alphabetical order)**
Preferred Components	**NNRTI-** **efavirenz[1] (AII)** **or** **PI-** **atazanavir + ritonavir (AIII)** **fosamprenavir + ritonavir (2x/day) (AII)** **lopinavir/ritonavir[2] (2x/day) (AII)** (coformulated)	+	**Preferred Components**	**tenofovir/emtricitabine[3]** (coformulated) **(AII); or** **zidovudine/lamivudine[3]** (coformulated) **(AII)**
Alternative to Preferred Components	**NNRTI –** **nevirapine[4] (BII)** **or** **PI-** **atazanavir[5] (BII)** **fosamprenavir (BII)** **fosamprenavir + ritonavir (1x/day) (BII)** **lopinavir/ritonavir (1x/day) (BII)** (coformulated)		**Alternative to Preferred Components**	**abacavir/lamivudine[3]** (coformulated) **(BII)** **didanosine + (emtricitabine or lamivudine) (BII)**
Other Possible Options	**Please** see **Table 6b**		**Other Possible Options**	**Please** see **Table 6b**

[1] Efavirenz is not recommended for use in the 1st trimester of pregnancy or in sexually active women with childbearing potential who are not using effective contraception.

[2] The pivotal study that led to the recommendation of lopinavir/ritonavir as a preferred PI component was based on twice-daily dosing *[137]*. A smaller study has shown similar efficacy with once-daily dosing but also showed a higher incidence of moderate to severe diarrhea with the once-daily regimen (16% vs. 5%) *[145]*.

[3] Emtricitabine may be used in place of lamivudine and vice versa.

[4] Nevirapine should not be initiated in women with CD4 count >250 cells/mm^3 or in men with CD4 count >400 cells/mm^3 because of increased risk of symptomatic hepatic events in these patients.

[5] Atazanavir must be boosted with ritonavir if used in combination with tenofovir.

Table 6b. Antiretroviral Components That Are Acceptable as Initial Antiretroviral Components but Are Inferior to Preferred or Alternative Components

Antiretroviral drugs or regimens (in alphabetical order)	**Reasons for generally not recommending the drugs or regimens as initial therapy**	**Special circumstances in which the drugs or regimens may be used**
Abacavir/lamivudine/ zidovudine (coformulated) as triple-NRTI combination regimen **(CII)**	• Inferior virologic efficacy	• When PI or NNRTI-based regimens cannot be used based on toxicities or concerns of significant drug-drug interactions
Nelfinavir **(CII)**	• Inferior virologic efficacy	
Saquinavir (ritonavir-boosted) **(CII)**	• Inferior to lopinavir/ritonavir • Minimal efficacy data in treatment-naïve patients	• When preferred or alternative PI components cannot be used based on toxicities or concerns of significant drug-drug interactions
Stavudine + lamivudine **(CII)**	• Significant toxicities including lipoatrophy, peripheral neuropathy, hyperlactatemia including symptomatic and life-threatening lactic acidosis, hepatic steatosis, and pancreatitis	• When preferred or alternative dual-NRTI combination cannot be used

Table 7. Antiretroviral Drugs and Components Not Recommended as Initial Therapy

Antiretroviral drugs or components (in alphabetical order)	**Reasons for not recommending as initial therapy**
Darunavir (ritonavir-boosted) **(DIII)**	• Insufficient data in treatment-naïve patients
Delavirdine **(DII)**	• Inferior virologic efficacy • Inconvenient (three times daily) dosing
Didanosine + tenofovir **(DII)**	• High rate of early virologic failure • Rapid selection of resistant mutations • Potential for immunologic non-response/CD4 decline
Enfuvirtide **(DIII** as initial regimen**)**	• No clinical trial experience in treatment-naïve patients • Requires twice-daily subcutaneous injections
Indinavir (unboosted) **(DIII)**	• Inconvenient dosing (three times daily with meal restrictions) • Fluid Requirement
Indinavir (ritonavir-boosted) **(DII)**	• High incidence of nephrolithiasis
Ritonavir as sole PI **(DIII)**	• High pill burden • Gastrointestinal intolerance
Saquinavir (unboosted) **(DII)**	• High pill burden • Inferior virologic efficacy
Tipranavir (ritonavir-boosted) **(DIII)**	• Lack of data in treatment-naïve patients

Table 8. Antiretroviral Regimens or Components That Should Not Be Offered At Any Time

	Rationale	Exception
Antiretroviral Regimens Not Recommended		
Monotherapy with NRTI or NNRTI (EII)	• Rapid development of resistance • Inferior antiretroviral activity when compared with combination with three or more antiretrovirals	• Pregnant women with pretreatment HIV RNA <1,000 copies/mL using ZDV monotherapy for prevention of perinatal HIV transmission, not for HIV treatment for the mother*; however, combination therapy is generally preferred.
Dual-NRTI regimens (EII)	• Rapid development of resistance • Inferior antiretroviral activity when compared with combination with three or more antiretrovirals	
Triple-NRTI regimens (EII) except for abacavir/zidovudine/lamivudine or possibly tenofovir + zidovudine/lamivudine	• High rate of early virologic nonresponse seen when triple NRTI combinations including ABC/TDF/3TC or TDF/ddI/3TC were used as initial regimen in treatment-naïve patients • Other 3-NRTI regimens have not been evaluated	• Abacavir/zidovudine/lamivudine **(CII)**; and possibly tenofovir + zidovudine/lamivudine **(DII)**
Antiretroviral Components Not Recommended as Part of Antiretroviral Regimen		
Atazanavir + indinavir (EIII)	• Potential additive hyperbilirubinemia	• No exception
Didanosine + stavudine (EIII)	• High incidence of toxicities: peripheral neuropathy, pancreatitis, and hyperlactatemia • Reports of serious, even fatal, cases of lactic acidosis with hepatic steatosis with or without pancreatitis in pregnant women*	• When no other antiretroviral options are available and potential benefits outweigh the risks* **(DIII)**
Efavirenz in first trimester of pregnancy or in women with significant child-bearing potential* (EIII)	• Teratogenic in nonhuman primates	• When no other antiretroviral options are available and potential benefits outweigh the risks* **(DIII)**
Emtricitabine + lamivudine (EIII)	• Similar resistance profile • No potential benefit	• No exception
Nevirapine initiation in treatment-naïve women with CD4 >250 cells/mm^3 or in treatment-naïve men with CD4 >400 cells/mm^3 (DI)	Higher incidence of symptomatic (including serious and even fatal) hepatic events in these patient groups	Only if the benefit clearly outweighs the risk
Saquinavir as single protease inhibitor (EIII)	• Poor oral bioavailability (4%) • Inferior antiretroviral activity when compared with other protease inhibitors	• No exception
Stavudine + zidovudine (EII)	• Antagonistic effect on HIV-1	• No exception

***** When constructing an antiretroviral regimen for an HIV-infected pregnant woman, please consult "Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States" in http://www.aidsinfo.nih.gov/guidelines/.

Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy

ARV Class	Antiretroviral Agent(s)	Advantages	Disadvantages
NNRTIs (in alphabetical order)		**NNRTI Class Advantages:** • Less fat maldistribution and dyslipidemia than PI-based regimens • Save PI options for future use	**NNRTI Class Disadvantages:** • Low genetic barrier to resistance (single mutation confers resistance) • Cross resistance among approved NNRTIs • Skin rash • Potential for CYP450 drug interactions (See **Tables 19–21b**)
	Efavirenz (EFV)	• Potent antiretroviral activity • Low pill burden; once-daily dosing • Fixed-dose combination with tenofovir + emtricitabine	• Neuropsychiatric side effects • Teratogenic in nonhuman primates, contraindicated in 1st trimester of pregnancy; avoid use in women with pregnancy potential
	Nevirapine (NVP)	• No food effect	• Higher incidence of rash than with other NNRTIs, including rare but serious hypersensitivity reactions (Stevens-Johnson syndrome or toxic epidermal necrolysis) • Higher incidence of hepatotoxicity than with other NNRTIs, including serious and even fatal cases of hepatic necrosis • Treament-naïve, female patients and treatment-naïve patients with high pre-NVP CD4 counts (>250 cells/mm^3 females, >400 cells/mm^3 males) are at higher risk of symptomatic hepatic events. NVP not recommended in these patients unless benefit clearly outweighs risk.
PIs (in alphabetical order)		**PI Class Advantage:** • Save NNRTI for future use • Higher genetic barrier to resistance	**PI Class Disadvantages:** • Metabolic complications: fat maldistribution, dyslipidemia, insulin resistance • CYP3A4 inhibitors & substrates – potential for drug interactions (more pronounced w/ RTV-based regimens) (See **Tables 19–21b**)
	Atazanavir (unboosted) (ATV)	• Less adverse effect on lipids than other PIs • Once-daily dosing • Low pill burden (2 pills per day)	• Indirect hyperbilirubinemia • PR interval prolongation – generally inconsequential unless combined with another drug with similar effect • Reduced drug exposure when used with TDF and EFV –need addition of RTV (ATV 300mg QD + RTV 100mg QD) • Absorption depends on food and low gastric pH – contraindicated with proton pump inhibitors; separate doses with antacid or H2 blockers
	Atazanavir/ ritonavir (ATV/r)	• RTV-boosting: higher trough ATV concentration & greater antiviral effect • Once-daily dosing	• Potentially more adverse effect on lipids than unboosted atazanavir
	Fosamprenavir (unboosted) (FPV)	• No food effect	• Skin rash
	Fosamprenavir/ ritonavir (FPV/r)	• Twice-daily dosing resulted in comparable efficacy as LPV/r • RTV-boosting: higher trough FPV concentration & greater antiviral effect • Once-daily can also be used • No food effect	• Skin rash • Once-daily dosing less effective than twice-daily dosing
	Lopinavir/ ritonavir (LPV/r)	• Coformulated as Kaletra® • Potential for once-daily dosing in treatment-naïve patients • No food restriction with oral tablet formulation	• Gastrointestinal intolerance (higher incidence with once-daily than twice-daily dosing) • Hyperlipidemia • Preliminary data- lower drug exposure in pregnant women • Once-daily dosing – lower trough concentration than BID

Table 9. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy

ARV Class	Antiretroviral Agent(s)	Advantages	Disadvantages
PIs (cont'd, in alphabetical order)	**Nelfinavir (NFV)**		• Diarrhea • Higher rate of virologic failure when compared with other PIs (LPV/r & FPV) and EFV in clinical trials • Food requirement
	Saquinavir + ritonavir (SQV/r)	• RTV boosting causes higher trough SQV concentration & greater antiviral effect	• Gastrointestinal intolerance • Need for use with RTV
Dual NRTIs		• Established backbone of combination antiretroviral therapy	• Rare but serious cases of lactic acidosis with hepatic steatosis reported (d4T>ddI=ZDV>TDF=ABC=3TC=FTC)
Dual-NRTI pairs (in alphabetical order)	**Abacavir + lamivudine (ABC + 3TC)**	• No food effect • Study showing noninferior to ZDV+ 3TC as dual-NRTI backbone • Once-daily dosing • Coformulation (Epzicom®)	• Potential for abacavir systemic hypersensitivity reaction
	Didanosine + lamivudine (ddI + 3TC)	• Once-daily dosing	• Peripheral neuropathy, pancreatitis – associated with didanosine • Food effect – needs to be taken on an empty stomach • Requires dosing separation from most PIs • Increase in toxicities when used with ribavirin, tenofovir, stavudine, or hydroxyurea
	Stavudine + lamivudine (d4T + 3TC)	• No food effect	• Peripheral neuropathy, lipoatrophy, hyperlactatemia and lactic acidosis, reports of progressive ascending motor weakness, potential for hyperlipidemia with stavudine use • d4T - Higher incidence of mitochondrial toxicity than with other NRTIs
	Tenofovir/ emtricitabine (or lamivudine) (TDF/FTC or 3TC)	• Good virologic response when used with efavirenz • Once-daily dosing • No food effect • Coformulated as Truvada™ (TDF/FTC) and Atripla™ (EFV/TDF/FTC)	• Tenofovir – some reports of renal impairment • Interactions with: 1. ATV - TDF reduces ATV levels – need to add low dose RTV ; and 2. ddI – TDF increases ddI level – need to reduce ddI dose
	Zidovudine + lamivudine (ZDV + 3TC)	• Extensive experience • Coformulated as Combivir® • No food effect	• Bone marrow suppression with zidovudine • Gastrointestinal intolerance
	emtricitabine (in place of lamivudine)	• Longer half-life than lamivudine • Once-daily dosing • Coformulation w/ TDF (Truvada™) & w/ EFV/TDF (Atripla™)	• Hyperpigmentation/skin discoloration
Triple-NRTI regimen	**Abacavir (ABC) + zidovudine (ZDV) + lamivudine (3TC) only**	• Coformulated as Trizivir® • Minimal drug-drug interactions • Low pill burden • Saves PI & NNRTI for future use	• Inferior virologic responses when compared with efavirenz-based and indinavir-based regimens • Potential for abacavir hypersensitivity reaction

Table 10. Treatment Outcome of Selected Clinical Trials of Combination Antiretroviral Regimens in Treatment-Naïve Patients with 48-Week Follow-Up Data

Three-Class Comparison Studies
PI-based vs. NNRTI-based vs. Triple-NRTI Regimens

ATLANTIC [167]

Arm	Regimen	N	Baseline CD4 Count*	Baseline Viral Load*	% Subjects with plasma HIV RNA (ITT) <500	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
A	d4T + ddI + IDV	100	417	4.3 $\log_{10}$	57	55	5	No difference among regimens except at 50 copy endpoint: Arm C is inferior to Arms A and B (p=0.004)	The triple-NRTI regimen is less potent than either the IDV or NVP based regimen.
B	d4T + ddI + NVP	89	394	4.3 $\log_{10}$	58	54	7		
C	d4T + ddI + 3TC	109	396	4.2 $\log_{10}$	59	46	6		

CLASS (GSK) [168]

Arm	Regimen	N	Baseline CD4 Count#	Baseline Viral Load#	% Subjects with plasma HIV RNA (ITT) <400	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Statistical Significance	Comments & Conclusion
A	ABC/3TC + EFV	97	307	4.90 $\log_{10}$	81	72	2	No sig. difference among arms at 400 copy endpoint; NNRTI performed better at 50 copy endpoint.	NNRTI arm tended to perform better at lower viral copy cutoff.
B	ABC/3TC + r/AMP	96	306	4.85 $\log_{10}$	75	59	5		
C	ABC/3TC + d4T	98	296	4.81 $\log_{10}$	80	60	6		

Two-Class Comparison Studies
PI-based vs. NNRTI-based Regimens

AACTG 384 [113, 119]

Arm	Regimen	N	Baseline CD4 Count*	Baseline Viral Load*	Probability of not experiencing 1st regimen failure by 48 wks**	No. of subjects with toxicity related failure of 1st regimen##	Premise	Comments & Conclusion
A	d4T + ddI + EFV	155	273	5.0 $\log_{10}$	62	20	Four-drug regimens might be superior to sequential three drug regimens.	No significant benefit to the 4-drug regimens in this study over ZDV+3TC+EFV
B	d4T + ddI + NFV	155	264	5.0 $\log_{10}$	63	19		
C	ZDV+3TC+EFV	155	272	4.9 $\log_{10}$	89	11		Best 1st regimen appeared to be ZDV+3TC + EFV
D	ZDV+3TC + NFV	155	307	4.9 $\log_{10}$	66	3	The way antiviral drugs are combined and sequenced is important.	
E	d4T + ddI + NFV + EFV	178	274	5.1 $\log_{10}$	77	23		The efficacy of ARVs depend on how they are combined.
F	ZDV+3TC + NFV + EFV	182	279	4.9 $\log_{10}$	84	12		

Value indicates mean * Value indicates median ## Any time during study follow-up ** First regimen failure = virologic failure or toxicity related failure. Criteria for virologic failure: (1) decrease by < a factor of 10 in HIV RNA by wk 8; or (2) increase by a factor of >10 above nadir measurement (and >2000 copies/mL within 24 wks); or (3) HIV RNA level >200 copies/mL in a subject with two previous measurements of less than 200 copies/mL, or at any time after wk 24

Table 10. Treatment Outcome of Selected Clinical Trials of Combination Antiretroviral Regimens in Treatment-Naïve Patients with 48-Week Follow-Up Data

[**Two-Class Comparison Studies (PI-based vs. NNRTI-based Regimens** (continued)]

AI 424-034 Atazanavir Study (BMS) *[124]*

Arm	Regimen	N	Baseline CD4 Count#	Baseline Viral Load#	% Subjects with plasma HIV RNA (ITT) <400	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
A	ZDV/3TC + ATV	404	286	4.87 $\log_{10}$	70	32	NA	No significant difference between the two arms at either viral load endpoint.	ATV not inferior to EFV with a ZDV/3TC backbone. Uncharacteristically low response rates in both arms attributed by investigators by plasma collection technique.
B	ZDV/3TC + EFV	401	280	4.91 $\log_{10}$	64	37	NA		

COMBINE *[156]*

Arm	Regimen	N	Baseline CD4 Count#	Baseline Viral Load#	% Subjects with plasma HIV RNA (ITT) <200	% Subjects with plasma HIV RNA (ITT) <20	Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
A	ZDV/3TC + NFV	70	347	5.21 $\log_{10}$	60	50	21	Virologic efficacy of regimens similar (no "*p*" values < 0.05).	NVP is at least as effective as NFV when combined with ZDV/3TC.
B	ZDV/3TC + NVP	72	396	5.07 $\log_{10}$	75	65	25		

DUPONT 006 *[117]*

Arm	Regimen	N	Baseline CD4 Count#	Baseline Viral Load#	% Subjects with plasma HIV RNA (ITT) <400	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
A	ZDV/3TC + EFV	154	350	4.77 $\log_{10}$	70	64	6	Arm A is superior to either of the other two arms.	EFV is superior to IDV with a ZDV/3TC nucleoside backbone.
B	ZDV/3TC + IDV	148	341	4.78 $\log_{10}$	48	43	20		
C	IDV + EFV	148	344	4.79 $\log_{10}$	53	47	6		

Value indicates mean
* Value indicates median

Table 10. Treatment Outcome of Selected Clinical Trials of Combination Antiretroviral Regimens in Treatment-Naïve Patients with 48-Week Follow-Up Data

Two-Class Comparison Studies
NNRTI-based vs. Triple-NRTI Regimens

AACTG 5095 [120]

Arm	Regimen	N	Baseline CD4 Count[#]	Baseline Viral Load[#]	% Subjects with plasma HIV RNA (ITT) <200	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %[ξξ]	Statistical Significance	Comments & Conclusion
A	ZDV/3TC/ABC	382	234	4.85 $\log_{10}$	74	61	<1%	Virologic failure on Arm A significantly earlier than on the pooled EFV-containing arms.	ZDV/3TC/ABC is inferior in a pooled analysis evaluating patients on either ZDV/3TC/ABC + EFV or ZDV/3TC + EFV.
B	ZDV/3TC/EFV								
C	Pooled Arm B (ZDV/3TC + EFV) and Arm C (ZDV/3TC/ABC + EFV)	765	242	4.86 $\log_{10}$	89	83	<1%		

Two-Class Comparison Studies
PI-based *vs.* Triple-NRTI Regimens

CNAAB3005 (GSK) [154]

Arm	Regimen	N	Baseline CD4 Count[*]	Baseline Viral Load[*]	% Subjects with plasma HIV RNA (ITT) <400	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
A	ZDV/3TC + ABC	282	359	4.85 $\log_{10}$	51	40	17	Neither arm is inferior to the other.	Arm A inferior to Arm B, except for patients with baseline HIV RNA > 100,000 copies/mL
B	ZDV/3TC + IDV	280	360	4.82 $\log_{10}$	51	46	22		

CNA 3014 (GSK) [155]

Arm	Regimen	N	Baseline CD4 Count[*]	Baseline Viral Load[*]	% Subjects with plasma HIV RNA (ITT) <400	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
A	ZDV/3TC + ABC	169	331	4.78 $\log_{10}$	64	59	10	Arm A superior to Arm B at < 400 copy viral load cutoff (p<0.002). Difference not statistically significant at <50 cutoff.	ABC superior to IDV with ZDV/3TC backbone.
B	ZDV/3TC + IDV	173	299	4.82 $\log_{10}$	50	48	13		

[#] Value indicates mean. [*] Value indicates median.

[ξξ] <1% dropped out of the study for an adverse event, 5-8% made protocol-permitted drug substitutions (d4T for ZDV, ddI for ABC, NVP for EFV) for treatment-limiting toxicities.

Table 10. Treatment Outcome of Selected Clinical Trials of Combination Antiretroviral Regimens in Treatment-Naïve Patients with 48-Week Follow-Up Data

Single-Class Comparison Studies
Comparison of NNRTI-Based Regimens

2NN *[122]*

Arm	Regimen	N	Baseline CD4 Count*	Baseline Viral Load*	% Subjects with plasma HIV RNA <50 (ITT)	Adverse Effects Dropout %	Statistical Significance	Comments & Conclusion
A	d4T + 3TC + NVP (400mg QD)	220	200	4.7 $\log_{10}$	70	24	Only statistically inferior arm (Treatment failure) is Arm D.	No significant difference between NVP QD & BID, NVP+EFV inferior to EFV (but not different from NVP QD).
B	d4T + 3TC + NVP (200mg BID)	387	170	4.7 $\log_{10}$	65	21		
C	d4T + 3TC + EFV	400	190	4.7 $\log_{10}$	70	16		NVP BID and EFV arms not significantly different but equivalence not clearly demonstrated. EFV+NVP not recommended because of adverse events.
D	d4T + 3TC + EFV + NVP	209	190	4.7 $\log_{10}$	63	30		

Single-Class Comparison Studies
Comparison of PI-Based Regimens

KLEAN (GSK) *[136]*

Arm	Regimen	N	Baseline CD4 Count#	Baseline Viral Load#	% Subjects with plasma HIV RNA (ITT)		Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
					<400	<50			
A	ABC + 3TC + FPV/r (BID)	434	188	5.1 $\log_{10}$	73	66	6.1%	Arm A is non-inferior to Arm B.	FPV/r given BID has similar virologic & immunologic responses as LPV/r BID when both were used with ABC + 3TC.
B	ABC + 3TC + LPV/r (BID)	444	194	5.1 $\log_{10}$	71	65	5.6%		

M98 863 (ABBOTT) *[137]*

Arm	Regimen	N	Baseline CD4 Count#	Baseline Viral Load#	% Subjects with plasma HIV RNA (ITT)		Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
					<400	<50			
A	d4T + 3TC + LPV/r	326	260	5.01 $\log_{10}$	75	67	3.4	Arm A superior to Arm B at either viral load endpoint (p<0.001)	LPV/r superior to NFV with D4T + 3TC nucleoside backbone.
B	d4T + 3TC + NFV	327	258	4.98 $\log_{10}$	63	52	3.7		

Value indicates mean * Value indicates median

Table 10. Treatment Outcome of Selected Clinical Trials of Combination Antiretroviral Regimens in Treatment-Naïve Patients with 48-Week Follow-Up Data

[**Single-Class Comparison Studies: Comparison of PI-Based Regimens** (continued)]

NEAT - APV 30001 (GSK) *[143]*

Arm	Regimen	N	Baseline CD4 Count*	Baseline Viral Load*	% Subjects with plasma HIV RNA (ITT) <400	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
A	ABC + 3TC + FPV (1400mg BID)	166	214	4.82 $\log_{10}$	66	58	6	Arm A virologically superior to Arm B (p<0.001)	FPV superior to NFV with ABC/3TC backbone.
B	ABC + 3TC + NFV	83	212	4.85 $\log_{10}$	51	42	5		

SOLO - APV 30002 (GSK) *[144]*

Arm	Regimen	N	Baseline CD4 Count*	Baseline Viral Load*	% Subjects with plasma HIV RNA (ITT) <400	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Statistical Significance	Comments & Conclusion
A	ABC + 3TC + r/FPV (200mg/1400mg QD)	322	166	4.8 $\log_{10}$	68	56	9	Arms A and B were not different in performance.	Daily r/FPV is no worse than NFV in an ABC/3TC backbone.
B	ABC + 3TC + NFV	327	177	4.8 $\log_{10}$	65	52	6		

AI424–007 (BMS) *[141]*

Arm	Regimen	N	Baseline CD4 Count#	Baseline Viral Load#	% Subjects with plasma HIV RNA (ITT) <400	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
A	d4T + ddI + ATV	103	357	4.65 $\log_{10}$	64	36	6	No significant difference between the two arms at either viral load endpoint.	ATV not inferior to NFV in D4T/ddI backbone.
B	d4T + ddI + NFV	103	341	4.79 $\log_{10}$	56	39	7		

AI424-008 (BMS) *[356]*

Arm	Regimen	N	Baseline CD4 Count#	Baseline Viral Load#	% Subjects with plasma HIV RNA (ITT) <400	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
A	d4T + 3TC + ATV	181	294	4.74 $\log_{10}$	67	33	1	Arm A not inferior to Arm B at either viral load endpoint.	ATV and NLF were comparable with a d4T and 3TC backbone
B	d4T + 3TC + NFV	91	283	4.73 $\log_{10}$	59	38	3		

Value indicates mean

* Value indicates median

Table 10. Treatment Outcome of Selected Clinical Trials of Combination Antiretroviral Regimens in Treatment-Naïve Patients with 48-Week Follow-Up Data

Nucleoside Backbone Comparison Studies

CNA 30024 (GSK) [157]

Arm	Regimen	N	Baseline CD4 Count*	Baseline Viral Load*	% Subjects with plasma HIV RNA (ITT) <400	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Statistical Significance	Comments & Conclusion
A	ZDV/3TC + EFV	325	258	4.76 $\log_{10}$	71	69	7.6	Arm A was non-inferior to Arm B at either viral load endpoint. Greater CD4 T-cell increases in Arm B than Arm A (p<0.005).	ZDV/3TC and ABC/3TC are equivalent with EFV background therapy.
B	ABC/3TC + EFV	324	267	4.81 $\log_{10}$	74	70	4.9		

FTC 301A (Triangle/Gilead) [35]

Arm	Regimen	N	Baseline CD4 Count#	Baseline Viral Load#	% Subjects with plasma HIV RNA (ITT) <400	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
A	FTC +ddI + EFV	286	312	4.8 $\log_{10}$	81	78	7	FTC & d4T would be of equal efficacy w/ ddI+EFV background.	FTC superior to d4T in ddI+EFV background.
B	d4T + ddI + EFV	285	324	4.8 $\log_{10}$	68	59	13		

Gilead 903 [116]

Arm	Regimen	N	Baseline CD4 Count#	Baseline Viral Load#	% Subjects with plasma HIV RNA (ITT) <400	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
A	TDF + 3 TC + EFV	299	276	4.91 $\log_{10}$	80	76	6	TDF and d4T would be of equal efficacy in a background of 3TC and EFV.	TDF and d4T virologically equivalent. d4T associated with more toxicity.
B	d4T + 3TC + EFV	301	283	4.91 $\log_{10}$	84	80	6		

Gilead 934 [150]

Arm	Regimen	N	Baseline CD4 Count*	Baseline Viral Load*	% Subjects with plasma HIV RNA (ITT) <400	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
A	TDF + FTC + EFV	255	233	5.0 $\log_{10}$	81	77	4	Arm A was noninferior and had significantly greater virologic response than Arm B (p=0.03).	TDF+FTC showed greater virologic response than ZDV+ 3TC when both were combined with EFV.
B	ZDV + 3TC + EFV	254	241	5.0 $\log_{10}$	70	68	9		

Value indicates mean

* Value indicates median

Table 10. Treatment Outcome of Selected Clinical Trials of Combination Antiretroviral Regimens in Treatment-Naïve Patients with 48-Week Follow-Up Data

[**Nucleoside Backbone Comparison Studies** (continued)]

START I [357]

Arm	Regimen	N	Baseline CD4 Count#	Baseline Viral Load#	% Subjects with plasma HIV RNA (ITT) <500	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
A	d4T + 3 TC + IDV	101	424	4.57 $\log_{10}$	53	49	5	d4T and ZDV would be equivalent in suppression of viral load in a background of IDV and 3TC	Arm A is as potent as arm B
B	ZDV + 3TC + IDV	103	422	4.46 $\log_{10}$	52	47	6		

Antiretroviral Dosage Comparison Studies

AGOURON Study 542 [358]

Arm	Regimen	N	Baseline CD4 Count#	Baseline Viral Load#	% Subjects with plasma HIV RNA (ITT) <400	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
A	d4T + 3TC + NFV (1250mg BID)	323	279	5.0 $\log_{10}$	61	54	3.4	Arm A noninferior to Arm B	BID and TID dosing regimens of NFV had comparable efficacy and safety
B	d4T + 3TC + NFV (750mg TID)	192	283	5.1 $\log_{10}$	58	51	3.7		

AI-454-148 (BMS) [359]

Arm	Regimen	N	Baseline CD4 Count*	Baseline Viral Load*	% Subjects with plasma HIV RNA (ITT) <400	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
A	ddI (tablets-QD) + d4T + NFV	503	363	4.7 $\log_{10}$	50	34	4	Arm A was inferior to Arm B.	once daily reduced mass ddI plus d4T was inferior to ZDV plus 3TC when used in combination with NFV
B	ZDV + 3TC + NFV	327	370	4.7 $\log_{10}$	59	47	2		

Value indicates mean

* Value indicates median

Table 10. Treatment Outcome of Selected Clinical Trials of Combination Antiretroviral Regimens in Treatment-Naïve Patients with 48-Week Follow-Up Data

AI454-152 (BMS) [360]

Arm	Regimen	N	Baseline CD4 Count#	Baseline Viral Load#	% Subjects with plasma HIV RNA (ITT) <400	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
A	ddI (QD EC capsules) + d4T + NLF	258	410	4.76 $\log_{10}$	55	33	6	Arm A non-inferior to Arm B	Two nucleoside backbones showed comparable efficacy in combination with NFV
B	ZDV + 3TC + NFV	253	410	4.77 $\log_{10}$	56	33	7		

EPV20001 (GSK) [361]

Arm	Regimen	N	Baseline CD4 Count#	Baseline Viral Load#	% Subjects with plasma HIV RNA (ITT) <400	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
A	ZDV+ 3TC (BID) + EFV	278	399	4.57 $\log_{10}$	65	63	12	Arm B is non-inferior to Arm A	QD and BID dosing regimen of 3TC were comparable for efficacy
B	ZDV + 3TC (QD) + EFV	276	376	4.58 $\log_{10}$	67	61	6		

CNA 30021 Study (GSK) [362]

Arm	Regimen	N	Baseline CD4 Count*	Baseline Viral Load*	% Subjects with plasma HIV RNA (ITT) <400	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
A	3TC + EFV + ABC (300mg BID)	386	259	4.87 $\log_{10}$	Not reported	68	6.5	Arm A noninferior to Arm B	QD and BID dosing regimens of ABC had comparable efficacy and safety
B	3TC + EFV + ABC (600mg QD)	384	264	4.91 $\log_{10}$	Not reported	66	5.7		

M02-418 (Abbott) [145]

Arm	Regimen	N	Baseline CD4 Count#	Baseline Viral Load#	% Subjects with plasma HIV RNA (ITT) <400	% Subjects with plasma HIV RNA (ITT) <50	Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
A	FTC + TDF + LPV/r (400mg/100mg BID)	75	232	4.6	Not reported	64	8%	Arm A non-inferior to Arm B	QD and BID dosing regimens of LPV/r had comparable efficacy; diarrhea (at least moderate in severity) occurs more frequently with QD regimen (16% vs. 5%)
B	FTC + TDF + LPV/r (800mg/200mg QD)	115	214	4.8	Not reported	70	12%		

Value indicates mean

* Value indicates median

Table 11. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations	Food Effect	Oral Bio-availability	Serum half-life	Intracellular half-life	Elimination	Adverse Events
Abacavir (ABC) **ZIAGEN** **TRIZIVIR** - w/ ZDV+3TC **EPZICOM** - w/ 3TC	ZIAGEN 300mg tablets or 20mg/mL oral solution TRIZIVIR- ABC 300mg + ZDV 300mg + 3TC 150mg EPZICOM- ABC 600mg + 3TC 300mg	300mg two times/day; or 600mg once daily; or as TRIZIVIR- 1 tablet two times/day EPZICOM- 1 tablet once daily	Take without regard to meals; Alcohol increases abacavir levels 41%; abacavir has no effect on alcohol	83%	1.5 hours	12–26 hours	Metabolized by alcohol dehydrogenase and glucuronyl transferase. Renal excretion of metabolites 82% TRIZIVIR & EPZICOM not for patients with CrCl < 50 mL/min	Hypersensitivity reaction that can be fatal, symptoms may include fever, rash, nausea, vomiting, malaise or fatigue, loss of appetite, respiratory symptoms such as sore throat, cough, shortness of breath
Didanosine (ddI) **VIDEX EC, Generic didanosine enteric coated (dose same as VIDEX EC)**	VIDEX EC 125, 200, 250, or 400mg Buffered tablets (non-EC) are no longer available.	Body weight ≥ **60kg:** 400mg once daily EC capsule with TDF: 250mg/day **< 60 kg**: 250mg daily EC capsule with TDF: 200mg/day	Levels decrease 55%; Take 1/2 hour before or 2 hours after meal	30–40%	1.5 hours	>20 hours	Renal excretion 50% Dosage adjustment in renal insufficiency (See **Table 15**)	Pancreatitis; peripheral neuropathy; nausea Lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity associated with use of NRTIs.
Emtricitabine (FTC) **EMTRIVA** Also available as : **ATRIPLA** - w/ EFV & TDF **TRUVADA** - w/ TDF	EMTRIVA- 200mg hard gelatin capsule and 10mg/mL oral solution ATRIPLA - EFV 600mg + FTC 200mg + TDF 300mg TRUVADA - FTC 200mg + TDF 300mg	EMTRIVA - 200mg capsule once daily or 240mg (24 mL) oral solution once daily ATRIPLA - One tablet once daily TRUVADA - One tablet once daily	Take without regard to meals	93%	10 hours	>20 hours	Renal excretion Dosage adjustment in renal insufficiency (See **Table 15**) ATRIPLA - not for patients with CrCl <50 mL/min TRUVADA - not for patients with CrCl < 30 mL/min	Minimal toxicity; lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with use of NRTIs.) Hyper-pigmentation/ skin discoloration
Lamivudine (3TC) **EPIVIR** **COMBIVIR**- w/ ZDV **EPZICOM** - w/ ABC **TRIZIVIR**- w/ ZDV+ABC	EPIVIR 150mg and 300mg tablets or 10mg/mL oral solution COMBIVIR- 3TC 150mg + ZDV 300mg EPZICOM - 3TC 300mg + ABC 600mg TRIZIVIR - 3TC 150mg + ZDV 300mg + ABC 300mg	EPIVIR 150mg two times/day; or 300mg daily COMBIVIR - 1 tablet two times/day EPZICOM - 1 tablet once daily TRIZIVIR - 1 tablet two times/day	Take without regard to meals	86%	5–7 hours	18–22 hours	Renal excretion Dosage adjustment in renal insufficiency (See **Table 15**) COMBIVIR, TRIZIVIR & EPZICOM not for patients with CrCl < 50 mL/min	Minimal toxicity; lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with use of NRTIs)

Table 11. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

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

Table 12. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

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

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

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

‡ Symptomatic, sometimes serious, and even fatal hepatic events (accompanied by rash in approximately 50% of cases) occur with significantly higher frequency in treatment-naive female patients with prenevirapine CD4 counts >250 cells/mm^3 or in treatment-naive male patients with prenevirapine CD4 counts >400 cells/mm^3. Nevirapine should not be initiated in these patients unless the benefit clearly outweighs the risk. This toxicity has not been observed when nevirapine is given as single doses to mothers or infants for prevention of mother-to-child HIV transmission.

Table 13. Characteristics of Protease Inhibitors (PIs)

Generic Name/ Trade Name	Formulation	Dosing Recommendations	Food Effect	Oral Bio-availability	Serum half-life	Route of Metabolism	Storage	Adverse Events
Atazanavir (ATV)/ REYATAZ	100, 150, 200mg capsules	400mg once daily If taken with efavirenz or tenofovir: RTV 100mg + ATV 300mg once daily	Administration with food increases bioavailability Take with food; avoid taking with antacids	Not determined	7 hours	Cytochrome P450 3A4 inhibitor and substrate Dosage adjustment in hepatic insufficiency recommended (See Table 15)	Room temperature (up to 25ºC or 77ºF)	• Indirect hyperbilirubinemia • Prolonged PR interval— 1st degree symptomatic AV block in some pts • Use with caution in pts with underlying conduction defects or on concomitant medications that can cause PR prolongation • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in pts with hemophilia
Darunavir (DRV)/ PREZISTA	300mg tablet	(DRV 600mg + RTV 100mg) twice daily	Food ↑ Cmax & AUC by 30% - should be administered with food	Absolute bioavailability: DRV alone – 37%; w/ RTV – 82%;	15 hours (when combined with RTV)	Cytochrome P450 3A4 inhibitor and substrate	Room temperature (up to 25ºC or 77ºF)	• Skin rash (7%) – DRV has a sulfonamide moiety; Stevens-Johnson syndrome & erythrema multiforme have been reported. • Diarrhea, nausea • Headache • Hyperlipidemia • Transaminase elevation • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in pts with hemophilia
Fosamprenavir (FPV)/ LEXIVA	700mg tablet Oral suspension: 50mg/mL	ARV-naïve patients: • FPV 1,400mg BID or • (FPV 1,400mg + RTV 200mg) QD or • (FPV 700mg + RTV 100mg) BID • (FPV 1,400mg + RTV 100mg) QD PI-experienced pts (QD not recommended): • (FPV 700mg + RTV 100mg) BID Coadministration w/ EFV (FPV boosted only): • (FPV 700mg + RTV 100mg) BID or • (FPV 1,400mg + RTV 300mg) QD	No significant change in amprenavir pharmacokinetics in fed or fasting state	Not established	7.7 hours (amprenavir)	Amprenavir is a cytochrome P450 3A4 inhibitor, inducer, and substrate Dosage adjustment in hepatic insufficiency recommended (See Table 15)	Room temperature (up to 25ºC or 77ºF)	• Skin rash (19%) • Diarrhea, nausea, vomiting • Headache • Hyperlipidemia • Transaminase elevation • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia
Indinavir/ CRIXIVAN	200, 333, 400mg capsules	800mg every 8 hours; With RTV: (IDV 800mg + RTV 100 or 200mg) every 12 hours	Unboosted IDV Levels decrease by 77% Take 1 hour before or 2 hours after meals; may take with skim milk or low-fat meal RTV-boosted IDV: Take with or without food	65%	1.5–2 hours	Cytochrome P450 3A4 inhibitor (less than ritonavir) Dosage adjustment in hepatic insufficiency recommended (See Table 15)	Room temperature 15º–30ºC (59º–86ºF), protect from moisture	• Nephrolithiasis • GI intolerance, nausea • Indirect hyperbilirubinemia • Hyperlipidemia • Headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, alopecia, and hemolytic anemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in pts with hemophilia

Table 13. Characteristics of Protease Inhibitors (PIs)

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations	Food Effect	Oral Bio-availability	Serum half-life	Route of Metabolism	Storage	Adverse Events
Lopinavir + Ritonavir (LPV/r)/ KALETRA	Each tablet contains LPV 200mg + RTV 50mg Oral solution: Each 5 mL contains LPV 400mg + RTV 100mg Note: Oral solution contains 42% alcohol	LPV 400mg + RTV 100mg (2 tablets or 5 mL) twice daily or LPV 800mg + RTV 200mg (4 tablets or 10mL) once daily (**Note:** once-daily dosing only recommended for treatment-naïve pts; not for patients receiving EFV, NVP, FPV, or NFV) With EFV or NVP: For treatment-experienced pts: LPV 600mg + RTV 150mg (3 oral tablets) twice daily or LPV 533 mg + RTV 133 mg (6.7 mL oral solution) twice daily with food	Oral tablet - No food effect; take with or without food Oral solution - Moderately fatty meal ↑ LPV AUC & Cmin by 80% & 54%, respectively; take with food	Not determined in humans	5–6 hours	Cytochrome P450 (3A4 inhibitor and substrate)	Oral tablet is stable at room temperature Oral solution is stable at 2°–8°C until date on label; is stable when stored at room temperature (up to 25ºC or 77ºF) for 2 months	• GI intolerance, nausea, vomiting, diarrhea (higher incidence with once-daily than twice-daily dosing) • Asthenia • Hyperlipidemia (esp. hypertriglyceridemia) • Elevated serum transaminases • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia
Nelfinavir (NFV)/ VIRACEPT	250mg tablets or 625 mg tablets 50mg/g oral powder	1,250mg two times/day or 750mg three times/day	Levels increase 2–3 fold Take with meal or snack	20%–80%	3.5–5 hours	Cytochrome P450 3A4 inhibitor and substrate	Room temperature 15º–30ºC (59º–86ºF)	• Diarrhea • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes among patients with hemophilia • Serum transaminase elevation
Ritonavir (RTV)/ NORVIR	100mg capsules or 600mg/7.5 mL solution	600mg every 12 hours* (when ritonavir is used as sole PI) As pharmacokinetic booster for other PIs – 100mg – 400mg per day in 1–2 divided doses	Levels increase 15% Take with food if possible; this may improve tolerability	Not determined	3–5 hours	Cytochrome P450 (3A4 > 2D6; Potent 3A4 inhibitor)	Refrigerate capsules Capsules can be left at room temperature (up to 25ºC or 77ºF) for ≤30 days; Oral solution should NOT be refrigerated	• GI intolerance, nausea, vomiting, diarrhea • Paresthesias – circumoral and extremities • Hyperlipidemia, esp. hypertriglyceridemia • Hepatitis • Asthenia • Taste perversion • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia
Saquinavir tablets and hard gel capsules (SQV)/ INVIRASE	200mg hard gel capsules, 500mg tablets	Unboosted SQV not recommended With RTV: 26(RTV 100mg + 27SQV 1,000mg) two 28times/day	Take within 2 hours of a meal when taken with RTV	4% erratic (when taken as sole PI)	1–2 hours	Cytochrome P450 (3A4 inhibitor and substrate)	Room temperature 15º–30ºC (59º–86ºF)	• GI intolerance, nausea and diarrhea • Headache • Elevated transaminase enzymes • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia

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

Table 13. Characteristics of Protease Inhibitors (PIs)

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations	Food Effect	Oral Bio-availability	Serum half-life	Route of Metabolism	Storage	Adverse Events
Tipranavir (TPV)/ APTIVUS	250mg capsules	500mg twice daily with ritonavir 200mg twice daily Unboosted tipranavir is **not** recommended	Take both TPV & RTV with food. Bio-availability increased with high-fat meal	Not determined	6 hours after single dose of TPV/ RTV	TPV – Cytochrome P450 (3A4 inducer and substrate) Net effect when combined with RTV – CYP 3A4 inhibitor and CYP 2D6 inhibitor	Refrigerated capsules are stable until date on label; if stored at room temperature (up to 25ºC or 77ºF) – must be used within 60 days	• Hepatotoxicity – clinical hepatitis including hepatic decompensation has been reported, monitor closely, esp. in patients with underlying liver diseases • Skin rash – TPV has a sulfonamide moiety, use with caution in patients with known sulfonamide allergy • Rare cases of fatal and nonfatal intracranial hemorrhages have been reported. Most patients had underlying comorbidity such as brain lesion, head trauma, recent neurosurgery, coagulopathy, hypertension, alcoholism, or on medication with increase risk for bleeding • Hyperlipidemia (esp. hypertriglyceridemia) • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in patients with hemophilia

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

Table 14a. Characteristics of Entry Inhibitors

Mechanism/ Generic Name/Trade Name	Formulation	Dosing Recommendations	Food Effect	Bio-availability	Serum Half-life	Route of Metabolism	Storage	Adverse Events
Fusion Inhibitor: Enfuvirtide (T20)/ FUZEON	• Injectable – in lyophilized powder • Each single-use vial contains 108 mg of enfuvirtide to be reconstituted with 1.1 mL of Sterile Water for injection for delivery of approximately 90mg/1 mL	90mg (1 mL) subcutaneously (SC) two times/day	84.3% (SC compared with IV)	3.8 hours	Expected to undergo catabolism to its constituent amino acids, with subsequent recycling of the amino acids in the body pool	Store at room temperature (up to 25ºC or 77ºF) Reconstituted solution should be stored under refrigeration at 2ºC–8ºC (36ºF–46Fº) and used within 24 hours	• Injectable – in lyophilized powder • Each single-use vial contains 108 mg of enfuvirtide to be reconstituted with 1.1 mL of Sterile Water for injection for delivery of approximately 90mg/1 mL	• Local injection site reactions – almost 100% of patients (pain, erythema, induration, nodules and cysts, pruritus, ecchymosis) • Increased rate of bacterial pneumonia • Hypersensitivity reaction (<1%) - symptoms may include rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases; rechallenge is not recommended
CCR5 Antagonist: Maraviroc (MVC)/ SELZENTRY	150mg and 300mg tablets	**150mg twice daily** when given with strong CYP3A inhibitors (with or without CYP3A inducers) including PIs (except tipranavir/ ritonavir) **300mg twice daily** when given with NRTIs, enfuvirtide, tipranavir/ ritonavir, nevirapine, and other drugs that are not strong CYP3A inhibitors **600mg twice daily** when given with CYP3A inducers, including efavirenz, rifampin, etc. (without a CYP3A inhibitor)	No food effect; take with or without food	23% for 100mg dose and 33% (predicted) for 300mg	14–18 hrs	Cytochrome P450 (CYP3A substrate)	Room temperature	Abdominal pain, cough, dizziness, musculoskeletal symptoms, pyrexia, rash, upper respiratory tract infections, hepatotoxicity, orthostatic hypotension.

Table 14b. Characteristics of Integrase Inhibitor

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

Table 15. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency

Antiretrovirals	Daily Dose	Dosing in Renal Insufficiency	Dosing in Hepatic Impairment
Nucleoside Reverse Transcriptase Inhibitors – Note: Use of fixed-dose combination NRTI (+/- NNRTI) of: ATRIPLA, COMBIVIR, TRIZIVIR, EPZICOM – not recommended in patients with CrCl <50 mL/min; use of TRUVADA – not recommended in patients with CrCl <30 mL/min			
Abacavir* (ZIAGEN)	300mg PO BID	No need for dosage adjustment	No dosage recommendation
Didanosine (VIDEX)	>60 kg 400mg PO QD <60 kg 250mg QD	**Dose** **CrCl (mL/min) >60 kg <60 kg** 30-59 200mg 125 mg 10-29 125 mg 100mg < 10 125 mg 75 mg CAPD or HD patients: use same dose as CrCl < 10 ml/min	No dosage recommendation
Emtricitabine (EMTRIVA)	200mg oral capsule PO QD or 240mg (24mL) oral solution PO QD	**CrCl capsule solution** 30-49 200mg q48h 120mg q24h 15-29 200mg q72h 80mg q24h <15 200mg q96h 60mg q24h or HD*	No dosage recommendation
Lamivudine* (EPIVIR)	300mg PO QD or 150mg PO BID	**CrCl (mL/min) Dose** 30-49 150mg QD 15-29 150mg x 1, then 100mg QD 5-14 150mg x 1, then 50mg QD <5 50mg x 1, then 25 mg QD or HD*	No dosage recommendation
Stavudine (ZERIT)	>60 kg 40mg PO BID <60 kg 30mg PO BID	**Dose** **CrCl (mL/min) >60 kg <60 kg** 5-8 20mg q12h 15 mg q12h 10-25 20mg q24h 15 mg q24h or HD*	No dosage recommendation
Tenofovir (VIREAD)	300mg PO QD	**CrCl (mL/min) Dose** 30-49 300mg q48h 10-29 300mg twice weekly ESRD 300mg q7d or HD*	No dosage recommendation
Tenofovir + Emtricitabine (TRUVADA)	1 tablet PO QD	**CrCl (mL/min) Dose** 30-49 tablet q48h <30 not recommended	No dosage recommendation
Zidovudine* (RETROVIR)	300mg PO BID	"Severe" renal impairment or HD*: 100mg TID or 300mg QD	No dosage recommendation
Non- Nucleoside Reverse Transcriptase Inhibitors			
Delavirdine (RESCRIPTOR)	400mg PO TID	No dosage adjustment necessary	No recommendation; use with caution in patients with hepatic impairment
Efavirenz (SUSTIVA) Efavirenz/tenofovir/ emtricitabine (ATRIPLA)	600mg PO QD One tablet PO QD	No dosage adjustment necessary Atripla™ - not recommended if CrCl <50 ml/min	No recommendation; use with caution in patients with hepatic impairment
Nevirapine (VIRAMUNE)	200mg PO BID	No dosage adjustment necessary	No data available; avoid use in patients with moderate to severe hepatic impairment

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

Table 15. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency

Antiretrovirals	Daily Dose	Dosing in Renal Insufficiency	Dosing in Hepatic Impairment
Protease Inhibitors			
Atazanavir (REYATAZ)	400mg PO QD	No dosage adjustment necessary	**Child-Pugh Class** **Dose** 7-9 300mg QD >9 not recommended
Darunavir (PREZISTA, DRV)	(DRV 600mg + RTV 100mg) PO BID	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment
Fosamprenavir (LEXIVA)	1,400mg PO BID	No dosage adjustment necessary	**Child-Pugh Score** **Dose** 5-8 700mg BID 9-12 not recommended ritonavir boosting should not be used in patients with hepatic impairment
Indinavir (CRIXIVAN)	800mg PO q8h	No dosage adjustment necessary	Mild to moderate hepatic insufficiency because of cirrhosis: 600mg q8h
Lopinavir/ritonavir (KALETRA)	400/100mg PO BID or 800/200mg PO QD (QD only for tx-naïve pats)	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment
Nelfinavir (VIRACEPT)	1,250mg PO BID	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment
Ritonavir (NORVIR)	600mg PO BID	No dosage adjustment necessary	No dosage adjustment in mild hepatic impairment; no data for moderate to severe impairment, use with caution
Saquinavir soft gel cap (FORTOVASE)	1,200mg TID	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment
Tipranavir (APTIVUS)	500mg PO BID with ritonavir 200mg PO BID	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment; TPV/RTV is contraindicated in pts with moderate to severe (Child-Pugh Class B & C) hepatic insufficiency
Entry Inhibitors			
Enfuvirtide (FUZEON)	90mg SQ q12h	No dosage adjustment necessary	No dosage recommendation
Maraviroc (SELZENTRY)	The recommended dose differs based on concomitant medications because of drug interactions: 150mg, 300mg, or 600mg twice daily. See **Table 14b** for details.	No dosage recommendation; use with caution. Patients with CrCL <50 mL/min should receive MVC and CYP3A inhibitor only if potential benefit outweigh the risk.	No dosage recommendations. Concentrations will likely be increased in patients with hepatic impairment.
Integrase Inhibitors			
Raltegravir (ISENTRESS)	400mg twice daily	No dosage adjustment.	No dosage adjustment.

Creatinine Clearance calculation:

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

Child-Pugh Score

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

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

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

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

Table 16. Strategies to Improve Adherence to Antiretroviral Therapy

- Establish readiness to start therapy
- Provide education on medication dosing
- Review potential side effects
- Anticipate and treat side effects
- Utilize educational aids including pictures, pillboxes, and calendars
- Engage family, friends
- Simplify regimens, dosing, and food requirements
- Utilize team approach with nurses, pharmacists, and peer counselors
- Provide accessible, trusting health care team

Table 17. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations

17a. Potentially Life-Threatening and Serious Adverse Events

Adverse effects	Causative ARVs	Onset/clinical manifestation	Estimated frequency	Risk Factors	Prevention/ monitoring	Management
POTENTIALLY LIFE-THREATENING ADVERSE EFFECTS (In alphabetical order)						
Hepatic Events (nevirapine-associated symptomatic events, including hepatic necrosis)	NVP	Onset: Greatest risk within first few weeks of therapy; can occur through 18 weeks Symptoms: Abrupt onset of flu-like symptoms (nausea, vomiting, myalgia, fatigue), abdominal pain, jaundice, or fever with or without skin rash; may progress to fulminant hepatic failure with encephalopathy Approximately 1/2 of the cases have accompanying skin rash Some may present as part of DRESS syndrome (drug rash with eosinophilia and systemic symptoms)	Symptomatic hepatic events: • 4% overall (2.5%–11% from different trials) • In women - 11% in those w/ pre-NVP CD4 >250 cells/mm^3 vs. 0.9% w/ CD4 <250 cells/mm^3; • In men - 6.3% w/ pre-NVP CD4 >400 cells/mm^3 vs. 2.3% w/ CD4 <400 cells/mm^3	•Treatment-naive patients with higher CD4 count at initiation (>250 cells/mm^3 in women & >400 cells/mm^3 in men) •Female gender (including pregnant women) •Elevated ALT or AST at baseline; •HBV and/or HCV coinfection; •Alcoholic liver disease •HIV (-) individuals when NVP is used for postexposure prophylaxis •High NVP concentration	•Avoid initiation of NVP in women w/ CD4 >250 cells/mm^3 or men w/ CD4 >400 cells/mm^3 unless the benefit clearly outweighs the risk •Counsel pts re: signs & symptoms of hepatitis; stop NVP & seek medical attention if signs & symptoms of hepatitis, severe skin rash, or hypersensitivity reactions appear •Monitoring of ALT & AST (every 2 weeks x 1st month, then monthly x 3 months, then every 3 months •Obtain AST & ALT in patients with rash •2-week dose escalation may reduce incidence of hepatic events	•Discontinue ARV including nevirapine (caution should be taken in discontinuation of 3TC, FTC, or TDF in HBV-coinfected patients) •Discontinue all other hepatotoxic agents if possible • Rule out other causes of hepatitis • Aggressive supportive care as indicated **Note:** Hepatic injury may progress despite treatment discontinuation. Careful monitoring should continue until symptom resolution. **Do not rechallenge patient with NVP** The safety of other NNRTIs (EFV or DLV) in patients who experienced significant hepatic event from NVP is unknown – use with caution.
Lactic acidosis/ hepatic steatosis +/- pancreatitis (severe mitochondrial toxicities)	NRTIs, esp. d4T, ddI, ZDV	Onset: months after initiation of NRTIs Symptoms: • Initial onset may be insidious with nonspecific gastrointestinal prodrome (nausea, anorexia, abdominal pain, vomiting), weight loss, and fatigue; • Subsequent symptoms may be rapidly progressive with tachycardia, tachypnea, hyperventilation, jaundice, muscular weakness, mental status changes, or respiratory distress • Some may present with multi-organ failure, such as fulminant hepatic failure, acute pancreatitis, encephalopathy, and respiratory failure Laboratory findings: • Increased lactate (often >5 mmole) • Low arterial pH (some as low as <7.0) • Low serum bicarbonate • Increased anion gap • Elevated serum transaminases, prothrombin time, bilirubin • Low serum albumin • Increase serum amylase & lipase in patients with pancreatitis • Histologic findings of the liver – microvesicular or macrovesicular steatosis	Rare One estimate 0.85 cases per 1,000 patient-years Mortality up to 50% in some case series, (esp. in patients with serum lactate > 10 mmole)	•d4T + ddI •d4T, ZDV, ddI use (d4T most frequently implicated) •Long duration of NRTI use •Female gender •Obesity •Pregnancy (esp. with d4T+ddI) •ddI + hydroxyurea or ribavirin •High baseline body mass index	•Routine monitoring of lactic acid is generally not recommended; •Consider obtaining lactate levels in patients with low serum bicarbonate or high anion gap and with complaints consistent with lactic acidosis; •Appropriate phlebotomy technique for obtaining lactate level should be employed	•Discontinue all ARVs if this syndrome is highly suspected (diagnosis is established by clinical correlations, drug history, and lactate level) •Symptomatic support with fluid hydration •Some patients may require IV bicarbonate infusion, hemodialysis or hemofiltration, parenteral nutrition or mechanical ventilation •IV thiamine and/or riboflavin – resulted in rapid resolution of hyperlactatemia in some case reports **Note:** •Interpretation of high lactate level should be done in the context of clinical findings. •The implication of asymptomatic hyperlactatemia is unknown at this point **ARV treatment options**: •May consider using NRTIs with less propensity of mitochondrial toxicities – (e.g., ABC, TDF, 3TC, FTC) – should not be introduced until lactate returns to normal. •Recommend close monitoring of serum lactate after restarting NRTIs •Some consider using NRTI-sparing regimens with PI + NNRTI +/- FI (e.g., IDV + EFV, LPV/r + EFV, etc)– efficacy and benefit of this type of regimen unknown, but currently under investigation

Table 17. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations

17a. Potentially Life-Threatening and Serious Adverse Events (continued)

Adverse effects	Causative ARVs	Onset/clinical manifestation	Estimated frequency	Risk Factors	Prevention/ monitoring	Management
POTENTIALLY LIFE-THREATENING ADVERSE EFFECTS (In alphabetical order)						
Hypersensitivity reaction (HSR)	ABC	Onset of 1st reaction: median onset – 9 days; approximately 90% within 1st 6 weeks Onset of rechallenge reactions: within hours of rechallenge dose Symptoms: acute onset of symptoms (in descending frequency): high fever, diffuse skin rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, respiratory symptoms (pharyngitis, dyspnea/tachypnea) *With continuation of ABC, symptoms may worsen to include*: hypotension, respiratory distress, vascular collapse *Rechallenge reactions:* generally greater intensity than 1st reaction, can mimic anaphylaxis	Approximately 8% in clinical trial (2%–9%); 5% in retrospective analysis	•HLA-B*5701, HLA-DR7, HLA-DQ3 (from Australian data) •ARV-naïve patients •Higher incidence of grade 3 or 4 HSR with 600mg once-daily dose than 300mg twice-daily dose in one study (5% vs. 2%)	•Educate patients about potential signs and symptoms of HSR and need for reporting of symptoms promptly •Wallet card with warning information for patients	•Discontinue ABC and other ARVs •Rule out other causes of symptoms (e.g., intercurrent illnesses such as viral syndromes, and other causes of skin rash, etc.) •Most signs and symptoms resolve 48 hours after discontinuation of ABC *More severe cases:* •Symptomatic support – antipyretic, fluid resuscitation, pressure support (if necessary) •**Do not rechallenge patients with ABC after suspected HSR**
Lactic acidosis/ Rapidly progressive ascending neuromuscular weakness	Most frequently implicated ARV: d4T	Onset: months after initiation of ARV; then dramatic motor weakness occurring within days to weeks Symptoms: very rapidly progressive ascending demyelinating polyneuropathy, may mimic Guillain-Barré syndrome; some patients may develop respiratory paralysis requiring mechanical ventilation; resulted in deaths in some patients Laboratory findings may include: •Low arterial pH •Increased lactate •Low serum bicarbonate •Increased anion gap •Markedly increased creatine phosphokinase	Rare	Prolonged d4T use (found in 61 of 69 [88%] cases in one report)	Early recognition and discontinuation of ARVs may avoid further progression	•Discontinuation of ARVs •Supportive care, including mechanical ventilation if needed (as in cases of lactic acidosis listed previously) •Other measures attempted with variable successes: plasmapheresis, high-dose corticosteroid, intravenous immunoglobulin, carnitine, acetylcarnitine •Recovery often takes months – ranging from complete recovery to substantial residual deficits •Symptoms may be irreversible in some patients **Do not rechallenge patient with offending agent**
Stevens-Johnson syndrome (SJS)/ Toxic epidermal necrosis (TEN)	NVP > EFV, DLV; Also reported with: APV, FPV, ABC, DRV, ZDV, ddI, IDV, LPV/r, ATV	Onset: first few days to weeks after initation of therapy Symptoms: *Cutaneous involvement:* •Skin eruption with mucosal ulcerations (may involve orogingival mucosa, conjunctiva, anogenital area); •Can rapidly evolve with blister or bullae formation; •May eventually evolve to epidermal detachment and/or necrosis *Systemic Symptoms:* fever, tachycardia, malaise, myalgia, arthralgia *Complications:* ↓ oral intake → fluid depletion; bacterial or fungal superinfection; multiorgan failure	NVP: 0.3%–1% DLV & EFV: 0.1% 1–2 case reports for ABC, FPV, ddI, ZDV, IDV, LPV/r, ATV, DRV	NVP – Female, Black, Asian, Hispanic	•2-week lead in period with 200mg once daily, then escalate to 200mg twice daily •Educate patients to report symptoms as soon as they appear •Avoid use of corticosteroid during NVP dose escalation – may increase incidence of rash	•Discontinue all ARVs and any other possible agent(s) (e.g., cotrimoxazole) Aggressive symptomatic support may include: •Intensive care support •Aggressive local wound care (e.g., in a burn unit) •Intravenous hydration •Parenteral nutrition, if necessary •Pain management •Antipyretics •Empiric broad-spectrum antimicrobial therapy if superinfection is suspected Controversial management strategies: •Corticosteroid •Intravenous immunoglobulin **Do not rechallenge patient with offending agent** ▪It is unknown whether patients who experienced SJS while on one NNRTI are more susceptible to SJS from another NNRTI – most experts would suggest avoiding use of this class unless no other option available

Table 17. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations

17a. Potentially Life-Threatening and Serious Adverse Events (continued)

Adverse effects	Causative ARVs	Onset/clinical manifestation	Estimated frequency	Risk Factors	Prevention/ monitoring	Management
POTENTIALLY SERIOUS ADVERSE EFFECTS (in alphabetical order)						
Bleeding episodes – increase in hemophiliac patients	PIs	Onset: few weeks Symptoms: ↑ spontaneous bleeding tendency – in joints, muscles, soft tissues, and hematuria	Frequency unknown	• PI use in hemophiliac patients	• Consider using NNRTI-based regimen • Monitor for spontaneous bleeding	• May require increase use of Factor VIII products
Bone marrow suppression	ZDV	Onset: few weeks to months Laboratory abnormalities: • Anemia • Neutropenia Symptoms: fatigue because of anemia; potential for increase of bacterial infections because of neutropenia	Anemia - 1.1%–4% Neutropenia – 1.8%–-8%	• Advanced HIV • High dose • Pre-existing anemia or neutropenia; • Concomitant use of bone marrow suppressants (such as cotrimoxazole, ribavirin, ganciclovir, etc.)	Avoid use in patients at risk Avoid other bone marrow suppressants if possible Monitor CBC with differential at least every three months (more frequently in patients at risk)	• Switch to another NRTI if there is alternative option; • Discontinue concomitant bone marrow suppressant if there is alternative option; otherwise: For neutropenia: • Identify and treat other causes • Consider treatment with filgrastim For anemia: • Identify and treat other causes of anemia (if present) • Blood transfusion if indicated • Consider erythropoietin therapy
Hepatotoxicity (clinical hepatitis or asymptomatic serum transaminase elevation)	All NNRTIs; All PIs; All NRTIs	Onset: NNRTI – for NVP - 2/3 within 1st 12 weeks NRTI – over months to years PI – generally after weeks to months Symptoms/Findings: **NNRTI** – asymptomatic to non-specific symptoms such as anorexia, weight loss, or fatigue. Approximately ½ of patients with NVP-associated symptomatic hepatic events present with skin rash. **NRTI** – • ZDV, ddI, d4T - may cause hepatotoxicity associated with lactic acidosis with microvesicular or macrovesicular hepatic steatosis because of mitochondrial toxicity • 3TC, FTC, or tenofovir – HBV-coinfected patients may develop severe hepatic flare when these drugs are withdrawn or when resistance develops. **PI** – • Clinical hepatitis & hepatic decompensation have been reported with TPV/RTV. Underlying liver disease increases risk. • Generally asymptomatic, some with anorexia, weight loss, jaundice, etc.	Varies with the different agents	• Hepatitis B or C coinfection • Alcoholism • Concomitant hepatotoxic drugs • For NVP-associated hepatic events – female w/ pre-NVP CD_4 >250cells/mm^3 or male w/ pre-NVP CD_4 >400cells/mm^3	NVP – monitor liver-associated enzymes at baseline, 2 & 4 weeks, then monthly for 1st 3 months; then every 3 months TPV/RTV- contraindicated in patients with moderate to severe hepatic insufficiency; for other patients follow "frequently" during treatment Other agents: monitor liver-associated enzymes at least every 3–4 months or more frequently in patients at risk	• Rule out other causes of hepatotoxicity – alcoholism, viral hepatitis, chronic HBV w/ 3TC, FTC, or TDF withdrawal, or HBV resistance, etc. For symptomatic patients: • Discontinue all ARV (with caution in patients with chronic HBV infection treated w/ 3TC, FTC, and/or TDF) and other potential hepatotoxic agents • After symptoms subside & serum transaminases returned to normal, construct a new ARV regimen without the potential offending agent(s) For asymptomatic patients: • If ALT >5–10x ULN, some may consider discontinuing ARVs, others may continue therapy with close monitoring • After serum transaminases returned to normal, construct a new ARV regimen without the potential offending agent(s) **Note:** Please refer to information regarding NVP-associated symptomatic hepatic events & NRTI-associated lactic acidosis with hepatic steatosis in this table
Nephrolithiasis/ urolithiasis/ crystalluria	IDV – most frequent	Onset: any time after beginning of therapy – especially at times of reduced fluid intake Laboratory abnormalities: pyuria, hematuria, crystalluria; rarely – rise in serum creatinine & acute renal failure Symptoms: flank pain and/or abdominal pain (can be severe), dysuria, frequency	12.4% of nephrolithiasis reported in clinical trials (4.7%–34.4% in different trials)	• History of nephrolithiasis • Patients unable to maintain adequate fluid intake • High peak IDV concentration • ↑ duration of exposure	• Drink at least 1.5 to 2 liters of non-caffeinated fluid (preferably water) per day • Increase fluid intake at first sign of darkened urine • Monitor urinalysis and serum creatinine every 3–6 months	• Increase hydration • Pain control • May consider switching to alternative agent or therapeutic drug monitoring if treatment option is limited • Stent placement may be required

Table 17. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations

17a. Potentially Life-Threatening and Serious Adverse Events (continued)

Adverse effects	Causative ARVs	Onset/clinical manifestation	Estimated frequency	Risk Factors	Prevention/ monitoring	Management
POTENTIALLY SERIOUS ADVERSE EFFECTS (in alphabetical order)						
Nephrotoxicity	IDV, potentially TDF	Onset: IDV – months after therapy TDF – weeks to months after therapy Laboratory and other findings: IDV: ↑ serum creatinine, pyruria; hydronephrosis or renal atrophy TDF: ↑ serum creatinine, proteinuria, hypophosphatemia, glycosuria, hypokalemia, non-anion gap metabolic acidosis Symptoms: IDV: asymptomatic; rarely develop to end stage renal disease TDF: asymptomatic to signs of nephrogenic diabetes insipidus, Fanconi syndrome	Not known	•History of renal disease •Concommitant use of nephrotoxic drugs	•Avoid use of other nephrotoxic drugs •Adequate hydration if on IDV therapy •Monitor serum creatinine, urinalysis, serum potassium and phosphorus in patients at risk	•Stop offending agent, generally reversible •Supportive care •Electrolyte replacement as indicated
Pancreatitis	ddI alone; ddI + d4T; ddI + hydroxyurea (HU) or ribavirin (RBV); 3TC in children	Onset: usually weeks to months Laboratory abnormalities: increased serum amylase and lipase Symptoms: postprandial abdominal pain, nausea, vomiting	ddI alone – 1%–7% ddI with HU - ↑ by 4–5 fold ddI with RBV, d4T, or TDF - ↑ frequency 3TC in children – early trials: 14%–18%; later trial - <1%	•High intraceullar and/or serum ddI concentrations •History of pancreatitis •Alcoholism •Hypertriglyceridemia •Concomitant use of ddI with d4T, HU, or RBV •Use of ddI + TDF without ddI dose reduction	•ddI should not be used in patients with history of pancreatitis •Avoid concomitant use of ddI with d4T, HU, or RBV •Reduce ddI dose when used with TDF •Monitoring of amylase/lipase in asymptomatic patients is generally not recommended	•Discontinue offending agent(s) •Symptomatic management of pancreatitis – bowel rest, IV hydration, pain control, then gradual resumption of oral intake •Parenteral nutrition may be necessary in patients with recurrent symptoms upon resumption of oral intake
Skin rash	NVP > EFV, DLV; ABC, APV, FPV, ATV, DRV TPV/RTV	Onset: within first few days to weeks after initiation of therapy Symptoms: most rashes are mild to moderate in nature; diffuse maculopapular rash with or without pruritus; severe rash, rash with fever or with mucus membrane involvement warrants immediate discontinuation of ARV TPV-RTV - Rash accompanied by joint pain/ stiffness, throat tightness, or generalized pruritus have been reported. **Note**: Please also see sections on Stevens-Johnson syndrome & systemic hypersensitivity reaction	All Grades (severe) NVP: 14.8% (1.5% severe) EFV: 26% (1% grades 3–4) DLV: 35.4% (4.4% grades 3–4) ABC: <5% in pts w/o HSR APV: 20%–27% (1.0% grades 3-4) FPV: 19% (< 1% grades 3–4) ATV: 21% (<1% severe) DRV: 7% (0.3% d/c therapy) TPV/RTV 14% female & 8%–10% male in Phase 2/3 trials; 33% in female HIV-subjects in Phase I study with ethinyl estradiol	• NVP – female, Black, Asian, Hispanic • FPV, APV, TPV – sulfonamide derivative – potential for cross hypersensitivity with other sulfa drugs • TPV – female gender associated with an increased frequency of skin rash associated with TPV • EFV – higher incidence in children	•NVP – always use a 2-week low-dose lead-in period •Avoid use of corticosteroid during NVP dose escalation – may increase incidence of rash •Patient education – advise to report first sign of rash •Most experts suggest avoidance of EFV or DLV in patients with history of severe rash from NVP, and vice versa	•Mild to moderate rash may be managed by symptomatic treatment with antihistamine and continuation of offending agent •Discontinue therapy if skin rash progresses to severe in nature (accompanied by blisters, fever, mucous membrane involvement, conjunctivitis, edema, or arthralgias) or in presence of systemic symptoms (including fever) **Do not restart offending medication in case of severe rash** •If rash develops during first 18 weeks of NVP treatment – obtain serum transaminases to rule out symptomatic hepatic event

Table 17. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations

17b. Adverse Events With Potential Long-Term Complications (in alphabetical order)

Adverse effects	Causative ARVs	Onset/clinical manifestation	Estimated frequency	Risk Factors	Prevention/ monitoring	Management
Cardiovascular effects	Possibly all PIs; maybe except for ATV	Onset: months to years after beginning of therapy Presentation: premature coronary artery disease	3–6 per 1,000/pt years	Other risk factors for cardiovascular disease such as smoking, age, hyperlipidemia, hypertension, diabetes mellitus, family history of premature coronary artery disease, and personal history of coronary artery disease	•Assess each patient's cardiac risk factors •Consider non-PI based regimen •Monitor & identify pts w/ hyperlipidemia or hyperglycemia •Counseling for life style modification - smoking cessation, diet, and exercise	•Early diagnosis, prevention, and pharmacologic management of other cardiovascular risk factors such as hyperlipidemia, hypertension, and insulin resistance/diabetes mellitus •Assess cardiac risk factors •Lifestyle modifications: diet, exercise, and/or smoking cessation •Switch to agents with less propensity for increasing cardiovascular risk factors, ie NNRTI- or ATV-based regimen & avoid d4T use
Hyperlipidemia	All PIs (except ATV); d4T; EFV (to a lesser extent)	Onset: weeks to months after beginning of therapy Presentation: All PIs except ATV – ↑ in LDL & total cholesterol (TC) & triglyceride (TG), ↓ in HDL LPV/r & RTV – disproportionate ↑ in TG d4T – mostly ↑ in TG; may also have ↑ in LDL & total cholesterol (TC) EFV or NVP: ↑ in HDL, slight ↑ TG	Varies with different agents; 47% –75% of pts receiving PI in some clinics; Swiss Cohort: ↑TC & TG – 1.7–2.3x higher in pts receiving (non-ATV) PI	•Underlying hyperlipidemia •Risk based on ARV therapy PI: LPV/r & RTV > NFV & APV > IDV & SQV > ATV; NNRTI: less than PIs; NRTI: d4T > ZDV & TDF	•Use non-PI, non-d4T based regimen •Use ATV-based regimen •Fasting lipid profile at baseline, 3–6 months after starting new regimen, then annually or more frequently if indicated (in high-risk patients, or patients with abnormal baseline levels)	•Follow ACTG guidelines's recommendations for management *[371]* •Assess cardiac risk factor •Lifestyle modification: diet, exercise, and/or smoking cessation •Switching to agents with less propensity for causing hyperlipidemia Pharmacologic Management: •↑ total cholesterol, LDL, TG 200-500mg/dL**:** "statins" – pravastatin or atorvastatin (See **Tables 19 & 20** for drug interaction information) •TG >500mg/dL – gemfibrozil or micronized fenofibrate
Insulin resistance/ Diabetes mellitus	All PIs	Onset: weeks to months after beginning of therapy Presentation: Polyuria, polydipsia, polyphagia, fatigue, weakness; exacerbation of hyperglycemia in patients with underlying diabetes	Up to 3%–5% of patients developed diabetes in some series	Underlying hyperglycemia, family history of diabetes mellitus	•Use PI-sparing regimens •Fasting blood glucose 1–3 months after starting new regimen, then at least every 3–6 months	•Diet and exercise •Consider switching to an NNRTI-based regimen •Metformin •"glitazones" •Sulfonylurea •Insulin
Osteonecrosis	All PIs	Clinical Presentation (generally similar to non-HIV population): •Insidious in onset, with subtle symptoms of mild to moderate periarticular pain •85% of the cases involving one or both femoral heads, but other bones may also be affected •Pain may be triggered by weight bearing or movement	Reported incidence on the rise. Symptomatic osteonecrosis: 0.08% to 1.33%; Asymptomatic osteonecrosis: 4% from MRI reports	•Diabetes •Prior steroid use •Old age •Alcohol use •Hyperlipidemia •Role of ARVs and osteonecrosis – still controversial	•Risk reduction (e.g., limit steroid and alcohol use) •Asymptomatic cases w/ <15% bony head involvement – follow with MRI every 3–6 months x 1 yr, then every 6 mon x 1 yr, then annually – to assess for disease progression	Conservative management**:** • ↓ weight bearing on affected joint; • Remove or reduce risk factors • Analgesics as needed Surgical Intervention: •Core decompression +/- bone grafting – for early stages of disease •For more severe and debilitating disease – total joint arthroplasty

Table 17. Antiretroviral Therapy Associated Adverse Effects and Management Recommendations

17c. Adverse Effects Compromising Quality of Life and/or With Potential Impact on Medication Adherence (in alphabetical order)

Adverse effects	Causative ARVs	Onset/clinical manifestation	Estimated frequency	Risk Factors	Prevention/ monitoring	Management
Central nervous system effects	EFV	Onset: begin with first few doses Symptoms: may include one or more of the following: drowsiness, somnolence, insomnia, abnormal dreams, dizziness, impaired concentration & attention span, depression, hallucination; exacerbation of psychiatric disorders; psychosis; suicidal ideation Most symptoms subside or diminish after 2–4 weeks	>50% of patients may have some symptoms	• Pre-existing or unstable psychiatric illnesses; • Use of concomitant drugs with CNS effects	• Take at bedtime or 2–3 hours before bedtime; • Take on an empty stomach to reduce drug concentration & CNS effects • Warn patients regarding restriction of risky activities – such as operating heavy machinery during the 1st 2–4 weeks of therapy	• Symptoms usually diminish or disappear after 2–4 weeks • May consider discontinuing therapy if symptoms persist and cause significant impairment in daily function or exacerbation of psychiatric illness
Fat maldistribution	PIs, d4T	Onset: gradual - months after initiation of therapy Symptoms: • Lipoatrophy – peripheral fat loss manifested as facial thinning, thinning of extremities and buttocks (d4T) • Increase in abdominal girth, breast size, and dorsocervical fat pad (buffalo hump)	High – exact frequency uncertain; increases with duration on offending agents	Lipoatrophy – low baseline body mass index	None to date	• Switching to other agents – may slow or halt progression; however, may not reverse effects • Injectable poly-L-lactic acid for treatment of facial lipoatrophy
Gastrointestinal (GI) intolerance	All PIs, ZDV, ddI	Onset: Begin within first doses Symptoms: • Nausea, vomiting, abdominal pain – all listed agents • Diarrhea – commonly seen with NFV, & LPV/r	Varies with different agents	All patients	• Taking with food may reduce symptoms (not recommended for ddI or unboosted IDV) • Some patients may require antiemetics or antidiarrheals pre-emptively to reduce symptoms	May spontaneously resolve or become tolerable with time; if not: For nausea & vomiting, consider: • Antiemetic prior to dosing • Switch to less emetogenic ARV For diarrhea, consider: • Antimotility agents – such as loperamide, diphenoxylate/atropine • Calcium tablets • Bulk-forming agents, such as psyllium products • Pancreatic enzymes In case of severe GI loss: • Rehydration & electrolyte replacement as indicated
Injection site reactions	Enfuvirtide	Onset: Within first few doses Symptoms: pain, pruritus, erythema, ecchymosis, warmth, nodules, rarely injection site infection	98%	All patients	Educate patients regarding use of sterile technique, ensure solution at room temperature before injection, rotate injection sites, avoid injection into sites with little subcutaneous fat or sites of existing or previous reactions	• Massaging area after injection may reduce pain • Wear loose clothing – especially around the injection site areas or areas of previous reactions • Rarely, warm compact or analgesics may be necessary
Peripheral neuropathy	ddI, d4T, ddC	Onset: weeks to months after initiation of therapy (may be sooner in patients with pre-existing neuropathy) Symptoms: • Begins with numbness & paresthesia of toes and feet; • May progress to painful neuropathy of feet and calf; • Upper extremities less frequently involved • Can be debilitating for some patients. • May be irreversible despite discontinuation of offending agent(s)	ddI: 12%–-34% in clinical trials d4T: 52% in monotherapy trial ddC: 22%–35% in clinical trials Incidence increases with prolonged exposure	• Pre-existing peripheral neuropathy; • Combined use of these NRTIs or concomitant use of other drugs that may cause neuropathy • Advanced HIV disease • High dose or concomitant use of drugs that may increase ddI intracellular activities (e.g., HU or RBV)	• Avoid using these agents in patients at risk – if possible • Avoid combined use of these agents • Patient query at each encounter	• May consider discontinuing offending agent before pain becomes disabling – may halt further progression, but symptoms may be irreversible Pharmacological management (with variable successes): • Gabapentin (most experience), tricyclic antidepressants, lamotrigine, oxycarbamazepine (potential for CYP interactions), topiramate, tramadol • Narcotic analgesics • Capsaicin cream • Topical lidocaine

Table 18. HIV-Related Drugs With Overlapping Toxicities

Bone Marrow Suppression	Peripheral Neuropathy	Pancreatitis	Nephrotoxicity	Hepato-toxicity	Rash	Diarrhea	Ocular Effects
Amphotericin B Cidofovir Cotrimoxazole Cytotoxic Chemotherapy Dapsone Flucytosine Ganciclovir Hydroxyurea Interferon-α Linezolid Peginterferon-α Primaquine Pyrimethamine Ribavirin Rifabutin Sulfadiazine Trimetrexate Valganciclovir Zidovudine	Didanosine Isoniazid Linezolid Stavudine	Cotrimoxazole Didanosine Lamivudine (children) Pentamidine Ritonavir Stavudine	Acyclovir (IV, high dose) Adefovir Aminoglycosides Amphotericin B Cidofovir Foscarnet Indinavir Pentamidine Tenofovir	Azithromycin Clarithromycin Delavirdine Efavirenz Fluconazole Isoniazid Itraconazole Ketoconazole Maraviroc Nevirapine NRTIs PIs (esp. Tipranavir) Rifabutin Rifampin Voriconazole	Abacavir Atazanavir Atovaquone Cotrimoxazole Dapsone Darunavir Delavirdine Efavirenz Fosamprenavir Maraviroc Nevirapine Sulfadiazine Tipranavir Voriconazole	Atovaquone Clindamycin Darunavir Fos-amprenavir Lopinavir/ ritonavir Nelfinavir Ritonavir Tipranavir	Cidofovir Didanosine Ethambutol Linezolid Rifabutin Voriconazole

Table 19. Adverse Drug Reactions and Related "Black Box Warnings" in Product Labeling for Antiretroviral Agents

Below is a list of antiretroviral drugs with "black box warnings" in their current product labels.

The Food and Drug Administration can require that warnings regarding special problems associated with a prescription drug, including those that might lead to death or serious injury, be placed in a prominently displayed box, commonly known as a "black box." Please note that other serious toxicities associated with antiretroviral agents are not listed in this table.

Antiretroviral Drug	Pertinent Black Box Warning Information
Abacavir (ZIAGEN®, or as combination products in EPZICOM and TRIZIVIR)	• Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir: – This is a multi-organ clinical syndrome, characterized by two or more groups of the following signs or symptoms including (1) fever, (2) rash, (3) gastrointestinal (e.g., nausea, vomiting, diarrhea, or abdominal pain), (4) constitutional (including generalized malaise, fatigue, or achiness), and (5) respiratory symptoms (including dyspnea, cough, or pharyngitis). – Abacavir should be discontinued as soon as hypersensitivity reaction is suspected. – Any product containing abacavir should be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible – because more severe symptoms can occur within hours after restarting abacavir and may include life-threatening hypotension and death. • Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination.
Didanosine (VIDEX-EC)	• Fatal and nonfatal pancreatitis have occurred with didanosine alone or in combination with other antiretroviral agents. – Didanosine should be withheld if pancreatitis is suspected. – Didanosine should be discontinued if pancreatitis is confirmed. • Fatal lactic acidosis has been reported among pregnant women who received a combination of didanosine and stavudine with other antiretroviral combinations. – Didanosine and stavudine combination should only be used during pregnancy if the potential benefit clearly outweighs the potential risks. • Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination.
Emtricitabine (EMTRIVA); or in combination product with tenofovir DF (TRUVADA) or with tenofovir DF and efavirenz (ATRIPLA)	• Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination with other antiretrovirals. • Emtricitabine is not indicated for the treatment of hepatitis B infection (HBV); the safety and efficacy have not been established in patients with HIV/HBV coinfection. • Severe acute exacerbations of hepatitis B have been reported in patients who discontinued emtricitabine – hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months after discontinuation of tenofovir in HIV/HBV coinfected patients. • If appropriate, initiation of anti-HBV therapy may be warranted after discontinuation of tenofovir.
Lamivudine (EPIVIR), or in combination products COMBIVIR, EPIZICOM, and TRIZIVIR)	• Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination. • Epivir tablets and oral solution (used to treat HIV infection) contain a higher dose of lamivudine than Epivir-HBV tablets and oral solution (used to treat chronic hepatitis B). **Patients with HIV infection should receive only dosage and formulations appropriate for treatment of HIV.** • Severe acute exacerbations of hepatitis B infection have been reported in HBV/HIV coinfected patients upon discontinuation of lamivudine-containing products. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months after discontinuation of lamivudine in patients with HIV/HBV coinfection. • If appropriate, initiation of anti-hepatitis B therapy may be warranted.

Table 19. Adverse Drug Reactions and Related "Black Box Warnings" in Product Labeling for Antiretroviral Agents

Antiretroviral Drug	Pertinent Black Box Warning Information
Maraviroc (SELZENTRY)	• Hepatotoxicity has been reported with maraviroc and may be preceded by evidence of a systemic allergic reaction (e.g., pruritic rash, eosinophilia, or elevated IgE). • Immediately evaluate patients with signs or symptoms of hepatitis or allergic reaction.
Nevirapine (VIRAMUNE)	• Severe, life-threatening, and in some cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure, has been reported. Patients may present with nonspecific prodromes of hepatitis and progress to hepatic failure. • Women with CD4 counts >250 cells/mm^3, including pregnant women receiving chronic treatment for HIV infection, are at considerably higher risk of hepatotoxicities. • Severe, life-threatening, and even fatal skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction have occurred with nevirapine treatment. • Patients should be monitored intensively during the first 18 weeks of nevirapine therapy to detect potentially life-threatening hepatotoxicity or skin reactions. • A 14-day lead-in period with nevirapine 200mg daily must be followed strictly. • Nevirapine should not be restarted after severe hepatic, skin, or hypersensitivity reactions.
Ritonavir (NORVIR)	• Coadministration of ritonavir with certain nonsedating antihistamines, sedative hypnotics, antiarrhythmics, or ergot alkaloids may result in potentially serious or life-threatening adverse events because of possible effects of ritonavir on hepatic metabolism of certain drugs.
Saquinavir (INVIRASE)	• INVIRASE may be used only if it is combined with ritonavir, which significantly inhibits saquinavir's metabolism to provide acceptable plasma saquinavir levels.
Stavudine (Zerit®)	• Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination. • Fatal lactic acidosis has been reported among pregnant women who received a combination of stavudine and didanosine with other antiretroviral combinations. • The stavudine and didanosine combination should only be used during pregnancy if the potential benefit clearly outweighs the potential risks. • Fatal and nonfatal pancreatitis have occurred when stavudine was part of a combination regimen with didanosine with or without hydroxyurea.
Tenofovir (VIREAD); or in combination product with emtricitabine (TRUVADA) or with efavirenz and emtricitabine (ATRIPLA)	• Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with other antiretrovirals. • Tenofovir is not indicated for the treatment of chronic hepatitis B (HBV) infection; safety and efficacy in patients with HIV/HBV coinfection have not been established. • Severe acute exacerbations of hepatitis B have been reported in patients who discontinued tenofovir – hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months after discontinuation of tenofovir in HIV/HBV-coinfected patients. • If appropriate, initiation of anti-HBV therapy may be warranted after discontinuation of tenofovir.
Tipranavir (APTIVUS)	• Tipranavir coadminstered with ritonavir 200mg twice daily has been associated with reports of both fatal and nonfatal intracranial hemorrhage. • Tipranavir coadminstered with ritonavir 200mg twice daily has been associated with reports of clinical hepatitis and hepatic decompensation including some fatalities. Extra vigilance is warranted in patients with chronic hepatitis B or hepatitis C coinfection, as these patients have an increased risk of hepatotoxicity.
Zidovudine (RETROVIR), or in combination products COMBIVIR and TRIZIVIR	• Zidovudine can be associated with hematologic toxicities, including granulocytopenia and severe anemia, including among advanced HIV patients. • Prolonged zidovudine use has been associated with symptomatic myopathy. • Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination.

Table 20. Drugs That Should Not Be Used With PI, NNRTI, or CCR5 Antagonist Antiretrovirals

Drug Category[#]	Calcium channel blocker	Cardiac	Lipid Lowering Agents	Anti-Mycobacterial[‡]	Anti-histamine[∂]	Gastro-intestinal drugs[∂]	Neuro-leptic	Psychotropic	Ergot Alkaloids (vasoconstrictor)	Herbs	Other
Protease Inhibitors											
Atazanavir	Bepridil	(none)	simvastatin lovastatin	rifampin rifapentine	astemizole terfenadine	cisapride proton pump inhibitors	pimozide	midazolam[Σ] triazolam	dihydroergotamine (D.H.E. 45) ergotamine[†] (various forms) ergonovine methylergonovine	St. John's wort	fluticasone indinavir irinotecan
Darunavir	(none)	(none)	simvastatin lovastatin	rifampin rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam[Σ] triazolam	dihydroergotamine (D.H.E. 45) ergotamine[†] (various forms) ergonovine methylergonovine	St. John's wort	carbamazepine phenobarbital phenytoin fluticasone[⊗]
Fosamprenavir	Bepridil	(none)	simvastatin lovastatin	rifampin rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam[Σ] triazolam	dihydroergotamine (D.H.E. 45) ergotamine[†] (various forms) ergonovine methylergonovine	St. John's wort	Delavirdine fluticasone oral contraceptives
Indinavir	(none)	amiodarone	simvastatin lovastatin	rifampin rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam[Σ] triazolam	dihydroergotamine (D.H.E. 45) ergotamine[†] (various forms) ergonovine methylergonovine	St. John's wort	Atazanavir
Lopinavir + Ritonavir	(none)	flecainide propafenone	simvastatin lovastatin	rifampin[∫] rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam[Σ] triazolam	dihydroergotamine (D.H.E. 45) ergotamine[†] (various forms) ergonovine methylergonovine	St. John's wort	fluticasone[⊗]
Nelfinavir	(none)	(none)	simvastatin lovastatin	rifampin rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam[Σ] triazolam	dihydroergotamine (D.H.E. 45) ergotamine[†] (various forms) ergonovine methylergonovine	St. John's wort	
Ritonavir	Bepridil	amiodarone flecainide propafenone quinidine	simvastatin lovastatin	rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam[Σ] triazolam	dihydroergotamine (D.H.E. 45) ergotamine[†] (various forms) ergonovine methylergonovine	St. John's wort	voriconazole (with RTV ≥ 400mg BID) fluticasone[⊗] alfuzosin
Saquinavir	(none)	(none)	simvastatin lovastatin	rifampin rifabutin[Δ] rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam [Σ] triazolam	dihydroergotamine (D.H.E. 45) ergotamine[†] (various forms) ergonovine methylergonovine	St. John's wort garlic supplements	fluticasone
Tipranavir	Bepridil	amiodarone flecainide propafenone quinidine	simvastatin lovastatin	rifampin rifapentine	astemizole terfenadine	cisapride	pimozide	midazolam [Σ] triazolam	dihydroergotamine (D.H.E. 45) ergotamine[†] (various forms) ergonovine methylergonovine	St. John's wort	fluticasone[⊗]
Non-nucleoside Reverse Transcriptase Inhibitors											
Delavirdine	(none)	(none)	simvastatin lovastatin	rifampin rifapentine[‡] rifabutin	astemizole terfenadine	cisapride H2 blockers proton pump inhibitors	(none)	alprazolam midazolam[Σ] triazolam	dihydroergotamine (D.H.E. 45) ergotamine[†] (various forms) ergonovine methylergonovine	St. John's wort	amprenavir fosamprenavir carbamazepine phenobarbital phenytoin
Efavirenz	(none)	(none)	(none)	rifapentine[‡]	astemizole terfenadine	cisapride	(none)	midazolam[Σ] triazolam	dihydroergotamine (D.H.E. 45) ergotamine[†] (various forms) ergonovine methylergonovine	St. John's wort	voriconazole
Nevirapine	(none)	(none)	(none)	rifampin rifapentine[‡]	(none)	(none)	(none)	(none)	(none)	St. John's wort	
CCR5 Antagonist Antiretrovirals											
Maraviroc	•	•	•	rifampin rifapentine	•	•	•	•	•	St. John's wort	•

\# Certain listed drugs are contraindicated based on theoretical considerations. Thus, drugs with narrow therapeutic indices and suspected metabolic involvement with P450–3A, 2D6, or unknown pathways are included in this table. Actual interactions may or may not occur among patients.

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

Δ Rifabutin may be used with saquinavir only if it is combined with ritonavir.

∫ In one small study, higher doses of RTV (additional 300mg BID) or a double dose of LPV/RTV offset rifampin-inducing activity of LPV. Of note, 28% of subjects discontinued because of increases in LFTs. The safety of this combination is still under evaluation. Further studies are needed.

Σ Midazolam can be used with caution as a single dose and given in a monitored situation for procedural sedation.

† This is likely a class effect.

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

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

Suggested Alternatives:

Cerivastatin (no longer marketed in the United States), simvastatin, lovastatin: Pravastatin and fluvastatin have the least potential for drug-drug interactions (except for pravastatin with darunavir/ritonavir, see **Table 21a**); atorvastatin should be used with caution, using the lowest possible starting dose and monitor closely; no pharmacokinetic data or safety data are available for coadministration of rosuvastatin with the antiretroviral agents.

Rifabutin: clarithromycin, azithromycin (MAI prophylaxis); clarithromycin, azithromycin, ethambutol (MAI treatment)

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

Midazolam, triazolam: temazepam, lorazepam

Table 21a. Drug Interactions Among Antiretrovirals and Other Drugs: PIs and Maraviroc

Drug Interactions Requiring Dose Modifications or Cautious Use		
Drugs Affected	**Atazanavir (ATV)**	**Fosamprenavir (FPV)**
ANTIFUNGALS		
Itraconazole	No data, but potential for bi-directional inhibition between itraconazole and PIs, monitor for toxicities.	No data, but potential for bi-directional inhibition between itraconazole and PIs, monitor for toxicities. Dose: Dose adjustment for patients receiving >400mg/day may be needed.
Ketoconazole	Unboosted: No dosage adjustment necessary. RTV boosted: See RTV recommendations.	No data, but presumably similar interaction as seen with APV with an increase in both APV and ketoconazole levels (APV ↑ 31%; ketoconazole ↑ 44%). Dose: Consider ketoconazole dose reduction if dose is >400mg/day. If FPV/r: Use with caution; do not exceed 200mg ketoconazole daily.
Voriconazole	RTV boosted: No data, but potential for bi-directional inhibition between voriconazole and PIs exists; monitor for toxicities. See RTV recommendations if boosted with RTV.	No data, but potential for bi-directional inhibition between voriconazole and PIs; monitor for toxicities. See RTV recommendations if boosted with RTV.
ANTI-MYCOBACTERIALS		
Clarithromycin	Levels: clarithromycin AUC ↑ 94% and may cause QTc prolongation. Clarithromycin active metabolite concentrations are significantly reduced. Dose: ↓ clarithromycin dose by 50%. Consider alternative therapy.	Presumably similar interaction and recommendation as APV. Levels: APV AUC ↑ 18%. No change in clarithromycin AUC. No dose adjustment.
Rifabutin	Levels: Rifabutin AUC ↑ 2.5-fold Dose: ↓ rifabutin dose to 150mg QOD or 3x/week[¢]	Rifabutin 150mg QOD + FPV 700/100mg BID, rifabutin unchanged. No data on FPV level. Dose: No change in FPV dose; decrease rifabutin to 150mg QD or 300mg 3x/week[¢]. If RTV-boosted FPV, reduce rifabutin dose to 150mg QOD or 3x/week[¢].
Rifampin	Should not be coadministered.	A substantial decrease in APV AUC (≈ ↓ 82%) is expected based on the interaction with APV. Should not be coadministered.
HORMONAL CONTRACEPTIVES		
	Levels: Ethinyl estradiol AUC ↑ 48%, norethindrone AUC ↑ 110% Dose: use lowest effective dose or alternative methods.	An increase in ethinyl estradiol and norethindrone levels occurred with APV, and APV levels ↓ 20%. Do not coadminister; alternative methods of contraception are recommended.
LIPID-LOWERING AGENTS		
Atorvastatin	Atorvastatin levels have potential for large increase. Use lowest possible starting dose of atorvastatin with careful monitoring.	Atorvastatin AUC ↑ 150% - use lowest possible starting dose of atorvastatin with careful monitoring.
Pravastatin	No data.	No data.
Simvastatin **Lovastatin**	Levels: Potential for large increase in statin levels. Avoid concomitant use.	Levels: Potential for large increase in statin levels. Avoid concomitant use

ANTICONVULSANTS		
Carbamazepine Phenobarbital Phenytoin	Unknown, but may decrease ATV levels substantially. Monitor anticonvulsant level and virologic response. Consider using alternative anticonvulsant or monitoring ATV level and boosting with RTV if necessary.	Unknown, but may decrease APV levels substantially. Monitor anticonvulsant levels and virologic response, or consider alternative anticonvulsant. Consider monitoring APV levels and boosting with RTV if necessary.
METHADONE	No change in methadone or ATV levels.	With APV, R-methadone levels ↓ 13%, and APV Cmin ↓ 25%. The interaction with FPV is presumed to be similar. Monitor and titrate methadone if needed.
ERECTILE DYSFUNCTION AGENTS		
Sildenafil	Sildenafil levels have potential for increase. Start with reduced dose of 25mg every 48 hours and monitor for adverse effects.	Sildenafil AUC ↑ 2- to 11-fold with APV. Use cautiously. Start with reduced dose of 25mg every 48 hours and monitor for adverse effects.
Tadalafil	Concomitant administration will result in substantial increase in tadalafil AUC and half-life (normal=17.5h). Start with a 5mg dose, and do not exceed a single dose of 10mg every 72 hours.	No data, but concomitant administration will result in substantial increase in tadalafil AUC and half-life (normal = 17.5 h). Start with a 5 mgdose, and do not exceed a single dose of 10mg every 72 hours.
Vardenafil	No data, but vardenafil AUC may be substantially increased. Start with a 2.5mg dose and do not exceed a single 2.5mg dose in 24 hours. Do not exceed 2.5mg in 72 hours if administered with RTV.	No data, but vardenafil AUC may be substantially increased. Start with a 2.5mg dose and do not exceed a single 2.5mg dose in 24 hours. Do not exceed 2.5mg in 72 hours if administered with RTV.
MISCELLANEOUS	Diltiazem: AUC ↑ 125%, ↓ diltiazem dose by 50%; ECG monitoring is recommended. Other calcium channel blockers: caution is warranted; dose titration should be considered; ECG monitoring is recommended. Irinotecan: ATV inhibits UGT and may interfere with irinotecan metabolism; avoid concomitant use. H2-receptor antagonists: reduced ATV concentrations with simultaneous administration; in treatment-naïve, give ATV at least 10 hrs after or 2 hrs before H2-receptor antagonist, or use ATV/r 300/100mg; in treatment-experienced, boost ATV and administer separately. Proton-Pump Inhibitors: Coadministration with these agents may significantly decrease ATV solubility. Do not coadminister. Antacids and buffered medications: Reduced ATV concentrations are expected with simultaneous administration; give ATV 2 hrs before or 1 hr after these medications.	H2 Blockers: Coadministration of ranitidine with FPV decreases (↓) APV AUC 30%; Cmin unchanged. Separate administration if coadministration is necessary. Monitor closely for desired virologic response. Consider boosting with RTV. Proton-Pump Inhibitors: No effect of esomeprazole 20mg on APV AUC, C_{max}, or C_{min}, regardless of whether FPV was given with or without ritonavir.

[¢] Rifabutin: At least 3x/week is recommended if CD4 cell count is <100/mm^3

Table 21a. Drug Interactions Among Antiretrovirals and Other Drugs: PIs and Maraviroc

Drug Interactions Requiring Dose Modifications or Cautious Use			
Drugs Affected	**Darunavir + Ritonavir (DRV/RTV)†**	**Indinavir (IDV)**	**Lopinavir + Ritonavir (LPV/r)**
ANTIFUNGALS			
Itraconazole	Level: No data. Dose: Use with caution; do not exceed 200mg itraconazole daily.	Level: IDV 600mg Q8H given with itraconazole 200mg BID: AUC similar to IDV 800mg Q8H. Dose: IDV 600mg Q8H; Itraconazole: Do not exceed 200mg BID.	Levels: Itraconazole ↑ when administered with LPV/r. Dose: Itraconazole – consider not exceeding 200mg/day, or monitor level and toxicity.
Ketoconazole	Levels: DRV AUC ↑ 42%. Azole AUC ↑ 3-fold. Dose: Use with caution; do not exceed 200mg ketoconazole QD.	Levels: IDV ↑ **68%.** Dose: IDV 600mg Q8H.	Levels: LPV AUC ↓ 13%. Azole ↑ 3-fold. Dose: Use with caution; do not exceed 200mg ketoconazole daily.
Voriconazole	Levels: No data with DRV/r. Voriconazole AUC ↓ 39% with RTV 100mg BID; coadministration not recommended unless benefit outweighs risk.	Levels: No significant changes in AUC of azole or IDV (healthy subjects). See RTV recommendations if boosted with RTV. Dose: Standard.	Voriconazole AUC ↓ 39% with RTV 100mg BID; Coadministration is not recommended unless the benefit outweighs the risk.
ANTI-MYCOBACTERIALS			
Clarithro-mycin	Levels: Clarithromycin AUC ↑ 57%. DRV:No significant effect. Dose: Adjust clarithromycin dose for moderate & severe renal impairment.	Levels: Clarithromycin ↑ 53%.No dose adjustment.	Levels: ↑ Clarithromycin AUC 77%. Dose: Adjust clarithromycin dose for moderate and severe renal impairment.
Rifabutin	Levels: No data Dose: Decrease rifabutin to 150mg QOD.	Levels: IDV ↓ 32%. Rifabutin ↑ 2X. Dose: ↓ rif to 150mg/d or 300mg 3x/week.[¢] IDV 1,000mg Q8H. If RTV boosted, rif 150mg QOD or 3x/week[¢] continue current dose of boosted IDV.	Levels: Rifabutin AUC ↑ 3-fold. 25-O-desacetyl metabolite ↑ 47.5-fold. Dose: Decrease rifabutin dose to 150mg QOD or 3x/week[¢]; LPV/r: Standard.
Rifampin	Levels: No data, but a significant decrease in DRV concs is expected. **Should not be coadministered.**	Levels: IDV (unboosted) ↓ 89%; IDV (boosted) ↓ 87%; **Should not be coadministered.**	Levels: LPV AUC ↓ 75%.* **Should not be coadministered.**
HORMONAL CONTRACEPTIVES			
	Levels: Potential for ↓ ethinyl estradiol from RTV. Use alternative or additional method with DRV/r.	Levels: Norethindrone ↑ 26%. Ethinylestradiol ↑ 24%. .No dose adjustment.	Levels: Ethinyl estradiol ↓ 42%. Use alternative or additional method.
LIPID-LOWERING AGENTS			
Atorvastatin	Statin exposure from 10mg QD with DRV/r gives similar exposure to 40mg QD alone. Use lowest possible statin starting dose w/careful monitoring.	Levels: Potential for increase in atorvastatin levels. Use lowest possible starting dose of atorvastatin with careful monitoring.	Atorvastatin AUC ↑ 5.88-fold. Use lowest possible starting dose of atorvastatin with careful monitoring.
Pravastatin	Levels: Mean ↑ in statin AUC was 81% with DRV/r. However, statin AUC increased by up to 5-fold in some subjects. Start at lowest dose and titrate up, monitor for toxicities.	No data.	Pravastatin AUC ↑ 33%; no dosage adjustment necessary.
Simvastatin Lovastatin	Levels: Potential for large increase in statin levels. Avoid concomitant use.	Levels: Potential for large increase in statin levels. Avoid concomitant use.	Levels: Potential for large increase in statin levels. Avoid concomitant use.
ANTICONVULSANTS			
Carbamazepine Phenobarbital Phenytoin	Coadministration is expected to result in significant decrease in DRV concentrations. Avoid concomitant use.	Carbamazepine markedly ↓ IDV AUC. Consider alternative anticonvulsant, RTV boosting, and/or monitoring IDV level.	Many possible interactions: carbamazepine: ↑ levels when co-administered with RTV. Use with caution. Monitor anticonvulsant levels. Phenytoin: ↓ levels of LPV, RTV, and of phenytoin when given together. Avoid concomitant use or monitor LPV level.
Methadone	Levels: No data with DRV/r. However, RTV is a known inducer of methadone metabolism. Monitor closely; increase methadone as clinically indicated.	No change in methadone levels.	Methadone AUC ↓ 53%. Opiate withdrawal may occur. Monitor and titrate dose if needed. May require ↑ methadone dose.
ERECTILE DYSFUNCTCION AGENTS			
Sildenafil	Sildenafil AUC from a 25 mg single dose given w/ DRV/r was similar to 100mg given alone. Do not exceed 25 mg q48h; monitor for adverse effects.	Sildenafil AUC ↑ 3-fold. Use cautiously. Start with reduced dose of 25 mg every 48 hours and monitor for adverse effects.	Sildenafil AUC ↑ 11-fold in combination with RTV. Do not exceed 25mg every 48 hours.
Tadalafil	No data, but concomitant administration is expected to result in substantial increase in tadalafil AUC and half-life (normal = 17.5h). Do not exceed a single dose of 10mg in 72h.	Concomitant administration will result in substantial increase in tadalafil AUC & half-life (normal=17.5h). Start with 5mg dose; do not exceed a single dose of 10mg q72h.	Tadalafil AUC ↑ 124% when coadministered with RTV. Do not exceed a single dose of 10mg every 72 hours.
Vardenafil	No data, but a substantial increase in vardenafil AUC is expected. Do not exceed a single dose of 2.5 mg in 72 hours.	Vardenafil AUC ↑ 16-fold. IDV (unboosted) AUC ↓ 30%. Dose: Consider sildenafil instead of vardenafil if IDV unboosted. Do not exceed vardenafil 2.5mg in 72h if administered w/RTV.	No data, but vardenafil AUC may be substantially increased. Do not exceed a single 2.5mg dose in 72 hours.
Miscellaneous	Paroxetine and Sertraline AUC's ↓ 39% and 49%, respectively. Patients initiated on DRV/r should be monitored closely for antidepressent response. Carefully titrate SSRI dose based on clincal assessment. DRV levels unchanged when DRV/r is administered with omeprazole or ranitidine.	Grapefruit juice ↓ IDV levels by 26%. Vitamin C ≥1 gram/day ↓ IDV AUC by 14% and Cmin by 32%.Amlodipine: Amlodipine AUC ↑ 90% when coadministered with IDV/RTV. No change in IDV/RTV levels. Monitor closely.	LPV/r levels unchanged when tablets are given with omeprazole or ranitidine.

† Darunavir interaction studies were conducted with RTV 100mg BID and mostly with darunavir doses of 300–400mg BID instead of the FDA approved dose of DRV 600mg BID

¢ Rifabutin: At least 3x/week is recommended if CD4 cell count is <100/mm^3.

* In one small study, higher doses of RTV (an additional 300mg BID) or a double dose of LPV/RTV offset rifampin-inducing activity of LPV. Of note, 28% of subjects discontinued treatment because of increases in LFTs. The safety of this combination is still under evaluation. Further studies are needed.

Table 21a. Drug Interactions Among Antiretrovirals and Other Drugs: PIs and Maraviroc

	Drug Interactions Requiring Dose Modifications or Cautious Use	
Drugs Affected	**Nelfinavir (NFV)**	**Ritonavir* (RTV)**
ANTIFUNGALS		
Itraconazole	No data, but potential for bi-directional inhibition between itraconazole and PIs; monitor for toxicities.	No data, but potential for bi-directional inhibition between itraconazole and RTV; monitor for toxicities. Dose: Dose adjustment for patients receiving >400mg itraconazole may be needed, or consider monitoring itraconazole level.
Ketoconazole	No dose adjustment necessary.	Levels: ketoconazole ↑ 3X. Dose: Use with caution; do not exceed 200mg ketoconazole daily.
Voriconazole	No data, but potential for bi-directional inhibition between voriconazole and PIs exists; monitor for toxicities.	Levels: voriconazole AUC ↓ 82% when coadministered with 400mg BID of RTV, and concomitant therapy of voriconazole with RTV 400mg BID or higher is contraindicated. Voriconazole AUC ↓ 39% with RTV 100mg BID; administration of voriconazole and RTV 100mg is not recommended unless benefit outweighs risk.
ANTI-MYCOBACTERIALS		
Clarithromycin	No data.	Levels: Clarithromycin ↑ 77%. Dose: Adjust clarithromycin dose for moderate and severe renal impairment.
Rifabutin	Levels: NFV ↓ 32% if 750mg Q8H dose given; no change if 1,250mg Q12H dose used. Rifabutin ↑ 2X. Dose: ↓ rifabutin to 150mg QD or 300mg 3x/wk.¢ NFV 1,250mg BID.	Levels: Rifabutin ↑ 4X. Dose: ↓ rifabutin to 150mg QOD or dose 3x/week.¢ RTV: Maintain current dose.
Rifampin	Levels: NFV ↓ 82%. **Should not be coadministered.**	Levels: RTV ↓ 35%. Increased liver toxicity possible. Coadministration may lead to loss of virologic response if RTV sole PI. Alternative antimycobacterial agents, such as rifabutin, should be considered. **Should not be coadministered.**
HORMONAL CONTRACEPTIVES		
	Levels: Norethindrone ↓ 18%. Ethinyl estradiol ↓ 47%. Use alternative or additional method.	Levels: Ethinyl estradiol ↓ 40%. Use alternative or additional method.
LIPID-LOWERING AGENTS		
Atorvastatin	Atorvastatin AUC ↑ 74%. Use lowest possible starting dose of atorvastatin with careful monitoring.	Levels: 450% ↑ when administered with SQV/RTV combination. Use lowest possible starting dose of atorvastatin with careful monitoring.
Pravastatin	No data.	Levels: 50% ↓ when administered with SQV/RTV combination. Dose: Pravastatin dosage adjustment based on lipid response.
Simvastatin **Lovastatin**	Simvastatin AUC ↑ 505%. Potential for large increase in lovastatin AUC. Avoid concomitant use.	Levels: Potential for large increase in statin levels. Avoid concomitant use.
ANTICONVULSANTS		
Carbamazepine **Phenobarbital** **Phenytoin**	Unknown, but may decrease NFV levels substantially. Monitor anticonvulsant levels and virologic response. Consider alternative anticonvulsant or NFV levels.	Carbamazepine: ↑ serum levels when coadministered with RTV. Use with caution. Monitor anticonvulsant levels.
METHADONE	NFV may decrease methadone levels, but opiate withdrawal rarely occurs. Monitor and titrate dose if needed. May require ↑ methadone dose.	Methadone ↓ 37%. Monitor and titrate dose if needed. May require ↑ methadone dose.
ERECTILE DYSFUNCTION AGENTS		
Sildenafil	Sildenafil AUC ↑ 2- to 11-fold. Use cautiously. Start with reduced dose of 25mg every 48 hours; monitor for adverse effects.	Sildenafil AUC ↑ 11-fold. Use cautiously. Start with reduced dose of 25 mg every 48 hours and monitor for adverse effects.
Tadalafil	Concomitant administration will result in substantial increase in tadalafil AUC and half-life (normal = 17.5 h). Start with a 5mg dose, and do not exceed a single dose of 10mg every 72 hours.	Tadalafil AUC ↑ 124%. Start with a 5mg dose, and do not exceed a single dose of 10mg every 72 hours.
Vardenafil	No data, but vardenafil AUC may be substantially increased. Start with a 2.5mg dose and do not exceed a single 2.5mg dose in 24 hours. Do not exceed 2.5mg in 72 hours if administered with RTV.	Vardenafil AUC ↑ 49-fold. RTV AUC ↓ 20%. Dose: Vafdenafil: Start with a 2.5mg dose and do not exceed a single 2.5mg dose in 72 hours. RTV: Maintain current dose.
MISCELLANEOUS		Many possible interactions. Desipramine ↑ 145%; reduce dose. Trazodone AUC ↑ 2.4-fold when given with RTV 200mg BID. Use lowest dose of trazodone and monitor for CNS and CV adverse effects. Theophylline ↓ 47%; monitor theophylline levels. RTV 100mg BID significantly increases systemic exposure of inhaled (oral or nasal) fluticasone and may predispose patients to systemic corticosteroid effects. Coadministration not recommended unless benefit of fluticasone outweighs the risk.

* Drugs for which plasma concentrations may be decreased by coadministration with ritonavir: anticoagulants (warfarin), anticonvulsants (phenytoin, divaproex, lamotrigine), antiparasitics (atovaquone).

¢ Rifabutin: At least 3x/week is recommended if CD4 cell count is <100/mm^3.

Table 21a. Drug Interactions Among Antiretrovirals and Other Drugs: PIs and Maraviroc

Drug Interactions Requiring Dose Modifications or Cautious Use			
Drugs Affected	**Saquinavir† (SQV)**	**Tipranavir + Ritonavir (TPV/RTV)**	**Maraviroc (MVC)**
ANTIFUNGALS			
Itraconazole	Bi-directional interaction between itraconazole & SQV has been observed. Dose: Not established, but decreased itraconazole dosage may be warranted. Consider therapeutic drug monitoring for both SQV (if unboosted) and itraconazole.	No data. Use with caution; do not exceed 200mg itraconazole daily.	Possible increase in maraviroc concentration. Dose: 150mg BID.
Ketoconazole	Levels: SQV ↑ 3X. Dose: No dosage adjustment necessary.	No data. Use with caution; do not exceed 200mg ketoconazole daily.	Levels: MVC AUC ↑ 5x. Dose: 150mg BID.
Voriconazole	No data, but potential for bi-directional inhibition between voriconazole and PIs, monitor for toxicities	Potential for bi-directional inhibition between voriconazole and PIs exists. Voriconazole AUC ↓ 39% with RTV 100mg BID; interaction between TPV and voriconazole unknown. Coadministration is not recommended unless the benefit outweighs the risk.	No data, monitor for toxicities.
ANTI-MYCOBACTERIALS			
Clarithromycin	Levels: Clarithromycin ↑ 45%. SQV ↑ 177%. Dose: No dose adjustment.	Levels: TPV ↑ 66%, Clarithromycin ↑ 19%, 14-hydroxy-clarithromycin metabolite ↓ 97%. Dose: No adjustment for patients with normal renal function; reduce clarithromycin dose by 50% for CrCl 30–60 mL/min; reduce clarithromycin dose by 75% for CrCl <30 mL/min.	Possible increase in maraviroc concentration. Dose: 150mg BID.
Rifampin	Levels: SQV ↓ 84%. Marked elevation of transaminases was seen in a pharmacokinetic study, where healthy volunteers received a combination of rifampin 600mg QD + RTV/SQV 100/1,000mg BID. This combination should not be used.	No data; should not be coadministered.	Levels: MVC AUC ↓ 64%. Dose: 600mg BID or use rifabutin instead of rifampin.
Rifabutin	Levels: SQV ↓ 40%. Contraindicated unless SQV/RTV. Dose: Rifabutin 150mg QOD or 3x/week.¢	Levels: Rifabutin AUC ↑ 2.9-fold. 25-O-desacetyl metabolite ↑ 20.7-fold. Dose: Decrease rifabutin dose to 150mg QOD or 3x/week.¢ Single-dose study, thus the effect of multiple doses of rifabutin on TPV/r PK was not assessed.	No data, potential for induction of MVC metabolism. If used without a strong CYP3A inducer or inhibitor: 300mg BID. Monitor for virologic response. If used with a strong CYP3A inhibitor: 150mg BID.
HORMONAL CONTRACEPTIVES			
	No data.	Levels: Ethinyl estradiol Cmax and AUC ↓ ~ 50%.[a] Use alternative or additional method. Women on estrogen may have increased risk of nonserious rash. Used as hormone replacement therapy, monitor clinically for signs of estrogen deficiency.	No significant interaction, safe to use in combination.
LIPID-LOWERING AGENTS			
Atorvastatin	Levels: 450% ↑ when administered with SQV/RTV combination. Use lowest possible starting dose of atorvastatin with careful monitoring.	Levels: Atorvastatin AUC ↑ 9-fold. Dose: Use lowest possible starting dose of atorvastatin with careful monitoring.	No data, potentially safe to use in combination.
Pravastatin	Levels: 50% ↓ when administered with SQV/RTV combination. No dose adjustment needed. Dose: Pravastatin dosage adjustment based on lipid response.	No data.	No data, potentially safe to use in combination.
Simvastatin **Lovastatin**	Levels: Potential for large increase in statin levels. Avoid concomitant use.	Potential for large increase in statin levels. Avoid concomitant use.	No data, potentially safe to use in combination.
ANTICONVULSANTS			
Carbamazepine **Phenobarbital** **Phenytoin**	Unknown, but may markedly ↓ SQV levels. Consider alternative anticonvulsant. Monitor anticonvulsant levels and consider monitoring SQV level.	No data. Consider alternative anticonvulsant. Monitor anticonvulsant levels and consider obtaining TPV level.	Possible decrease in maraviroc concentration Dose: 600mg BID or use alternative antiepileptic agent.
METHADONE	Methadone AUC ↓ 20% when coadministered with SQV/RTV 400/400mg BID. Dose: No adjustment for this PI regimen, but monitor and titrate to methadone response as necessary.	No data. Dosage of methadone may need to be increased when coadministered with TPV/r.	No data, potentially safe to use in combination.

ERECTILE DYSFUNCTION AGENTS			
Sildenafil	Sildenafil AUC ↑ 2-fold. Use a 25mg starting dose of sildenafil.	No data. Starting dose should not exceed 25 mg sildenafil within 48 hours.	No data, potentially safe to use in combination.
Tadalafil	Concomitant administration will result in substantial increase in tadalafil AUC and half-life (normal = 17.5 h). Start with a 5mg dose, and do not exceed a single dose of 10mg every 72 hours.	No data. Starting dose should not exceed 10mg tadalafil every 72 hours.	No data, potentially safe to use in combination.
Vardenafil	No data, but vardenafil AUC may be substantially increased. Start with a 2.5mg dose and do not exceed a single 2.5mg dose in 24 hours. Do not exceed a single 2.5mg dose in 72 hours if administered with RTV.	No data. Starting dose should not exceed 2.5mg vardenafil every 72 hours.	No data, potentially safe to use in combination.
MISCELLANEOUS	Grapefruit juice ↑ SQV levels. Dexamethasone ↓ SQV levels.	Abacavir ↓ 35%–44%.[a] Appropriate doses for the combination of ABC and TPV/r have not been established. Zidovudine ↓ 31%–43%. Appropriate doses for the combination of ZDV and TPV/r have not been established. Loperamide ↓ 51%.[a] TPV Cmin ↓ 26% with loperamide. Antacids ↓ TPV ~30%, TPV should be administered 2 hrs before or 1 hr after these medications. Fluconazole: Doses >200mg/day are not recommended to be given with TPV. TPV capsules contain alcohol. Avoid use of disulfiram and metronidazole.	No data.

[a] Study conducted with TPV/r dose(s) other than FDA-approved dose of 500/200mg BID.
[†] Some drug interaction studies were conducted with Invirase® soft gel capsule. May not necessarily apply to use with Fortovase.

Table 21b. Drug Interactions Among Antiretrovirals and Other Drugs: NNRTIs

Drug Interactions Requiring Dose Modifications or Cautious Use			
Drugs Affected	**Delavirdine (DLV)**	**Efavirenz (EFV)**	**Nevirapine (NVP)**
ANTIFUNGALS			
Fluconazole	No clinically significant changes in DLV or fluconazole concentrations.	No clinically significant changes in EFV or fluconazole concentrations.	Levels: NVP: Cmax, AUC, and Cmin ↑ 100%. Fluconazole: No change. Risk of hepatotoxicity may ↑ with this combination. If coadministered, monitor NVP toxicity.
Ketoconazole	DLV: Cmin ↑ 50%. Ketoconazole: No data. Dose: Standard.	No data.	Levels: Keto ↓ 63%. NVP ↑ 15%–30%. Dose: Not recommended.
Voriconazole	Metabolism of voriconazole may be inhibited by DLV. Voriconazole may inhibit NNRTI metabolism. Frequently monitor for NNRTI toxicity and antifungal outcome.	Levels: EFV ↑ 44%. Voriconazole ↓ 77%. This combination is not recommended.	Metabolism of voriconazole may be induced by NVP. Voriconazole may inhibit NNRTI metabolism. Carefully monitor for NNRTI toxicity and antifungal outcome.
ANTI-MYCOBACTERIALS			
Clarithromycin	Levels: Clarithromycin ↑ 100%. DLV ↑ 44%. Adjust dosage for renal failure.	Levels: Clarithromycin ↓ 39%. Monitor for efficacy or use alternative agent.	Levels: NVP ↑ 26%. Clarithromycin ↓ 30%. Monitor for efficacy or use alternative agent.
Rifabutin	Levels: DLV ↓ 80%. Rifabutin ↑ 100%. Not recommended.	Levels: EFV unchanged. Rif ↓ 35%. Dose: ↑ rifabutin dose to 450–600mg QD or 600mg 3x/week.* EFV: Standard.	Levels: NVP ↓ 16%. No dose adjustment.*
Rifampin	Levels: DLV ↓ 96%. Contraindicated.	Levels: EFV ↓ 25%. Dose: Maintain EFV dose at 600mg QD in patients weighing <50 kg or consider ↑ EFV to 800mg QD.	Levels: NVP ↓ 20%–58%. Virologic consequences are uncertain; the potential for additive hepatotoxicity exists. Combination is not recommended; if used, coadministration should be done with careful monitoring.
HORMONAL CONTRACEPTIVES			
	Levels of ethinyl estradiol may increase. Clinical significance is unknown.	Levels: Ethinyl estradiol ↑ 37%. No data on other component. Use alternative or additional methods.	Levels: Ethinyl estradiol ↓ approx 20%. Use alternative or additional methods.
LIPID-LOWERING AGENTS			
Atorvastatin	Potential for inhibition of atorvastatin metabolism. Use lowest possible dose and monitor for toxicity.	Levels: Atorvastatin AUC ↓43%; EFV unchanged. Dose: Adjust atorvastatin dose according to lipid responses, not to exceed the maximum recommended dose.	No data.
Pravastatin	No data.	No data.	No data.
Simvastatin **Lovastatin**	Levels: Potential for large increase in statin levels. Avoid concomitant use.	Levels: Simvastatin AUC ↓ by 58%; EFV unchanged. Dose: Adjust simvastatin dose according to lipid responses, not to exceed the maximum recommended dose.	No data.
ANTICONVULSANTS			
Carbamazepine **Phenobarbital** **Phenytoin**	Levels: DLV Cmin ↓ 90% when coadministered with phenytoin, phenobarbital, or carbamazepine. Contraindicated.	Use with caution. CBZ and EFV AUCs ↓ 27% and 36%, respectively, when combined. One case report showed low EFV concs with phenytoin. Monitor anticonvulsant and EFV levels. If possible, use alternative anticonvulsant.	
METHADONE	Levels: DLV unchanged; no data on methadone levels but potential for increased levels. Monitor for methadone toxicity; may require a dose reduction.	Levels: Methadone ↓ 60%. Opiate withdrawal common; increased methadone dose often necessary. Titrate methadone dose to effect.	Levels: NVP unchanged. Methadone ↓ significantly. Opiate withdrawal common when this combination is used; increased methadone dose often necessary. Titrate methadone dose to effect.
MISCELLANEOUS	May increase levels of dapsone, warfarin, and quinidine. Sildenafil: Potential for increased concentrations and adverse effects. Use cautiously. Start with reduced dose of 25mg every 48 hours and monitor for adverse effects. Vardenafil: No data, but vardenafil AUC may be substantially increased.Start with a 2.5mg dose and do not exceed a single 2.5mg dose in 24 hours. Tadalafil: No data, but concomitant administration will likely result in substantial increase in tadalafil AUC and half-life (normal = 17.5 h). Start with a 5mg dose and do not exceed a single dose of 10mg every 72 hours. Coadministration of fluoxetine increases DLV Cmin 50%.	Monitor warfarin when used concomitantly.	No data.

* These recommendations apply to regimens that do not include PIs, which can substantially increase rifabutin levels.

Table 21c. Drug Interactions Among Antiretrovirals and Other Drugs: NRTIs

Drug Interactions Requiring Dose Modifications or Cautious Use				
Drugs Affected	**Didanosine (ddI)**	**Stavudine (d4T)**	**Tenofovir (TDF)**	**Zidovudine (ZDV)**
Atazanavir (ATV)	Levels: Simultaneous EC ddI + ATV (with food): ↓ AUC of ddI 34%. ATV no change. Administer separately; ATV should be taken with food and ddI-EC on an empty stomach.	No data.	ATV 400mg + TDF 300mg - Levels: ATV AUC ↓ 25% and Cmin ↓ 40%. TDF AUC ↑ 24%. Avoid concomitant use without RTV. ATV + RTV 300/100mg QD + TDF 300mg QD - Levels: ATV AUC ↓ 25% and Cmin ↓23%; ATV Cmin higher with RTV than without . TDF AUC ↑ 30%; monitor for toxicities. Dose: ATV + RTV 300/100mg QD coadministered with TDF 300mg QD.	ZDV: No change in AUC but 30% ↓ in Cmin. Significance unknown.
Cidofovir, Ganciclovir, Valganciclovir	Buffered ddI + ganciclovir (GCV): ddI AUC ↑ 50%–111%; GCV AUC ↓ 21% when ddI administered 2 hours prior to oral GCV; no change in IV GCV concentrations. Appropriate doses for the combination of ddI and GCV have not been established.	No data.	Serum concentration of these drugs and/or tenofovir may be increased. Monitor for dose-related toxicities.	Ganciclovir + ZDV: No significant changes in levels for either drug. Potential increase in hematologic toxicities.
Darunavir (DRV)	No data	No data.	Levels: Tenofovir AUC ↑ 22%, Cmax ↑ 24% and Cmin ↑ 37%. Clinical significance unknown; monitor for tenofovir toxicity.	No data.
Didanosine	•	Peripheral neuropathy, lactic acidosis, and pancreatitis seen with this combination; should be avoided unless potential benefit far outweighs potential risks.	Levels: ddI EC AUC ↑ by 48%–60%, Cmax ↑ by 48%–64% For patients >60 kg, 250mg/day of ddI EC is recommended; for patients <60 kg, 200mg EC ddI is recommended; the ddI doses apply to patients with creatinine clearanace >60 mL/min. Monitor for ddI-associated toxicities.	No significant interactions.
Indinavir (IDV)	EC ddI can be taken together with IDV.	No significant PK interaction.	Levels: IDV Cmax ↑ 14%. Dose: Standard.	No significant PK interaction.
Lopinavir/ritonavir (LPV/r)	No data.	No data.	LPV/r 400/100mg AUC ↓ 15%; TDF AUC ↑ 34%; clinical significance of interaction is unknown; monitor for tenofovir toxicities.	No data.
Methadone	Levels: EC ddI unchanged. Dose: No change EC ddI.	Levels: d4T ↓ 27%; methadone unchanged. Dose: No dose adjustment.	No change in methadone or TDF levels.	ZDV AUC ↑ 43%. Monitor for ZDV-related adverse effects.
Ribavirin	Coadministration not recommended. Ribavirin increases the intracellular levels of the active metabolite of ddI and may cause serious toxicities.	No data.	Level: Ribavirin unchanged; no data on TDF level.	Ribavirin inhibits phosphorylation of ZDV; this combination should be avoided if possible, or closely monitor virologic response.
Tipranavir/ ritonavir	Levels: EC ddI ↓ 10%.[a] TPV Cmin ↓ 34% with EC ddI.[a] Dose: EC ddI and TPV/r should be separated by at least 2 hours.	No significant PK interaction.	TPV AUC and Cmin ↓ 9%–18% and 12%–21%, respectively[a]; clinical significance is unknown.	Levels: ZDV AUC and Cmax ↓ 31%–42% and 46%–51%, respectively.[a] Appropriate doses for the combination of ZDV and TPV/r have not been established.

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

Table 22a. Drug Effects on Concentration of PIs

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

* Several drug interaction studies have been completed with saquinavir given as Invirase or Fortovase. Results from studies conducted with Invirase may not be applicable to Fortovase.
† Study conducted with Fortovase.
‡ Study conducted with Invirase.

Table 22b. Drug Effects on Concentration of NNRTIs and Maraviroc

Drug Affected	Delavirdine	Efavirenz	Nevirapine	Maraviroc
Fosamprenavir (FPV)	Levels: Presumably, similar PK effects as APV: APV AUC ↑ 130%, and DLV AUC ↓ 61%. Dose: Coadministration not recommended.	Levels: FPV Cmin ↓ 36% (when dosed at 1,400mg QD with 200mg RTV). Dose: FPV 1,400mg + RTV 300mg QD; or FPV 700mg + RTV 100mg BID.	No data.	Levels: Unknown, possibly ↑ MVC conc. Dose: 150mg BID
Atazanavir (ATV)	No data.	Levels: With unboosted ATV, ATV AUC ↓ 74%. EFV no change. Dose: ATV 300 + RTV 100mg QD with food - ATV concentrations similar to unboosted ATV; if desired ATV concentrations not achieved with ATV/r 300/100mg, may need to increase the dose of ATV/r - insufficient information for specific recommendation. EFV dose - standard.	No data. A decrease in ATV levels is expected. Coadministration is not recommended. Effect of NVP on ritonavir-boosted ATV combination unknown; if used, consider monitoring ATV level.	Levels : With unboosted ATV, MVC AUC ↑ 3.6x. With ATV/r, MVC AUC ↑ 5x. Dose: With unboosted ATV or ATV/r, 150mg BID.
Darunavir (DRV)	No data.	Levels: DRV AUC and Cmin ↓ 13% and 31%, respectively. EFV AUC and Cmin ↑ 21% and 17%, respectively. Dose: Clinical significance unknown. Use standard doses and monitor closely. Consider monitoring levels.	Levels: NVP AUC and Cmin ↑ 27% and 47%, respectively. DRV unchanged.† Dose: Standard.	Levels: With DRV/r, MVC AUC ↑ 4x. Dose: 150mg BID.
Delavirdine (DLV)	•	•	•	Levels: Unknown, possibly ↑ MVC conc. Dose: 150mg BID.
Efavirenz (EFV)	•	•	•	Levels: MVC AUC ↓ 45%. Dose: 600mg BID.
EFV + LPV/r or SQV/r	•	•	•	Levels: MVC AUC ↑ 2.5–5x. Dose: 150mg BID.
Indinavir (IDV)	Levels: IDV ↑ >40%; DLV-No effect. Dose: IDV 600mg q8h. DLV standard.	Levels: IDV ↓ 31%. Dose: IDV 1,000mg q8h; consider IDV/RTV. EFV standard.	Levels: IDV ↓ 28%; NVP no effect. Dose: IDV 1,000mg q8h, or consider IDV/RTV. NVP standard.	Levels: Unknown, possibly ↑ MVC conc. Dose: 150mg BID.
Lopinavir/ Ritonavir (LPV/r)	Levels: LPV levels expected to increase. Dose: Insufficient data.	Levels: With LPV/r tablets 600/150mg BID + EFV 600mg QD, LPV Cmin and AUC ↑ 35% and 36%, respectively. No formal study of LPV/r tablets 400/100mg BID + EFV. EFV no change. Dose: LPV/r tablets 600/150mg BID, when used in with EFV in tx-experienced patients. EFV dose - standard.	Levels: With LPV/r capsules, LPV Cmin dec. 55%. Dose: LPV/r tablets 600/150mg BID, when used in combination with NVP in tx-experienced patients. NVP standard.	Levels: MVC AUC ↑ 4x. Dose: 150mg BID.

Table 22b. Drug Effects on Concentration of NNRTIs and Maraviroc

Nelfinavir (NFV)	Levels: NFV ↑ 2 times. DLV ↓50%. Dose: No data.	Levels: NFV ↑ 20%. Dose: Standard.	Levels: NFV ↑ 10%. NVP no effect. Dose: Standard.	Levels: Unknown, possibly ↑ MVC conc. Dose: 150mg BID.
Nevirapine (NVP)	No data.	Levels: NVP-no effect. EFV AUC ↓ 22%.	•	Levels: No significant change. Dose: 300mg BID if use without PI 150mg BID – if used with PI (except TPV/r).
Ritonavir (RTV)	Levels: RTV ↑ 70%. DLV no effect. Dose: Appropriate doses not established.	Levels: RTV ↑ 18%. EFV ↑ 21%. Dose: Standard.	Levels: RTV ↓ 11%. NVP no effect. Dose: Standard.	Levels: With RTV 100 mg BID, MVC AUC ↑ 2.6x. Dose: 150mg BID.
Saquinavir (SQV)	Levels: SQV‡ ↑ 5 times; DLV no effect. Dose: Fortovase 800mg TID. DLV standard; monitor transaminase levels.	Levels: SQV‡ ↓ 62%. EFV ↓ 12%. SQV is not recommended as sole PI when EFV is used. Dose: Consider SQV/RTV 400/400mg BID.	Levels: SQV ↓ 25%. NVP no effect. Dose: Consider SQV-sgc/RTV 400/400mg or 1,000/100mg BID or SQV- hgc/RTV 1,000/100mg BID.	Levels: With SQV/r, MVC AUC ↑ 9.8x. Dose: 150mg BID.
Tipranavir (TPV)	No data.	Levels: With TPV/r 500/100mg BID, TPV AUC and Cmin ↓ 31% and 42%, respectively. EFV unchanged. With TPV/r 750/200mg BID, TPV PK unchanged. Dose: No dose adjustments necessary.	Levels: No data on the effect of NVP on TPV/r PK. NVP PK unchanged.[a]	Levels: With TPV/r, no significant change. Dose: 300mg BID.

‡ Study conducted with Invirase.
† Based on between-study comparison.
[a] Study conducted with TPV/r dose(s) other than FDA-approved dose of 500/200mg BID.

Table 23. Suggested Minimum Target Trough Concentrations for Persons With Wild-Type HIV-1 *[275-277, 279]*

Drug	Concentration (ng/mL)
Amprenavir (AGENERASE) or Fosamprenavir (LEXIVA)	400 (measured as amprenavir concentration)
Atazanavir (REYATAZ)	150
Indinavir (CRIXIVAN)	100
Lopinavir/ritonavir (KALETRA)	1,000
Nelfinavir (VIRACEPT) [a]	800
Ritonavir (NORVIR) [b]	2100
Saquinavir (INVIRASE)	100–250
Efavirenz (SUSTIVA)	1,000

a. Measurable active (M8) metabolite.
b. Ritonavir given as a single PI.

Table 24. Associated Signs and Symptoms of Acute Retroviral Syndrome and Percentage of Expected Frequency *[294]*

- Fever 96%
- Lymphadenopathy 74%
- Pharyngitis 70%
- Rash 70%
  - ✓ Erythematous maculopapular with lesions on face trunk and sometimes extremities (including palms and soles).
  - ✓ Mucocutaneous ulceration involving mouth, esophagus, or genitals.
- Myalgia or arthralgia 54%
- Diarrhea 32%
- Headache 32%
- Nausea and vomiting 27%
- Hepatosplenomegaly 14%
- Weight Loss 13%
- Thrush 12%
- Neurologic symptoms 12%
  - ✓ Meningoencephalitis or aseptic meningitis
  - ✓ Peripheral neuropathy or radiculopathy
  - ✓ Facial palsy
  - ✓ Guillain-Barré syndrome
  - ✓ Brachial neuritis
  - ✓ Cognitive impairment or psychosis

Table 25. Preclinical and Clinical Data Relevant to the Use of Antiretrovirals in Pregnancy

*(See **Safety and Toxicity of Individual Antiretroviral Drugs in Pregnancy** for more detail on drugs. Table adopted from Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States.)*

Antiretroviral drug	FDA pregnancy category †	Placental passage (newborn: mother drug ratio)	Long-term animal carcinogenicity studies	Animal teratogen studies
Nucleoside and nucleotide analogue reverse transcriptase inhibitors				
Abacavir (Ziagen, ABC)	C	Yes (rats)	Positive (malignant and nonmalignant tumors of liver, thyroid in female rats, and preputial and clitoral gland of mice and rats)	Positive (rodent anasarca and skeletal malformations at 1,000mg/kg (35x human exposure) during organogenesis; not seen in rabbits)
Didanosine (Videx, ddI)	B	Yes (human) [0.5]	Negative (no tumors, lifetime rodent study)	Negative
Emtricitabine (Emtriva, FTC)	B	Yes (mice and rabbits) [0.4–0.5]	Negative (no tumors, lifetime rodent study)	Negative
Lamivudine (Epivir, 3TC)	C	Yes (human) [~1.0]	Negative (no tumors, lifetime rodent study)	Negative
Stavudine (Zerit, d4T)	C	Yes (rhesus monkey) [0.76]	Positive (mice and rats, at very high dose exposure, liver and bladder tumors)	Negative (but sternal bone calcium decreases in rodents)
Tenofovir DF (Viread)	B	Yes (human) [0.95–0.99]	Positive (hepatic adenomas in female mice at high doses)	Negative (osteomalacia when given to juvenile animals at high doses)
Zidovudine† (Retrovir, AZT, ZDV)	C	Yes (human) [0.85]	Positive (rodent, noninvasive vaginal epithelial tumors)	Positive (rodent-near lethal dose)
Non-nucleoside reverse transcriptase inhibitors				
Delavirdine (Rescriptor)	C	Unknown	Positive (hepatocellular adenomas and carcinomas in male and female mice but not rats, bladder tumors in male mice)	Positive (rodent-ventricular septal defect)
Efavirenz (Sustiva)	D	Yes (cynomologus monkey, rat, rabbit) [~1.0]	Positive (hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas in female but not male mice)	Positive (cynomologus monkey-anencephaly, anophthalmia, microophthalmia)
Nevirapine (Viramune)	B	Yes (human) [~1.0]	Positive (hepatocellular adenomas and carcinomas in mice and rats)	Negative
Protease inhibitors				
Amprenavir (Agenerase)*	C	Minimal/variable (human)	Positive (hepatocellular adenomas and carcinomas in male mice and rats)	Negative (but deficient ossification and thymic elongation in rats and rabbits)
Atazanavir	B	Minimal/variable (human)	Positive (hepatocellular adenomas in female mice)	Negative
Darunavir (Prezista)	B	Unknown	Not completed	Negative
Fosamprenavir (Lexiva)	C	Unknown	Positive (benign and malignant liver tumors in male rodents)	Negative (deficient ossification with amprenavir but not fosamprenavir)
Indinavir (Crixivan)	C	Minimal (human)	Positive (thyroid adenomas in male rats at highest dose)	Negative (but extra ribs in rodents)
Lopinavir/Ritonavir (Kaletra)	C	Yes (human) [0.20 +/- 0.13]	Positive (hepatocellular adenomas and carcinomas in mice and rats)	Negative (but delayed skeletal ossification and increase in skeletal variations in rats at maternally toxic doses)
Nelfinavir (Viracept)	B	Minimal/variable (human)	Positive (thyroid follicular adenomas and carcinomas in rats)	Negative
Ritonavir (Norvir)	B	Minimal (human)	Positive (liver adenomas and carcinomas in male mice)	Negative (but cryptorchidism in rodents)
Saquinavir (Fortovase)	B	Minimal (human)	Negative	Negative
Tipranavir (Aptivus)	C	Unknown	In progress	Negative (decreased ossification and pup weights in rats at maternally toxic doses)
Entry inhibitors				
Enfuvirtide (Fuzeon)	B	Unknown	Not done	Negative
Maraviroc (Selzentry)	B	Unknown	Negative	Negative

* No longer available in the United States.

† Food and Drug Administration Pregnancy Categories:
A - Adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and no evidence exists of risk during later trimesters).
B - Animal reproduction studies fail to demonstrate a risk to the fetus, and adequate but well-controlled studies of pregnant women have not been conducted.

C - Safety in human pregnancy has not been determined; animal studies are either positive for fetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the fetus.
D - Positive evidence of human fetal risk that is based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug among pregnant women might be acceptable despite its potential risks.
X - Studies among animals or reports of adverse reactions have indicated that the risk associated with the use of the drug for pregnant women clearly outweighs any possible benefit.

Table 26. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

(See *also "Safety and Toxicity of Individual Antiretroviral Drugs in Pregnancy" for additional toxicity data. Table adopted from "Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States". Please see this document for detailed guidelines on treatment options.*)

Antiretroviral Drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Rationale for Recommended Use in Pregnancy
NRTIs/ NtRTIs		See text for discussion of potential maternal and infant mitochondrial toxicity.	NRTIs are recommended for use as part of combination regimens, usually including two NRTIs with either an NNRTI or one or more PIs. Use of single or dual NRTIs alone is not recommended for treatment of HIV infection (ZDV alone may be considered for prophylaxis of perinatal transmission in pregnant women with HIV RNA <1,000 copies/mL).
Recommended agents			
Zidovudine*	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated *[364]*	No evidence of human teratogenicity *[127]*. Well-tolerated, short-term safety demonstrated for mother and infant.	Preferred NRTI for use in combination antiretroviral regimens in pregnancy based on efficacy studies and extensive experience; should be included in regimen unless significant toxicity or stavudine use.
Lamivudine*	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated *[365]*	No evidence of human teratogenicity *[127]*. Well-tolerated, short-term safety demonstrated for mother and infant.	Because of extensive experience with lamivudine in pregnancy in combination with zidovudine, lamivudine plus zidovudine is the recommended dual NRTI backbone for pregnant women.
Alternate agents			
Didanosine	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated *[366]*.	Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving didanosine and stavudine together *[367, 368]*.	Alternate NRTI for dual nucleoside backbone of combination regimens. Didanosine should be used with stavudine only if no other alternatives are available.
Emtricitabine†	No pharmacokinetic studies in human pregnancy.	No studies in human pregnancy.	Alternate NRTI for dual nucleoside backbone of combination regimens.
Stavudine	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated *[369]*.	No evidence of human teratogenicity *[370]*. Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving didanosine and stavudine together *[367, 368]*.	Alternate NRTI for dual nucleoside backbone of combination regimens. Stavudine should be used with didanosine only if no other alternatives are available. Do not use with zidovudine due to potential for antagonism.
Abacavir*	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.	Hypersensitivity reactions occur in ~5%–8% of nonpregnant persons; a much smaller percentage are fatal and are usually associated with rechallenge. Rate in pregnancy unknown. Patient should be educated regarding symptoms of hypersensitivity reaction.	Alternate NRTI for dual nucleoside backbone of combination regimens. See footnote regarding use in triple NRTI regimen.#
Insufficient data to recommend use			
Tenofovir†	Limited studies in human pregnancy; data indicate AUC lower in third trimester than postpartum but trough levels similar. Phase I study in late pregnancy in progress.	Studies in monkeys show decreased fetal growth and reduction in fetal bone porosity within 2 months of starting maternal therapy *[371]*. Clinical studies in humans (particularly children) show bone demineralization with chronic use; clinical significance unknown *[252, 372]*. Significant placental passage in humans (cord:maternal blood ratio ~1.0).	Because of lack of data on use in human pregnancy and concern regarding potential fetal bone effects, tenofovir should be used as a component of a maternal combination regimen only after careful consideration of alternatives.
Not recommended			
Zalcitabine *(no longer available in the United States.)*	No studies in human pregnancy.	Rodent studies indicate potential for teratogenicity and developmental toxicity.	Given lack of data and concerns regarding teratogenicity in animals, not recommended for use in human pregnancy unless alternatives are not available.

Table 26. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Antiretroviral Drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Rationale for Recommended Use in Pregnancy
NNRTIs		Hypersensitivity reactions, including hepatic toxicity, and rash more common in women, unclear if increased in pregnancy	NNRTIs are recommended for use in combination regimens with 2 NRTI drugs.
Recommended agents			
Nevirapine	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated *[373, 374]*.	No evidence of human teratogenicity *[127]*. Increased risk of symptomatic, often rash-associated, and potentially fatal liver toxicity among women with CD4 counts >250/mm^3 when first initiating therapy *[128, 196]*; unclear if pregnancy increases risk.	Nevirapine should be initiated in pregnant women with CD4 counts >250 cells/mm^3 only if benefit clearly outweighs risk, due to the increased risk of potentially life-threatening hepatotoxicity in women with high CD4 counts. Women who enter pregnancy on nevirapine regimens and are tolerating them well may continue therapy, regardless of CD4 count.
Not recommended			
Efavirenz†	No studies in human pregnancy.	FDA Pregnancy Class D; significant malformations (anencephaly, anophthalmia, cleft palate) were observed in 3 (15%) of 20 infants born to cynomolgus monkeys receiving efavirenz during the first trimester at a dose giving plasma levels comparable to systemic human therapeutic exposure; there are three case reports of neural tube defects in humans after first trimester exposure *[126, 127, 375]*, relative risk unclear.	Use of efavirenz should be avoided in the first trimester, and women of childbearing potential must be counseled regarding risks and avoidance of pregnancy. Because of the known failure rates of contraception, alternate regimens should be strongly considered in women of childbearing potential. Use after the second trimester of pregnancy can be considered if other alternatives are not available and if adequate contraception can be assured postpartum.
Delavirdine	No pharmacokinetic studies in human pregnancy.	Rodent studies indicate potential for carcinogenicity and teratogenicity (see **Table 25**).	Given lack of data and concerns regarding teratogenicity in animals, not recommended for use in human pregnancy unless alternatives are not available.
Protease inhibitors		Hyperglycemia, new onset or exacerbation of diabetes mellitus, and diabetic ketoacidosis reported with PI use; unclear if pregnancy increases risk. Conflicting data regarding preterm delivery in women receiving PIs (see text).	PIs are recommended for use in combination regimens with 2 NRTI drugs.
Recommended agents			
Lopinavir/ ritonavir	Pharmacokinetic studies of standard dose of lopinavir/ritonavir capsules (3 capsules twice daily) during 3rd trimester indicated levels were significantly lower than during postpartum period and in nonpregnant adults *[140]*; an increased dose of 4 capsules of lopinavir/ritonavir twice daily starting in the 3rd trimester resulted in adequate lopinavir exposure *[376]*; by 2 weeks postpartum, standard dosing was again appropriate. Pharmacokinetic studies of the new lopinavir/ritonavir tablet formulation are under way, but data are not yet available.	No evidence of human teratogenicity *[127]*. Well-tolerated, short-term safety demonstrated in Phase I/II studies.	The capsule formulation is no longer available. Pharmacokinetic studies of the new tablet formulation are under way, but there are currently insufficient data to make a definitive recommendation regarding dosing in pregnancy. Some experts would administer standard dosing (2 tablets twice daily) throughout pregnancy and monitor virologic response and lopinavir drug levels, if available. Other experts, extrapolating from the capsule formulation pharmacokinetic data, would increase the dose of the tablet formulation during the 3rd trimester (from 2 tablets to 3 tablets twice daily), returning to standard dosing postpartum. Once daily lopinavir/ritonavir dosing is not recommended during pregnancy because there are no data to address whether drug levels are adequate with such administration.

Table 26. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Antiretroviral Drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Rationale for Recommended Use in Pregnancy
Alternate agents			
Indinavir	Two studies including 18 women receiving indinavir 800mg three times daily showed markedly lower levels during pregnancy compared to postpartum, although suppression of HIV RNA was seen *[377, 378]*	Theoretical concern re: increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinemia in the neonate, but minimal placental passage. Use of unboosted indinavir during pregnancy is not recommended.	Alternate PI to consider if unable to use nelfinavir or saquinavir-HGC/ritonavir, but would need to give indinavir as ritonavir-boosted regimen. Optimal dosing for the combination of indinavir/ritonavir in pregnancy is unknown.
Ritonavir	Phase I/II study in pregnancy showed lower levels during pregnancy compared to postpartum *[379]*	Limited experience at full dose in human pregnancy; has been used as low-dose ritonavir boosting with other PIs.	Given low levels in pregnant women when used alone, recommended for use in combination with second PI as low-dose ritonavir "boost" to increase levels of second PI.
Saquinavir-hard gel capsule [HGC] (Invirase®)/ ritonavir	Pharmaockinetic studies of saquinavir-soft gel capsules (SGC) indicated that inadequate drug levels were observed in pregnant women given 1,200mg of saquinavir-SGC as a sole PI three times daily *[380, 381]* , but adequate levels were achieved when 800mg saquinavir-SGC boosted with ritonavir 100mg was given twice daily *[382]*. However, saquinavir-SGC are no longer produced. Limited pharmacokinetic data on saquinavir-hard gel capsule (HGC), and the new 500mg tablet formulation, suggest that 1,000mg saquinavir-HGC/100mg ritonavir given twice daily achieves adequate saquinavir drug levels in pregnant women *[383]*.	Well-tolerated, short-term safety demonstrated for mother and infant for both saquinavir-SGC and -HGC in combination with low-dose ritonavir.	Saquinavir-SGC are no longer available. There are only limited pharmacokinetic data on saquinavir-HGC and the new tablet formulation in pregnancy. Ritonavir-boosted saquinavir-HGC or saquinavir tablets are alternative PIs for combination regimens in pregnancy, and are alternative initial antiretroviral recommendations for nonpregnant adults.
Insufficient data to recommend use			
Amprenavir *(no longer available in the United States.)*	Limited studies in human pregnancy.	Oral solution contraindicated in pregnant women because of high levels of propylene glycol, which may not be adequately metabolized during pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use of capsules during pregnancy.
Atazanavir	Limited studies in small number of pregnant women atazanavir (N=33) and atazanavir-ritonavir (N=9) suggest standard dosing achieves adequate drug levels *[384, 385]*.	Theoretical concern re: increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinemia in the neonate, although transplacental passage is very low and likely to be variable (10%).	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.
Darunavir	No pharmacokinetic studies in human pregnancy.	No experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.
Fosamprenavir	No pharmacokinetic studies in human pregnancy.	Limited experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.
Tipranavir	No pharmacokinetic studies in human pregnancy.	No experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.

Table 26. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy

Antiretroviral Drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Rationale for Recommended Use in Pregnancy
Not Recommended			
Nelfinavir	Adequate drug levels are achieved in pregnant women with nelfinavir 1,250mg given twice daily although levels are variable in late pregnancy *[148, 386]*. In a similar study of pregnant women in their second and third trimester dosed at 1,250mg given twice daily, women in the third trimester had lower concentration of nelfinavir than women in their second trimester *[387]*. In a study of the new 625mg tablet formulation dosed at 1,250mg twice daily, lower AUC and peak levels were observed during the third trimester of pregnancy than postpartum *[388]*.	In September 2007, the manufacturer (Pfizer) sent a letter to providers regarding the presence of low levels of ethyl methane sulfonate (EMS), a process-related impurity, in nelfinavir. EMS is teratogenic, mutagenic, and carcinogenic in animals, although no data from humans exists and no increase in birth defects has been observed in the Antiretroviral Pregnancy Registry.	Not currently recommended to be used in pregnancy until further notice unless no alternative is available (see text, **Recommendations for Use of Antiretroviral Drugs in Pregnancy**).
Entry Inhibitors			
Insufficient data to recommend use			
Enfuvirtide	No pharmacokinetic studies in human pregnancy.	Minimal data in human pregnancy *[389]*.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.
Maraviroc	No pharmacokinetic studies in human pregnancy.	No experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.

HGC = hard gel capsule; NRTI = nucleoside reverse transcriptase inhibitor; NtRTI = nucleotide reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; SGC = soft gel capsule.

* Zidovudine and lamivudine are included as a fixed-dose combination in Combivir®; zidovudine, lamivudine, and abacavir are included as a fixed-dose combination in Trizivir®.

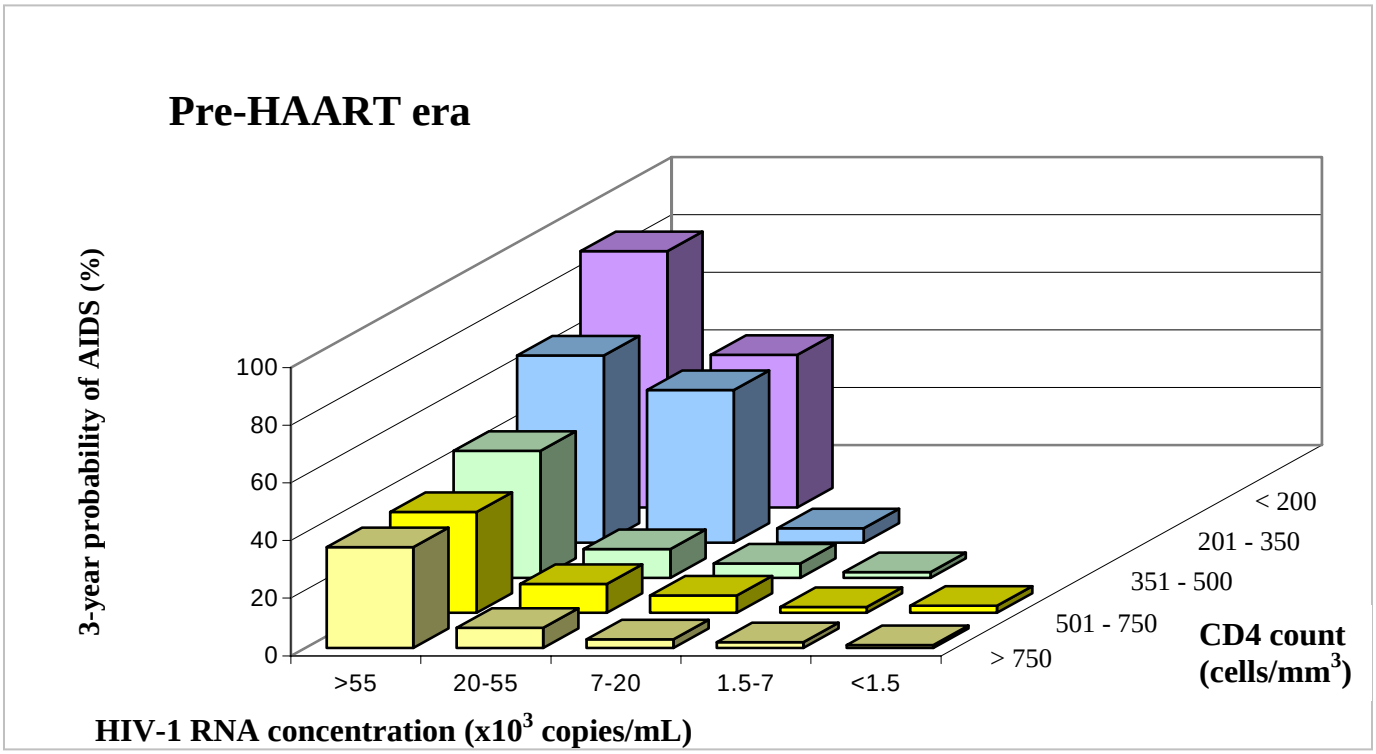
† Emtricitabine and tenofovir are included as a fixed-dose combination in Truvada®; emtricitabine, tenofovir, and efavirenz are included as a fixed-dose combination in Atripla™.

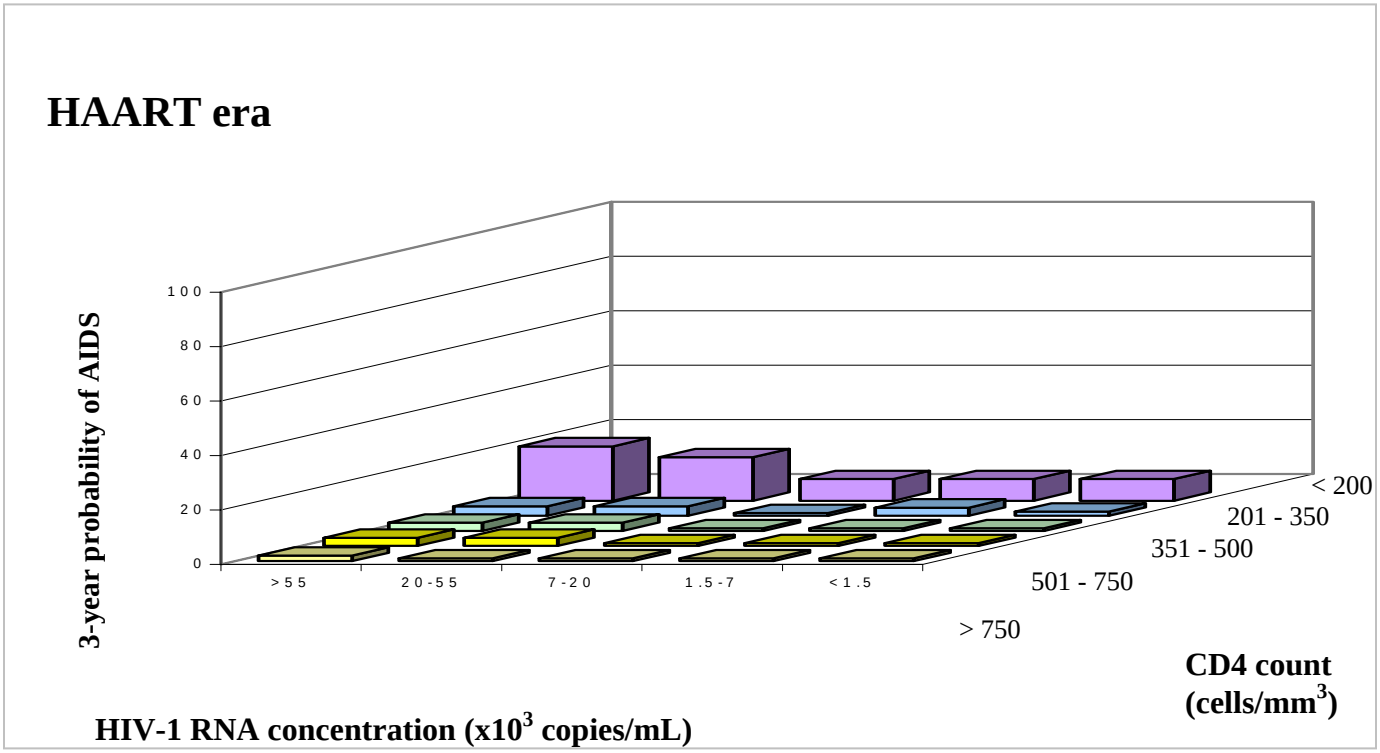
\# Triple NRTI regimens including abacavir have been less potent virologically compared to PI-based HAART regimens. Triple NRTI regimens should be used only when an NNRTI- or PI-based HAART regimen cannot be used (e.g., due to significant drug interactions). A study evaluating use of zidovudine/lamivudine/abacavir among pregnant women with HIV RNA <55,000 copies/mL as a class-sparing regimen is in development.

Table 27. Antiretroviral Agents Available Through Expanded Access Program (EAP)

Drug	**TMC-125 (etravirine)**
Source	1-866-889-2074 TMC125EAP@i3research.com **http://www.tibotec.com/**
Class	Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)
Dose	TMC-125 200mg twice daily + optimized background therapy (based on prior history and resistance testing)
Enrollment Criteria	Inclusion Criteria: • ≥18 years old • Limited or no treatment options because of virologic failure or intolerance to multiple antiretroviral regimens • Unable to use currently approved NNRTIs because of resistance and/or intolerance • Have received licensed oral therapy with each of the three major classes (PI, NRTIs, and NNRTI) of antiretrovirals • Have received two different PI-based regimens in the past • Primary NNRTI resistance can be included if experienced with at least two classes of antiretrovirals (PI, NRTI). • Have not participated in TMC-125 trials

Figure A: Prognosis According to CD4 Cell Count and Viral Load in the Pre-HAART and HAART Eras





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Appendix A: Financial Disclosure for Members of the DHHS Panel on Antiretroviral Guidelines for Adult and Adolescents (A Working Group of OARAC) – February 2007

[Note: The Financial Disclosure for Panel Members will be updated after February 2008. The new disclosure listing will be posted on the **http://aidsinfo.nih.gov** Web site.]

Name	Panel Status*	Company	Relationship
Jean R. Anderson	M	Abbott Laboratories Glaxo Smith Kline Pfizer	• Speakers Bureau • Speakers Bureau • Advisory Board; Grant recipient; Speakers Bureau; Stock Holder.
A. Cornelius Baker	M	Gilead Sciences Glaxo Smith Kline	• Travel support for international AIDS conference and company presentation • Honoraria
John G. Bartlett	C	Abbott Laboratories Bristol Myers Squibb Gilead Sciences Glaxo Smith Kline Pfizer Tibotec	• Advisory Board; Honoraria • Advisory Board • Grant recipient • Advisory Board • Advisory Board • DSMB Member
Victoria Cargill-Swiren	M	None	N/A
Charles Carpenter	M	Bristol Myers Squibb	• Consultant
Laura W. Cheever	M	None	N/A
Judith Currier	M	Abbott Laboratories Achillon Pharmaceuticals Boehringer-Ingelheim Bristol Myers Squibb Gilead Sciences Glaxo Smith Kline Merck Schering Plough Theratechnologies Tibotec Vertex	• Advisory Board; Grant recipient • DSMB Member • Advisory Board (2005) • Advisory Board • Advisory Board, DSMB member • Advisory Board; Grant recipient • Advisory Board; Grant recipient • Grant Recipient • Grant Recipient • Advisory Board; Grant recipient; Consultant • Grant Recipient
Paul Dalton	M	Napo Pfizer Tibotec	• Advisory Board • Advisory Board • Consultant
Steven G. Deeks	M	Bristol Myers Squibb Gilead Sciences Glaxo Smith Kline Monogram	• Consultant • Honoraria • Consultant

Name	Panel Status*	Company	Relationship
		Pfizer Roche Tibotec Trimeris	• Consultant • DSMB Member • Grant recipient; Consultant • Consultant • Consultant
Carlos del Rio	M	Abbott Bristol Myers Squibb Gilead Sciences Glaxo Smith Kline Merck & Co. Pfizer Tibotec	• Honoraria • Consultant • Research support • Research support • Research support • Research support • Research support
Wafaa El-Sadr	M	None	N/A
Courtney V. Fletcher	M	Bristol Myers Squibb Glaxo Smith Kline Tibotec	• Ad-hoc advisory board • Ad-hoc advisory board • Ad-hoc advisory board
Joel E. Gallant	M	Abbott Laboratories Boehringer-Ingelheim Bristol Myers Squibb Gilead Sciences Glaxo Smith Kline Merck Monogram Biosciences Panacos Pfizer Roche Tibotec	• Honoraria • Grant recipient • Advisory Board • Advisory Board; Grant recipient; Honoraria • Advisory Board; Grant recipient • Advisory Board; Grant recipient • Advisory Board • Advisory Board • Advisory Board; Grant recipient • Grant recipient; Honoraria • Advisory Board; Grant recipient
Eric P. Goosby	M	Abbott Pharmaceuticals Chevron Corporation Gilead Sciences Pfizer Pharmaceuticals	• Grant recipient • Grant recipient • Grant recipient; Speakers Bureau; Consultant • Grant recipient
Roy M. Gulick	M	Abbott Laboratories Bristol Myers Squibb Gilead Sciences Glaxo Smith Kline Merck Monogram Panacos Pfizer Roche-Trimeris Schering-Plough Tibotec	• Consultant • Consultant • Grant recipient; Consultant • Consultant • Grant recipient • Honoraria; Consultant • Grant recipient • Grant recipient; Consultant • Consultant • Grant recipient; Consultant • Grant recipient; Consultant

Name	Panel Status*	Company	Relationship
Mark Harrington	M	None	N/A
W. Keith Henry	M	Bristol Myers Squibb Gilead Sciences Glaxo Smith Kline Pfizer Roche Serono Theratechnologies	• Research Support; Speakers Bureau; Honoraria; Consultant • Speakers Bureau; Honoraria; Consultant • Research Support; Advisory Board; Speakers Bureau; Honoraria; Consultant • Research Support; Honoraria • Speakers Bureau; Honoraria • Research Support • Research Support
Martin S. Hirsch	M	Merck Schering Plough Tibotec	• DSMB member • Consultant • Consultant
Morris Jackson	M	Abbott Laboratories Glaxo Smith Kline	• National Advocate Summit • Summer Summit 2004
Wilbert Jordan	M	Abbott Laboratories Bristol Myers Squibb Gilead Sciences Glaxo Smith Kline Pfizer Roche Serono Tibotec	• Advisory Board; Grant recipient; Speakers Bureau; Honoraria • Advisory Board; Speakers Bureau; Honoraria; Consultant • Advisory Board; Grant recipient; Speakers Bureau; Honoraria • Advisory Board; Grant recipient; Speakers Bureau; Honoraria • Advisory Board; Grant recipient; Speakers Bureau; Honoraria • Grant recipient; Speakers Bureau; Honoraria • Speakers Bureau; Honoraria • Advisory Board; Speakers Bureau; Honoraria
Jonathan E. Kaplan	M	None	N/A
H. Clifford Lane	C	Novartis	• NIH patent on aldesleukin licensed to Novartis; CRADA with Novartis
Henry Masur	M	None	N/A
John W. Mellors	M	Abbott Laboratories Achillon Boehringer Ingelheim Gilead Sciences Glaxo Smith Kline Merck Pfizer Pharmasset Trimeris	• Scientific Advisory Board • Stock Option • Scientific Advisory Board • Scientific Advisory Board • Scientific Advisory Board • Scientific Advisory Board • Scientific Advisory Board • Stock Option • Scientific Advisory Board

Name	Panel Status*	Company	Relationship
Lynne Mofenson	M	None	N/A
Jeff Murray	M	None	N/A
Heidi M. Nass	M	Tibotec	• Advisory Board
James Neaton	M	Amgen Bristol Myers Squibb Chiron/Novartis Merck	• DSMB member (Not HIV-related) • DSMB member (Not HIV-related) • Grant recipient • DSMB member; Consultant (Not HIV-related)
James Oleske	M	None	N/A
Alice Pau	ES	None	N/A
Michael Saag	M	Achillion Pharmaceutica Avexa Boehringer-Ingelheim Bristol Myers Squibb Gilead Sciences Glaxo Smith Kline Merck Monogram Biosciences Panacos Pfizer/Agouron Progenics Roche Laboratories Serono Tanox Tibotec Tibotec/Virco Trimeris Vertex	• Grant/Research Support; Consultant; Speakers Bureau • Consultant; Speakers Bureau • Grant/Research Support; Consultant; Speakers Bureau • Consultant; Speakers Bureau • Grant/Research Support; Consultant; Speakers Bureau • Grant/Research Support; Consultant; Speakers Bureau • Grant/Research Support; Consultant; Speakers Bureau • Consultant; Speakers Bureau • Grant/Research Support; Consultant; Speakers Bureau • Grant/Research Support; Consultant; Speakers Bureau • Grant/Research Support; Consultant; Speakers Bureau • Grant/Research Support; Consultant; Speakers Bureau • Grant/Research Support; Speakers Bureau • Consultant; Speakers Bureau • Grant/Research Support; Speakers Bureau • Consultant; Speakers Bureau • Grant/Research Support; Consultant; Speakers Bureau • Grant/Research Support; Consultant; Speakers Bureau
Renslow Sherer	M	Abbott Laboratories Glaxo Smith Kline Johnson & Johnson Pfizer Tibotec	• Advisory Board; Grant Recipient; Speakers Bureau; Honoraria • Advisory Board; Honoraria • Grant Recipient • Grant Recepient • Advisory Board; Honoraria
Kimberly Struble	M	None	N/A

Name	Panel Status*	Company	Relationship
Paul Volberding	M	Bristol Myers Squibb Gilead Sciences Glaxo Smith Kline Merck Pfizer Schering	• Advisory Board • Advisory Board; Honoraria • Advisory Board • Advisory Board • Advisory Board • Advisory Board; Endpoints Adjudication Cmte.
Sue Willard	M	Abbott Laboratories Boehringer-Ingelheim	• Advisory Board; Speakers Bureau; Honoraria • Advisory Board; Grant recipient; Honoraria

- C = Co-Chair; ES = Executive Secretary; M = member

DSMB = Data Safety Monitoring Board; N/A = not applicable