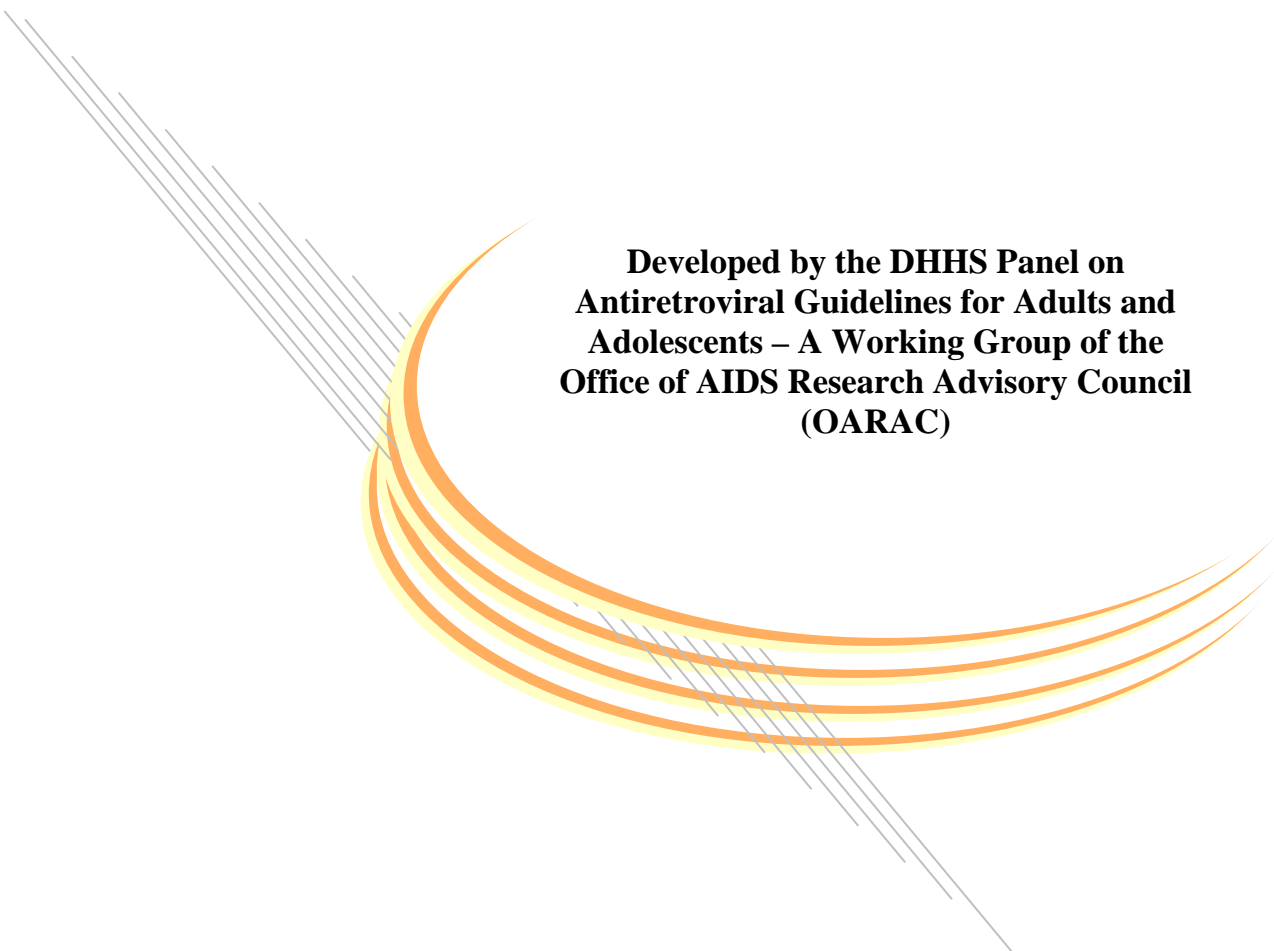# Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

October 10, 2006

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 *AIDSinfo* Web site (**http://*AIDSinfo*.nih.gov**).

What's New in the Document?

The following changes have been made to the May 4, 2006 version of the guidelines:

What to Start Recommendations

- The Panel confirms that the regimens with the most experience in demonstrating virologic and immunologic efficacy are those composed of 1 NNRTI + 2 NRTI or of a PI (with or without ritonavir boosting) + 2 NRTI. The Panel also confirms that selection of an antiretroviral regimen should be individualized based on patient- and drug-specific factors.

- The Panel revised its recommendations for preferred and alternative antiretroviral components based on reported results from several randomized trials in treatment-naïve patients and on safety data that have emerged since the last revision. Specific recommendations can be found in Tables 6a and 6b. Rationale for the recommendations is outlined in the text.

- The revised recommendations for antiretroviral-naïve patients are summarized below. Clinicians are recommended to construct a regimen by choosing one component from Column A + one component from Column B.

	Column A		Column B
	NNRTI	PI	2-NRTI
Preferred (alphabetical order)	Efavirenz **(AII)**	Atazanavir + ritonavir **(AIII)** Fosamprenavir + ritonavir BID **(AII)** Lopinavir/ritonavir BID **(AII)**	Tenofovir/emtricitabine **(AII)** Zidovudine/lamivudine **(AII)**
Alternative (alphabetical order)	Nevirapine **(BII)**	Atazanavir (unboosted) **(BII)** Fosamprenavir (unboosted) **(BII)** Fosamprenavir + ritonavir once daily **(BII)** Lopinavir/ritonavir once daily **(BII)**	Abacavir/lamivudine **(BII)** Didanosine + lamivudine **(BII)**

- Several options are considered acceptable as initial components but, in the view of the Panel, are inferior to the preferred or alternative components; however, they may be preferred in selected settings. These options include nelfinavir, ritonavir-boosted saquinavir, stavudine + lamivudine, and a triple-NRTI regimen containing abacavir + zidovudine + lamivudine.

The following tables have been updated:

- Table 6 has been revised and divided into Tables 6a and 6b to reflect the above revisions.
- Tables 7 and 9 have been updated to reflect changes in the recommendations.
- Table 10 has been updated with results from several recently published clinical trials.
- Tables 11-13, 15, and 17-19 have been updated to include information regarding darunavir and the fixed-dose combination of efavirenz/emtricitabine/ tenofovir (Atripla™) and new safety information and black box warnings regarding rare cases of intracranial hemorrhages occurring in patients receiving tipranavir.
- Tables 20-22b have been updated to include darunavir drug-drug interactions.
- Tables 28 and 29 have been revised according to updates in the Perinatal Guidelines to incorporate preclinical and clinical data relevant to the use of darunavir during pregnancy and new recommendations on antiretroviral use during pregnancy.
- Table 30 has been updated to include information on expanded access programs for two investigational agents, TMC125 and MK-0518.

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The Panel would also like to acknowledge the following individuals for their assistance in the review and preparation of this document:
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Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

Introduction

Antiretroviral therapy 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, offering added dosing convenience and improved safety profiles, while 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. 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:

- *When should therapy be started in patients with established asymptomatic infection?* The Panel reaffirms the desirability of initiating therapy before the CD4 cell count falls below 200 cells/mm^3. In addition, there are inconsistent data documenting added value in treating before the count falls below 350 cell/mm^3, but some clinicians opt to consider treatment in patients with CD4 count >350 cell/mm^3 and HIV RNA >100,000 copies/mL. A review of the literature on this issue can be seen in the **When to Treat: Indications for Antiretroviral Therapy** section.

- *Which regimens are preferred for initial therapy?* The Panel continues to select several regimens as preferred, while appreciating that patient or provider preferences, or underlying co-morbidities, may make an alternative regimen better in such instances. The Panel recommends that an initial regimen contain two nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) and either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a ritonavir-boosted or unboosted protease inhibitor (PI).

- *What drugs or drug combinations should not be used?* The Panel notes that certain drugs are so similar, for example, lamivudine and emtricitabine, that they should not be combined. Others have additive or synergistic toxicity, such as stavudine with didanosine, and should generally be avoided. Still others have intracellular interactions that decrease their antiviral activities, notably zidovudine with stavudine, and should thus be avoided.

- *What are some limitations to the safety and efficacy of antiretroviral therapy?* The Panel notes the high degree of medication adherence with all ARV regimens needed to prevent the selection of drug resistance. It also appreciates that short term and, even more concerning, longer term toxicity may limit the duration of treatment needed in what can be seen as a chronic disease. Finally, drug interactions among the antiretroviral drugs and with other necessary drugs are challenging and require special attention in prescribing and monitoring.

- *What is the role of resistance testing in guiding therapy decisions?* Resistance testing continues to be an important component of optimizing drug selection after treatment failure. Transmission of drug-resistant HIV strains has been well

documented and has been associated with suboptimal virologic response to initial antiretroviral therapy in some patients. Therefore, the Panel also recommends performance of drug resistance testing prior to initiation of therapy in treatment-naïve patients.

- *What are the goals of therapy in treatment-experienced patients?* When possible, suppression of viremia to less than detection limits remains the goal of therapy. When this is not possible, the Panel recommends maintenance of even partial viremic suppression by selection of an optimal regimen based on resistance testing results. Either way, the ultimate goals are to prevent further immune deterioration and to avoid HIV-associated morbidity and mortality. The Panel recommends against complete antiretroviral cessation in late failure as this has resulted in rapid progression to AIDS and death.

- *Are there special populations which may require specific considerations when using antiretroviral therapy?* The Panel recognizes that there are subgroups of patients where specific considerations are critical when selecting and monitoring antiretroviral therapy, in order to assure safe and effective treatment. The Panel addresses some important antiretroviral related issues for these special populations, which include patients with acute HIV infection, HIV-infected adolescents, injection drug users, women of child bearing potential and pregnant women, and those with hepatitis B, hepatitis C, or tuberculosis co-infections.

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 *AIDSinfo* 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 in 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 HIV-infected patients and preferably at least 50 HIV-infected patients. Many authoritative groups have combined the recommendation based on active patients, along with fulfilling ongoing CME requirements on HIV-related topics.

BASIC EVALUATION

Pretreatment 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 co-infections, 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:

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 prior to initiation of therapy (***BIII***); if therapy is to be deferred, resistance testing may still be considered **(CIII).** (See **Utilization of Drug Resistance Testing in Clinical Practice** section.)

- In addition:
- An optional test for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in order to identify high risk behavior and the need for STD therapy **(BII)**; and
- 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, co-morbidities, 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.

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 (or viral load).

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 percentage point change in CD4 percentage.

- **Use of CD4$^+$ T Cell Count for Initial Assessment**. The CD4$^+$ 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 cell count are found in the **When to Treat: 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 three to six months to (1) determine when to start antiretroviral 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. 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 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 with over 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 non-adherence, 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**).

UTILIZATION OF DRUG RESISTANCE TESTING IN CLINICAL PRACTICE

Panel's Recommendations:
- *HIV drug resistance testing is recommended for persons with acute HIV infection if the decision is made to initiate therapy at this time (**BIII**). If therapy is deferred, resistance testing at this time should still be considered (**CIII**).*
- *Drug resistance testing is also recommended for persons with chronic HIV infection prior to initiation of therapy (**BIII**). Earlier testing may be considered (**CIII**).*
- *A genotypic assay is generally preferred for antiretroviral-naïve persons (**BIII**).*
- *HIV drug resistance testing should be performed to assist in selecting active drugs when changing antiretroviral regimens in cases of virologic failure (**BII**).*
- *Drug resistance testing should also be considered when managing suboptimal viral load reduction (**BIII**).*
- *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 (**BII**).*
- *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 the 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 are selected for by different antiretroviral drugs 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.) (Note
that current commercially available tests do not detect
resistance-associated mutations in the envelope gene.)
Various techniques, such as rules-based algorithms and
Virtual Phenotype, are now available to assist the
provider in interpreting genotypic test results *[9-12]*. The
benefit of consultation with specialists in HIV drug
resistance has been demonstrated in clinical trials *[13]*.
Clinicians are encouraged to consult a specialist in order
to facilitate interpretation of genotypic results to help
design an optimal new regimen.

Phenotypic Assays. Phenotypic assays measure a
virus's ability to grow in different concentrations of
antiretroviral drugs. Automated, recombinant
phenotypic assays are commercially available with
results available in 2-3 weeks. However, phenotypic
assays are more costly to perform than genotypic
assays. Recombinant phenotypic assays involve
insertion of the reverse transcriptase and protease gene
sequences derived from patient plasma HIV RNA 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.
Drug concentrations that inhibit 50% and 90% of viral
replication (i.e., the median inhibitory concentration
[IC] IC_{50} and IC_{90}) are 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).
Interpretation of phenotypic assay results is
complicated by the paucity of data 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 *[14-16]*. Again, consultation with a
specialist can be helpful for interpreting test results.

Further limitations of both genotypic and phenotypic
assays include the 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 is often observed,
resulting in a decrease of the proportion of virus with
resistance mutations to below these thresholds *[17-19]*.
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,
in which it can be demonstrated that the virus present
at failure is derived from previously archived resistant
virus *[20]*. Therefore, resistance testing is of greatest
value when performed before or within 4 weeks after
drugs are discontinued **(BII)**. Since detectable resistant
virus may persist in the plasma of some patients for
longer periods of time, resistance testing beyond 4-6
weeks post-discontinuation may provide valuable
information. Yet, the absence of detectable resistance
in such patients must be interpreted with caution in
designing subsequent antiretroviral regimens.

Using 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, since 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 *[21-23]*. 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% *[24-27]*, with 3%–5% of transmitted viruses
exhibiting reduced susceptibility to drugs from more than
one class *[21, 27]* 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 **(BIII)**. Because of its more rapid
turnaround time, a genotypic assay is generally preferred
(BIII). 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 considered (**CIII**). However, the genotypic resistance test result may need to be kept on record for several years before it becomes clinically useful.

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 [28, 29]. 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 [22, 23, 30-33]. In addition, a cost-effectiveness analysis of early genotypic resistance testing suggests that baseline testing in this population should be performed [34]. Therefore, resistance testing prior to initiation of therapy in chronically infected persons is recommended (**BIII**). Genotypic testing is generally preferred in this situation (**BIII**). Earlier testing may be considered because of the potentially greater likelihood that transmitted resistance-associated mutations will be detected earlier in the course of HIV infection (**CIII**).

Use of Resistance Assays in 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 are derived from trials in which test utility was assessed for cases of virologic failure. These studies involved genotypic assays, phenotypic assays, or both [9, 13, 35-40]. In general, these studies indicated that the virologic response to therapy was increased when results of resistance testing were available, compared with responses observed when changes in therapy were guided by clinical judgment only. Thus, resistance testing appears to be a useful tool in selecting active drugs when changing antiretroviral regimens in cases of virologic failure, as measured by the early virologic response to the salvage regimen (**BII**). (See **Management of the Treatment-Experienced Patient**.)

Resistance testing can also help guide treatment decisions for patients with suboptimal viral load reduction (**BIII**). Virologic failure in the setting of combination antiretroviral therapy is, for certain patients, associated with resistance to one component of the regimen only [41, 42]. 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 purpose of antiretroviral therapy is to reduce plasma HIV RNA to less than the limit of detection, for the benefit of both mother and child. Genotypic resistance testing is recommended for all pregnant women prior to initiation of therapy and for those entering pregnancy with detectable HIV RNA levels while on therapy. Optimal prevention of perinatal transmission may require initiation of antiretroviral therapy before results of resistance testing are available.

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 [43] and persists with a long half-life, even with prolonged suppression of plasma viremia [44-47]. Therefore, once the decision is made to initiate therapy, the primary goals of antiretroviral therapy are to:

- reduce HIV-related morbidity and mortality,
- improve quality of life,
- restore and preserve immunologic function, and
- maximally and durably suppress viral load.

Adoption of treatment strategies recommended in these guidelines has resulted in substantial reductions in HIV-related morbidity and mortality [32, 48, 49].

Plasma viremia is a strong prognostic indicator of HIV disease progression [50]. Reductions in plasma viremia achieved with antiretroviral therapy account for substantial clinical benefits [51]. Therefore, suppression of plasma viremia as much as possible for as long as possible is a critical goal of antiretroviral therapy. (See **Basic Evaluation: Initial Assessment and Monitoring for Therapeutic Response.**) This goal, however, must be balanced against the need to preserve effective treatment options in patients who do not achieve undetectable viral load because of extensive viral resistance or persistent medication non-adherence.

Viral load reduction to below limits of assay detection in a treatment-naïve patient usually occurs within the first 16-24 weeks of therapy. However, maintenance of excellent treatment response is highly variable. Predictors of long-term virologic success include:

- potency of antiretroviral regimen,
- adherence to treatment regimen *[52, 53]*,
- low baseline viremia,
- higher baseline CD4$^+$ cell count *[52, 53]*, and
- rapid (i.e., ≥ 1 log $_{10}$ in 1-4 months) reduction of viremia in response to treatment *[53]*.

Successful outcomes have not been observed across all patient populations, however. Studies have shown that approximately 70% of patients in urban clinic settings achieve the goal of no detectable virus compared with 80%-90% in many clinical trials *[54]*.

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 Combination Regimen. Several preferred and alternative antiretroviral regimens are recommended for use. (See **What to Start With: 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 with fewer side effects. Individual tailoring is based on such considerations as lifestyle, comorbidities, interactions with other medications, and results of pretreatment genotypic drug resistance testing.

Preservation of Future Treatment Options. Multiple changes in antiretroviral regimens, prompted by virologic failure because of drug resistant virus or patient non-adherence, can rapidly exhaust treatment options. Although these are valid reasons to prompt a change in therapy, they should be carefully considered. (See **Management of the Treatment-Experienced Patient: Assessment of Antiretroviral Treatment Failure and Changing Therapy**.)

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

Drug Sequencing. Appropriate sequencing of drugs for use in initial and subsequent salvage therapy preserves future treatment options and is another tool to maximize benefit from antiretroviral therapy. Currently recommended strategies spare at least two classes of drugs for later use and potentially avoid or delay certain class-specific side effects.

Improving Adherence. The reasons for variability in response to antiretrovirals are complex but may include inadequate adherence because of multiple social issues that confront patients *[55-57]*. Patient factors clearly associated with the risk of decreased adherence—such as active substance abuse, depression, and lack of social support—need to be addressed with patients before initiation of antiretroviral therapy *[58, 59]*. Strategies to improve medication adherence can improve outcomes.

WHEN TO TREAT: Indications for Antiretroviral Therapy

Panel's Recommendations (Table 5):

- *Antiretroviral therapy is recommended for all patients with history of an AIDS-defining illness or severe symptoms of HIV infection regardless of CD4$^+$ T cell count (AI).*
- *Antiretroviral therapy is also recommended for asymptomatic patients with <200 CD4$^+$ T cells/mm^3 (AI).*
- *Asymptomatic patients with CD4$^+$ T cell counts of 201–350 cells/mm^3 should be offered treatment (BII).*
- *For asymptomatic patients with CD4$^+$ T cell of >350 cells/mm^3 and plasma HIV RNA >100,000 copies/mL most experienced clinicians defer therapy but some clinicians may consider initiating treatment (CII).*
- *Therapy should be deferred for patients with CD4$^+$ T cell counts of >350 cells /mm^3 and plasma HIV RNA <100,000 copies/mL (DII).*

The decision to begin therapy for the asymptomatic patient is complex and must be made in the setting of careful patient counseling and education.

Considerations of initiating antiretroviral therapy should be primarily based on the prognosis of disease-free survival as determined by baseline CD4^{+} T cell count *[60-62]* (**Figure A** and **Tables 4a**, **4b**). Also important are baseline viral load *[60-62]*, readiness of the patient to begin therapy; and assessment of potential benefits and risks of initiating therapy for asymptomatic persons, including short-and long-term adverse drug effects; the likelihood, after counseling and education, of adherence to the prescribed treatment regimen.

Recommendations vary according to the CD4 count and viral load of the patient, as follows.

<200 CD4^{+} T cell count, with AIDS-defining illness, or symptomatic. Randomized clinical trials provide strong evidence of improved survival and reduced disease progression by treating symptomatic patients and patients with <200 CD4^{+} T cells/mm^{3} *[63-66]*. Observational cohorts indicate a strong relationship between lower CD4^{+} T cell counts and higher plasma HIV RNA levels in terms of risk for progression to AIDS for untreated persons and antiretroviral-naïve patients beginning treatment. These data provide strong support for the conclusion that therapy should be initiated in patients with CD4^{+} T cell count <200 cells/mm^{3} (**Figure A** and **Table 4a**) **(AI)** *[60, 61]*.

200-350 CD4^{+} T cell count, patient asymptomatic. The optimal time to initiate antiretroviral therapy among asymptomatic patients with CD4^{+} T cell counts >200 cells/mm^{3} is unknown. For these patients, the strength of the recommendation for therapy must balance other considerations, such as patient readiness for treatment and potential drug toxicities.

After considering available data in terms of the relative risk for progression to AIDS at certain CD4^{+} T cell counts and viral loads, and the potential risks and benefits associated with initiating therapy, most specialists in this area believe that the evidence supports initiating therapy in asymptomatic HIV-infected persons with a CD4^{+} T cell count of 200-350 cells/mm^{3} **(BII)**.

There is a paucity of data from randomized, controlled trials concerning clinical endpoints (e.g., the development of AIDS-defining illnesses or death) for asymptomatic persons with >200 CD4^{+} T cells/mm^{3} to guide decisions on when to initiate therapy. Observational data from cohorts of HIV-infected persons provide some guidance to assist in risk assessment for disease progression.

One source of observational data comes from cohorts of untreated individuals with regular measurements of CD4^{+} T cell counts and HIV RNA levels. **Table 4b** is taken from a report by the CASCADE Collaboration, composed of 20 cohorts in Europe and Australia *[62]*. The information in this table provides an estimate of the short-term (6-month) risk of AIDS progression according to CD4^{+} T cell count, HIV RNA level, and age. These estimates can be considered in making the decision about whether to start antiretroviral therapy before the next clinic visit.

Another source of observational data is from cohorts that follow patients after the initiation of antiretroviral treatment. A pooled analysis of 13 cohorts from Europe and North America provide the most precise information on prognosis following the initiation of treatment *[61]*. These data indicate that CD4^{+} T cell count is a much more important prognostic indicator than viral load for those initiating therapy. In this study, risk of progression was also greater for those with a viral load >100,000, older patients, those infected through injecting drug use, and those with a previous diagnosis of AIDS. The following chart shows the risk of progression to AIDS or death after 3 years, according to CD4^{+} T cell count and HIV RNA level at the time antiretroviral therapy was initiated. These data are from a large subset of patients less than 50 years old and without a history of an AIDS-defining illness or injection drug use:

CD4^{+} T cell count	3 yr-probability	
	VL <10[5]	VL >10[5]
0 - 49 cells/mm^{3}	16 %	20%
50 - 99 cells/mm^{3}	12 %	16%
100 - 199 cells/mm^{3}	9.3 %	12%
200 - 349 cells/mm^{3}	4.7 %	6.1%
≥350 cells/mm^{3}	3.4 %	4.4%

These data provide strong support for the recommendation, based on observational cohort , that therapy should be initiated before the CD4^{+} T cell count declines to <200 cells/mm^{3}. However, differences in risk for those with CD4^{+} T cell counts between 200–350 and >350 cells/mm^{3} are based on too few events, and too short a follow-up period, to make reliable statements about when treatment should be started.

Athough there are clear strengths to these observational data, there are also important limitations. Uncontrolled confounding factors could impact estimates in both studies. Furthermore, neither study provides direct evidence on the optimum CD4^{+}

T cell count to begin therapy. Such data will have to come from studies that follow patients who start therapy at different CD4$^+$ T cell counts greater than 200 cells/mm^3 and compare them with a similar group of patients (e.g., with similar CD4$^+$ T cell count and HIV RNA level) who defer treatment. To completely balance the benefits and risks of therapy, follow-up will have to examine progression to AIDS, major toxicities, and death.

>350 CD4$^+$ T cell count, patient asymptomatic. There is little evidence on the benefit of initiating therapy in asymptomatic patients with CD4$^+$ T cell count > 350 cells/mm^3. Most clinicians would defer therapy.

- The deferred treatment approach is based on the recognition that robust immune reconstitution still occurs in the majority of patients who initiate treatment while CD4$^+$ T cell counts are in the 200–350 cells/mm^{3}range. Also, toxicity risks and adherence challenges generally outweigh the benefits of initiating therapy at CD4$^+$ T cell counts >350 cells/mm^3. In the deferred treatment approach, increased levels of plasma HIV RNA (i.e., >100,000 copies/mL) are an indication for monitoring of CD4$^+$ T cell counts and plasma HIV RNA levels at least every three months, but not necessarily for initiation of therapy. For patients with HIV RNA <100,000 copies/mL, therapy should be deferred **(DII)**.

- In the early treatment approach, asymptomatic patients with CD4$^+$ T cell counts >350 cells/mm^3 and levels of plasma HIV RNA >100,000 copies/mL would be treated because of the risk for immunologic deterioration and disease progression **(CII)**.

An estimate of the short term risk of AIDS progression may be useful in guiding clinicians and patients as they weigh the risks and benefits of initiating versus deferring therapy in this CD4 cell range. As cited above, **Table 4b** provides an analysis of data from the CASCADE Collaboration, demonstrating the risk of AIDS progression within 6 months for different strata of CD4$^+$ T cell count, viral load, and age. As seen in **Table 4b**, a 55 year old with a CD4$^+$ T cell count of 350 and a HIV viral load of 300,000 copies/mL has a 5% chance of progression to an AIDS-defining diagnosis in 6 months, compared with a 1.2% chance for a similar patient with a viral load of 3,000 copies/mL.

Benefits and Risks of Treatment

In addition to the risks of disease progression, the decision to initiate antiretroviral therapy also is influenced by an assessment of other potential risks and benefits associated with treatment. Potential benefits and risks of early (CD4$^+$ T cell counts >350 cells/mm^3) or deferred (CD4$^+$ T cell count 200-350 cells/mm^3) therapy initiation for the asymptomatic patient should be considered by the clinician and patient.

Potential Benefits of Deferred Therapy include:
- avoidance of treatment-related negative effects on quality of life and drug-related toxicities;
- preservation of treatment options;
- delay in development of drug resistance if there is incomplete viral suppression;
- more time for the patient to have a greater understanding of treatment demands;
- decreased total time on medication with reduced chance of treatment fatigue; and
- more time for the development of more potent, less toxic, and better studied combinations of antiretrovirals.

Potential Risks of Deferred Therapy include:
- the possibility that damage to the immune system, which might otherwise be salvaged by earlier therapy, is irreversible;
- the increased possibility of progression to AIDS; and
- the increased risk for HIV transmission to others during a longer untreated period.

Gender Differences. The recommendation of when to start antiretroviral therapy is the same for HIV-infected adult male and female patients. Data regarding sex-specific differences in viral load and CD4$^+$ T cell counts are conflicting. Certain studies [67-73], although not others [74-77], have concluded that after adjustment for CD4$^+$ T cell counts, levels of HIV RNA are lower in women than in men. Although viral load is lower in women at seroconversion, the differences decrease with time, and the median viral load in women and men become similar within 5–6 years after seroconversion [68, 69, 73]. Importantly, rates of disease progression do not differ by gender [71, 73, 78, 79]. These data demonstrate that sex-based differences in viral load occur predominantly during a window of time when the CD4$^+$ T cell count is relatively preserved, when treatment is recommended only in the setting of increased levels of plasma HIV RNA.

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 *[80].* Depression and substance abuse may negatively impact adherence and response to therapy, therefore, should be addressed, whenever possible, prior to initiating therapy. However, no patient should automatically be excluded from consideration for antiretroviral therapy simply because he or she exhibits a behavior or other characteristic judged by the clinician to lend itself to non-adherence. Rather, the likelihood of patient adherence to a long-term drug regimen should be discussed and determined 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 *[81].* As of August 2006, there are over 20 approved antiretroviral drugs belonging to four mechanistic classes, with which to design combination regimens. These four classes include the nucleoside/nucleotide reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), and entry inhibitors (EI).

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 for 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^{+} T cell count). Few of these trials include clinical endpoints, such as development of AIDS-defining illness or death. Thus, assessment of regimen efficacy and potency 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:

- co-morbidity or conditions such as tuberculosis, 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^{+} T cell 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 *[82, 83]* and a triple-NRTI + NNRTI regimen *[84]* showed 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^{+} T cell counts $\leq$250 cells/mm^{3} and adult males with CD4^{+} T cell counts $\leq$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 *[24, 25, 29]* 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 **Utilization of Drug Resistance Testing in Clinical Practice** 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/or 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) or in women who are planning to conceive or 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^{+} T cell counts $\leq$250 cells/mm^{3} or

adult males with pretreatment CD4^{+} T cell counts $\leq$400 cells/mm^{3} **(BII).** Symptomatic, sometimes serious or life-threatening hepatic events were observed with much greater frequency in women with pretreatment CD4^{+} T cell counts >250/mm^{3} and men with pretreatment CD4^{+} T cell 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 up to 3 years of follow-up *[84, 85].* 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 *[86],* lopinavir/ritonavir *[87],* and nelfinavir *[88]* and to triple-NRTI-based regimens *[89, 90]* and had comparable activities to nevirapine- *[91, 92]* and atazanavir-based regimens *[93].*

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) *[87].* 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), while the dual-NRTI + lopinavir/ritonavir regimen had significantly better CD4^{+} T cell 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 *[91].*

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 non-human primates at drug exposure levels similar to those achieved in humans *[94].* Several cases of neural tube defects in human newborns, when mothers were exposed to efavirenz during first trimester of pregnancy, have been identified *[95, 96].*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 co-formulated 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) *[91].* 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^{+} T cell counts appear to be at highest risk *[97, 98].* In a recent analysis, a 12-fold higher incidence of symptomatic hepatic events was seen in women (including pregnant women) with CD4^{+} T cell counts of >250 cells/mm^{3} at the time of nevirapine initiation when compared with women with CD4^{+} T cell counts $\leq$250 cells/mm^{3} (11.0% vs. 0.9%). An increased risk was also seen in men with pre-nevirapine CD4^{+} T cell counts >400 cells/mm^{3} when compared with men with pre-nevirapine CD4^{+} T cell 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 *[97, 99].* 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$^+$ T cell counts $\leq$250 cells/mm^3 or adult male patients with CD4$^+$ T cell counts $\leq$400 cells/mm^3 (**BII).** In female patients with CD4$^+$ T cell counts >250 cells/mm^3 or male patients with CD4$^+$ T cell counts >400 cells/mm^3, nevirapine should not be initiated unless 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 (co-formulated) twice-daily (AII)*
>
> *Alternative PIs (BII):*
> - *atazanavir***
> - *fosamprenavir*
> - *fosamprenavir + ritonavir* once-daily*
> - *lopinavir/ritonavir (co-formulated) 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, ten 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** & **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 ten 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 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 *[100-102]*. 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 (co-formulated, 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 *[103]*. 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 *[104]* 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 which 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 protease inhibitor 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% 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 *[105]*.

Lopinavir/ritonavir (co-formulated; 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) *[106]*. 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 *[107]*. 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 *[108]*. 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 *[109]*. The implication of this pharmacokinetic change on virologic outcome in the mother and the risk of perinatal HIV transmission remain unknown. Further studies are underway 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 *[93, 110, 111]*. 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 which 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 [112, 113]. 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 [112]. Once-daily ritonavir-boosted fosamprenavir had similar virologic activity to nelfinavir in the second trial [113].

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 [114]. 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 [110] and to once-daily ritonavir-boosted fosamprenavir [115] but inferior to twice-daily lopinavir/ritonavir [106], unboosted fosamprenavir [112], and efavirenz [88] 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 [107, 116]. 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 [107, 116]. 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 as compared with non-pregnant state [117]. 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 pre-dose 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 [101]. However, a similarly designed study demonstrated decreased virologic responses with ritonavir-boosted saquinavir compared with lopinavir/ritonavir [102].

Dual-Nucleoside Options as Part of Initial Combination Therapy

Panel's Recommendations:
Preferred dual-NRTI (AII):
- *tenofovir/emtricitabine*(co-formulated)*
- *zidovudine/lamivudine*(co-formulated)*

Alternative dual-NRTI (BII):
- *abacavir/lamivudine*(co-formulated)*
- *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 (NRTIs) are currently approved in the U.S. 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 [118].

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 (co-formulated) (AII). Tenofovir is a nucleotide analog with potent activity against HIV and hepatitis B virus 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 [85] and was not inferior to zidovudine/lamivudine in virologic efficacy at 48 and 96 weeks [119, 120]. 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 [119]. 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 [114].

Renal impairment, manifested by increases in serum creatinine, glycosuria, hypophosphatemia, and acute tubular necrosis, has been reported with tenofovir use [121, 122]. 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 (co-formulated) (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 [86, 88, 89, 93, 123-125]. 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 (co-formulated) (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) [126]. However, the potential for serious abacavir-associated hypersensitivity reactions in 5%-8% of patients warrants placement of abacavir/lamivudine as an alternative dual-NRTI option at this time. 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) *[30]*. 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 *[127]*. 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 *[85, 128]*, long-term use of stavudine has been associated with irreversible and sometimes serious toxicities, such as peripheral neuropathy, lipoatrophy, and serious and life-threatening lactic acidosis with hepatic steatosis with or without pancreatitis, and rapidly progressive neuromuscular weakness *[129-131]*. 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 hepatitis B virus. Lamivudine is currently approved as a treatment for hepatitis B infection. It is important to note that patients with hepatitis B and HIV co-infection may be at risk of acute exacerbation of hepatitis after initiation or upon discontinuation of these drugs *[132-134]*. 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 Co-Infection 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 *[89, 90, 135-139]*.

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 (co-formulated) (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 *[123, 124]* and nelfinavir *[140]* but was inferior virologically to an efavirenz-based regimen *[89]*.

Zidovudine/lamivudine + tenofovir (DII): The DART study demonstrated virologic responses in patients taking zidovudine/lamivudine + tenofovir *[141]*; 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 pharmacological 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 *[142]* or atazanavir *[143]*, 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 *[144, 145]* **(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 post-partum 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 *[146]*.

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 *[90, 135-139]* 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)*

Amprenavir oral solution in pregnant women; children <4 years of age; patients with renal or hepatic failure; and patients treated with metronidazole or disulfiram (EII). The large amount of propylene glycol used as an excipient may be toxic to high-risk patients.

Amprenavir oral solution + fosamprenavir (EIII). Fosamprenavir is the prodrug of amprenavir. There is no additional benefit, and potential additive toxicities, when using these agents together.

Amprenavir oral solution + ritonavir oral solution (EIII). The large amount of propylene glycol used as a vehicle in amprenavir oral solution may compete with the ethanol (vehicle of oral ritonavir solution) for the same metabolic pathway for elimination. This may lead to accumulation of either one of the vehicles.

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 *[88, 129, 130]*.This combination has been implicated in several deaths in HIV-1 infected pregnant women secondary to severe lactic acidosis with or without hepatic steatosis and pancreatitis *[147]*.

Efavirenz in first trimester of pregnancy and 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 *[95, 96]*. 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 *[148]*.

Nevirapine initiated in treatment-naïve women with CD4$^+$ T cell counts >250 cells/mm^3 or in treatment-naïve men with CD4$^+$ T cell 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 *[97-99]*.

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 [149]* and *in vivo [150]*.

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: non-adherence 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 [151, 152], and improved survival [153] 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. While 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 [154, 155]. The clinician's estimate of the likelihood of a patient's adherence has also been proven to be an unreliable predictor of patient adherence [156].

Regimen complexity and pill burden were the most common reasons for non-adherence 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 in 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 [157, 158]. 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 [159]. 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 [160], 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 non-adherence and prompt intervention can greatly reduce the chance of virologic failure and development 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 non-adherence [161]. In a review of over 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 [162]. 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 *[97, 163, 164]* or lactic acidosis from NRTIs *[165]*. Other factors may also contribute to the development of adverse events, such as: use of concomitant medications with overlapping and additive toxicities; co-morbid conditions that may increase risk of or exacerbate adverse effects (e.g., alcoholism *[166]*, or hepatitis B or hepatitis C co-infection may increase risk of hepatotoxicity *[167-169])*; or drug-drug interactions that may lead to an increase in dose-related toxicities (e.g., concomitant use of hydroxyurea *[170, 171]* or ribavirin *[172-174]* with didanosine, increasing didanosine-associated toxicities).

While 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:
1. **Tables 11-14** summarize common adverse effects of individual antiretroviral agents;
2. **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 and/or may impact on overall medication adherence.
3. **Table 18** includes a list of overlapping toxicities of antiretroviral agents and other drugs commonly used in HIV patients.
4. **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 *[175]*. All PIs and NNRTIs are metabolized in the liver by the cytochrome P450 (CYP) system, particularly by the CYP3A4 isoenzyme. The list of drugs that may have significant interactions with PIs and/or NNRTIs is extensive and continuously expanding. Some examples of these drugs include medications that are commonly prescribed for HIV patients for non-HIV medical conditions, such as lipid-lowering agents (the "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 contraceptive, and methadone. Unapproved therapies, such as St. John's Wort, can also cause negative interactions.

All PIs are substrates of CYP3A4, where 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 [176]. 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 $t_{1/2}$ of the active PIs [177]. 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 $t_{1/2}$ 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/or therapeutic drug monitoring, 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 [178, 179]. As rifabutin is a less potent inducer, it is generally considered a reasonable alternative to rifampin for the treatment of tuberculosis when it is used with a PI- or NNRTI-based regimen, despite wider experience with rifampin use [180]. **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 [181, 182] or ribavirin [174]; additive bone marrow suppressive effects of zidovudine and ganciclovir [183]; and antagonism of intracellular phosphorylation

with the combination of zidovudine and stavudine [149]. 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 [184, 185], and decreases in atazanavir concentration when it is co-administered with tenofovir [186, 187]. **Table 21** lists significant interactions with NRTIs.

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.

MANAGEMENT OF THE TREATMENT – EXPERIENCED PATIENT

Panel's Recommendations:
- *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 HIV RNA level >400 copies/mL after prior suppression of viremia to <400 copies/mL.*
- *Evaluation of antiretroviral treatment failure should include assessing 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; and the results of prior drug resistance testing.*
- *Drug resistance testing should be obtained while the patient is taking the failing antiretroviral regimen (or within 4 weeks of treatment discontinuation).*
- *In managing virologic failure, the provider should make a distinction between limited, intermediate, and extensive prior treatment exposure and resistance.*
- *The goal of treatment for patients with prior drug exposure and drug resistance is to re-establish maximal virologic suppression.*
- *For some patients with extensive prior drug exposure and drug resistance where viral suppression is difficult or impossible to achieve with currently available drugs, the goal of treatment is preservation of immune function and prevention of clinical progression.*
- *Assessing and managing a patient with extensive prior antiretroviral experience and drug resistance who is experiencing treatment failure is complex and expert advice is critical.*

The Treatment-Experienced Patient

Most patients experience benefits from antiretroviral therapy regimens. In clinical trials of potent combination regimens, a majority of study subjects maintained virologic suppression for 3-6 years *[85, 188, 189]*. In clinic patients, higher virologic failure rates have been reported *[56, 190]*, but are decreasing *[54, 61]*. In a patient on antiretroviral therapy with virologic suppression, adherence to antiretroviral drugs should be assessed on an ongoing basis (See **Adherence** section.) Antiretroviral treatment failure is common and increases the risk of HIV disease progression and 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 (See below.)

Many factors increase the likelihood of treatment failure, including:

- baseline patient factors such as: earlier calendar year of starting therapy, higher pretreatment or baseline HIV RNA level (depending on the specific regimen used), lower pretreatment or nadir CD4 cell count, prior AIDS diagnosis, co-morbidities (e.g., depression, active substance use), presence of drug-resistant virus, 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.

Some patient cohorts suggest that suboptimal adherence and toxicity accounted for 28%-40% of treatment failure and regimen discontinuation *[191, 192]*. Multiple reasons for treatment failure can occur in one patient. Some factors which have not been associated with treatment failure include: gender, race, pregnancy, history of past substance use.

Virologic Failure can be defined as incomplete or lack of HIV RNA response to antiretroviral therapy:

- *Incomplete virologic response*: This can be defined as repeated HIV RNA >400 copies/mL after 24 weeks or >50 copies/mL by 48 weeks in a treatment-naïve patient initiating therapy. Baseline HIV RNA may impact 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 *[193]*. For example, most patients with an adequate virologic response at 24 weeks had at least a 1 $\log_{10}$ copies/mL HIV RNA decrease at 1-4 weeks after starting therapy *[194-196]*.

- *Virologic rebound*: After virologic suppression, repeated detection of HIV RNA.

Immunologic Failure can be defined as failure to increase the CD4 cell count by 25-50 cells/mm^3 above the baseline count over the first year of therapy, or a decrease to below the baseline CD4 cell count on therapy. Mean increases in CD4 cell counts in treatment-naïve patients with initial antiretroviral regimens are approximately 150 cells/mm^3 over the first year *[197]*. A lower baseline CD4 cell count may be associated with less of a response to therapy. For reasons not fully understood, some patients may have initial CD4 cell increases, but then minimal subsequent increases.

Immunologic failure (i.e., return to baseline CD4 cell count) occurred an average of 3 years following virologic failure in patients remaining on the same PI-containing antiretroviral regimen *[198]*.

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 *[199, 200]*. 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 over 2.5 years *[190]*.

Relationship Across Virologic Failure, Immunologic Failure, and Clinical Progression. Some patients demonstrate discordant responses in virologic, immunologic and clinical parameters *[201]*. 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.

Although heterogeneous, patients who experience treatment failure may be divided into those with

- limited prior treatment and drug resistance who have adequate treatment options;
- an intermediate amount of prior treatment and drug resistance with some available treatment options; and
- extensive prior treatment and drug resistance who have some or no adequate treatment options.

The assessment, goals of therapy and approach to managing treatment failure differ for each of these three groups.

Assessment of Antiretroviral Treatment Failure and Changing Therapy

In general, the cause of treatment failure should be explored by reviewing the medical history and performing a physical examination to assess for signs of clinical progression. Important elements of the medical history include: change in HIV RNA and CD4 cell count over time; occurrence of HIV-related clinical events; antiretroviral treatment history and results of prior resistance testing (if any); medication-taking behavior, including adherence to recommended drug doses, dosing frequency and food/fasting requirements; tolerance of the medications; concomitant medications (with consideration for adverse drug-drug interactions); and co-morbidities (including substance use). In many cases the cause(s) of treatment failure will be readily apparent. In some cases, no obvious cause may be identified.

For more information about the approach to treatment failure, see **Tables 23–25.**

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 treatment will differ. The following assessments should be initially undertaken:

- **Adherence.** Assess the patient's adherence to the regimen. For incomplete adherence, identify and address the underlying cause(s) for non-adherence (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:
  - ♦ use symptomatic treatment (e.g., antiemetics, antidiarrheals);
  - ♦ change one drug to another within the same drug class, if needed (e.g., change to tenofovir for zidovudine-related gastrointestinal symptoms or anemia; change to nevirapine for efavirenz-related central nervous system symptoms) **(AII)**;
  - ♦ change drug classes (e.g., from a PI to an NNRTI or vice versa) 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. (See **Utilization of Drug Resistance in Clinical Practice**.)

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

1. **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 >400 copies/mL after suppression to <400 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 *[202]* and may limit future treatment options. Isolated episodes of viremia ("blips", e.g., single levels of 50-1,000 copies/mL) may simply represent laboratory

variation *[203]* 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 *[204, 205]*.

When assessing virologic failure, one should distinguish between limited, intermediate and extensive drug resistance, taking into account prior treatment history and prior resistance test results. Drug resistance tends to be cumulative for a given individual and thus all prior treatment history and resistance test results should be taken into account. **Table 23** provides potential management strategies in different clinical scenarios.

- *Prior Treatment With No Resistance Identified.* Consider the timing of the drug resistance test (e.g., was the patient off antiretroviral medications?) and/or non-adherence. Consider resuming the same regimen or starting a new regimen and then repeating genotypic testing early (e.g., in 2–4 weeks) to determine if a resistant viral strain emerges **(CIII)**. Consider intensifying with one drug (e.g., tenofovir) **(BII)** *[206]* or pharmacokinetic enhancement (use of ritonavir boosting of a protease inhibitor) **(BII)** *[100]*.

- *Limited Prior Treatment and Drug Resistance.* The goal in this situation is to re-suppress HIV RNA levels maximally and 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. Change at least 2 drugs in the regimen to active agents **(BII)**. A single drug substitution (made on the basis of resistance testing) can be considered, but is unproven in this setting **(CIII)**.

- *Intermediate Prior Treatment and Drug Resistance.* The goal in this situation usually is to re-suppress HIV RNA levels maximally and prevent further selection of resistance mutations. Change at least 2 drugs in the regimen to active agents **(BII)**.

- *Extensive prior treatment and drug resistance* (**Tables 23–25**): The goal is to re-suppress the HIV RNA levels maximally, however, viral suppression may be difficult to achieve in some patients. In this case, the goal is to preserve immunologic function and prevent clinical progression (even with ongoing viremia). Even partial virologic suppression of HIV RNA >0.5 log10 copies/mL from baseline correlates with clinical benefits *[207]*; however, this must be

balanced with the ongoing risk of accumulating additional resistance mutations. It is reasonable to observe a patient on the same regimen, rather than changing the regimen (depending on the stage of HIV disease), if there are few or no treatment options **(BII)**. There is evidence from cohort studies that continuing therapy, even in the presence of viremia and the absence of CD4 cell increases, decreases the risk of disease progression *[18]*. Other cohort studies suggest continued immunologic and clinical benefits if the HIV RNA level is maintained <10,000-20,000 copies/mL *[208, 209]*. In a patient with a lower CD4 cell count (e.g., <100 cells/mm^3), a change in therapy may be critical to prevent further immunologic decline and clinical progression and is therefore indicated **(BIII)**. A patient with a higher CD4 cell count may not be at significant risk for clinical progression, so a change in therapy is optional **(CIII)**. Discontinuing or briefly interrupting therapy (even with ongoing viremia) may lead to a rapid increase in HIV RNA, a decrease in CD4 cell count, and increases the risk for clinical progression *[210, 211]* and therefore is not recommended **(DIII)**.

2. **Immunologic Failure.** Immunologic failure may not warrant a change in therapy in the setting of suppressed viremia. Assessment should include an evaluation for other possible causes of immunosuppression (e.g., HIV-2, HTLV-1, HTLV-2, drug toxicity). The combination of didanosine and tenofovir has been associated with CD4 cell declines or blunted CD4 cell responses *[212-214]*. In the setting of immunologic failure, it would be reasonable to change one of these drugs **(BIII)**. Although some clinicians have explored the use of intensification with additional antiretroviral drugs *[215]* or immune-based therapies (e.g., interleukin-2) to improve immunologic responses *[216]*, such therapies remain unproven and generally should not be offered in the setting of immunologic failure **(DII)**.

3. **Clinical Progression.** Consider the possibility of immune reconstitution syndromes *[199, 200]* that typically occur within the first 3 months after starting effective antiretroviral therapy and that 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 **(BIII)**.

Changing an Antiretroviral Therapy Regimen for Virologic Failure

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Panel's Recommendations:

- *For the patient with virologic failure, perform resistance testing while the patient still is taking the drug regimen or within 4 weeks after regimen discontinuation (AII).*

- *Use the treatment history and past and current resistance test results to identify active agents (preferably at least two fully active agents) to design a new regimen (AII). A fully active agent is one likely to demonstrate antiretroviral activity on the basis of both the treatment history and susceptibility on drug-resistance testing.*

- *If at least two fully active agents cannot be identified, consider pharmacokinetic enhancement of protease inhibitors (with the exception of nelfinavir) with ritonavir (BII) and/or re-using other prior antiretroviral agents to provide partial antiretroviral activity (CIII).*

- *Adding a drug with activity against drug-resistant virus (e.g., a potent ritonavir-boosted PI) and a drug with a new mechanism of action (e.g., HIV entry inhibitor) to an optimized background antiretroviral regimen can provide significant antiretroviral activity (BII).*

- *In general, one active drug should not be added to a failing regimen because drug resistance is likely to develop quickly (DII). However, in patients with advanced HIV disease (e.g., CD4 <100) and higher risk of clinical progression, adding one active agent (with an optimized background regimen) may provide clinical benefits and should be considered (CIII).*

General Approach (See **Tables 23–25**.) Ideally, one should design a regimen with two or more fully active drugs (on the basis of resistance testing or new mechanistic class) **(BII)** *[36, 217]*. Some antiretroviral drugs (e.g., NRTIs) may contribute partial antiretroviral activity to an antiretroviral regimen. Note that using "new" drugs that the patient has not yet taken may not be sufficient because of cross resistance within drug classes that reduces drug activity. As such, drug potency is more important than the number of drugs prescribed.

Early studies of treatment-experienced patients identified factors associated with better virologic responses to subsequent regimens *[218, 219]*.They include: lower HIV RNA at the time of therapy change, using a new (i.e., not yet taken) class of drugs (e.g., NNRTI, HIV entry inhibitors), and using ritonavir-boosted PIs in PI-experienced patients. With its novel mechanism of action, the HIV entry inhibitor enfuvirtide (T-20), was approved for treatment-

experienced patients based on its demonstrated potent antiretroviral activity in heavily treatment-experienced patients *[220-222]*. Enfuvirtide has not been well studied in patients at earlier stages of HIV infection.

Although enfuvirtide routinely is given by subcutaneous injection twice daily, a needleless system (Biojector) may be more acceptable to some patients and better tolerated *[223]*.

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. Novel early mutations to some protease inhibitors (e.g., amprenavir, atazanavir, nelfinavir, saquinavir) that do not confer cross resistance to other PIs may occur initially, but then subsequent accumulation of additional mutations confers broad cross resistance to the entire protease inhibitor class.

Tipranavir and darunavir are two new protease inhibitors approved for patients who are highly treatment-experienced or have HIV-1 strains resistant to multiple PIs based on its demonstrated activity against PI-resistant viruses *[224, 225]*. However, with ongoing viremia and the accumulation of additional mutations, antiretroviral activity is time-limited unless the regimen contains other active drugs (e.g., an HIV entry inhibitor).

New Agents. Investigational reverse transcriptase inhibitors (e.g., TMC-125) with distinct resistance patterns and activity against drug-resistant viruses are currently under investigation in clinical trials *[226]*.

Investigational drugs with newer mechanisms of action (e.g., HIV chemokine receptor inhibitors; HIV integrase inhibitors) demonstrate short-term antiretroviral activity in patients with resistance to the reverse transcriptase inhibitors and PIs *[227-231]* and are also under investigation in clinical trials.

Current Approach. Several clinical trials illustrate effective therapeutic strategies for heavily treatment-experienced patients *[220, 224, 225]*. In these studies, patients received an antiretroviral regimen optimized on the basis of 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 enfuvirtide), had a better and more prolonged virologic response than those with fewer active drugs in the regimen *[222, 224]*.

These studies illustrate and support the strategy of conducting resistance testing while a treatment-experienced patient is taking their 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.

In general, using a single active antiretroviral drug in a new regimen is not recommended because of the risk of rapidly developing resistance to that drug. However, in patients with advanced HIV disease with a high likelihood of clinical progression (e.g., a CD4 cell count less than 100/mm^3), adding a single drug may reduce the risk of immediate clinical progression, because even transient decreases in HIV RNA and/or transient increases in CD4 cell counts have been associated with clinical benefits. 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.

Therapeutic Drug Monitoring (TDM) for Antiretroviral Agents

Therapeutic drug monitoring (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/or reducing the frequency of drug-associated adverse reactions.

Current antiretroviral agents meet most of the characteristics of agents that can be considered candidates for a TDM strategy *[232]*. The rationale for TDM in managing antiretroviral therapy arises because of:
- data showing that considerable inter-patient 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 *[233-236]*. While 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 are 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;
- **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** whose safety and efficacy have not been established in clinical trials;
- **concentration-dependent toxicities**; and
- **lack of expected virologic resp**onse 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 *[233]* (See **http://www.hivpharmacology.com** *[237]*.)

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:
- Lack of prospective studies demonstrating that TDM improves clinical outcome. This is the most important limiting factor for the implementation of TDM at present.
- Lack of established therapeutic range of concentrations associated with achieving the desired therapeutic response and/or reducing the frequency of drug-associated adverse reactions; and
- 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 26** presents a synthesis of recommendations *[233-235, 237]* 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 non-availability. 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^{+} cell 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 *[106]*. (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 *[211, 238-240]*. 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^{+} cell count above the level currently recommended for treatment initiation and whose baseline CD4^{+} 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^{+} T cell counts above those currently recommended for initiating therapy. Several clinical trials have been designed to determine the safety of such interruptions, in which re-initiation is triggered by pre-determined CD4^{+} T cell count thresholds. In these trials, various CD4^{+} T cell count levels have been set to guide both treatment interruption and re-initiation. Recently, two separate, randomized clinical trials of intentional, CD4^{+} T cell—guided, treatment interruption have been reported. In the SMART study, interrupting treatment with CD4^{+} T cell levels greater than 350 cells/mm^3 and re-initiating when less than 250 cells/mm^3 was associated with an increased risk of disease progression and death compared with the trial arm of continuous antiretroviral therapy *[241]*. In the TRIVACAN study, the same CD4^{+} T cell count triggers were used for stopping and restarting treatment *[242]*. 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 *[243-245]*. Other trials continue to collect data using other designs, including using higher CD4^{+} T cell 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 cell 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^{+} T cell

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 over 3 weeks *[246, 247]*. 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 polymorphism may be more common among specific ethnic groups, such as African Americans and Hispanics *[248, 249]*. Some experts recommend stopping the NNRTI but continuing the other antiretroviral drugs for a period of time. The optimal time sequence for staggered component discontinuation has not been determined. A study in South Africa demonstrated that giving four or seven days of zidovudine plus lamivudine after a single dose of nevirapine reduced the risk of postnatal nevirapine resistance from 60% to 10%-12% *[250]*. 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 three weeks, some suggest that the PI-based regimen may need to be continued for up to four 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 two-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 two weeks and is to be restarted later, nevirapine

should be reintroduced with a dose escalation period of 200mg once daily for 14 days, then a 200mg twice-daily regimen (**AII**).

- **Discontinuation of emtricitabine, lamivudine, or tenofovir in patients with hepatitis B co-infection**. Patients with hepatitis B co-infection (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 *[133, 134]*. 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 Co-Infection** 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$^+$ T cell 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 27**) *[251-254]*. 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 27**) 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, since 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 **Utilization of Drug Resistance Testing in Clinical Practice** 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 *[255-259]*.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 Non-Acute 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 *[260]*.

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 Treat: Indications for 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$^+$ T cell count and toxicity monitoring should be performed as described in **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 U.S. are in people 13 to 24 years of age *[261]*. 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 *[262]*.

Antiretroviral Therapy Considerations in Adolescents. Adult guidelines for antiretroviral therapy are usually appropriate for post pubertal 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 *[263, 264]*. 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 *[265]*, continued use of pediatric doses in puberty-delayed adolescents can result in medication

doses that are higher than usual adult doses. Since 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 with complex regimens is particularly challenging at a time of life when adolescents do not want to be different from their peers. Direct observed therapy, while considered impractical for all adolescents, might be important for selected adolescents infected with HIV *[266, 267]*. 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** *[268]*.

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 and 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 child bearing 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** *[145]*.

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 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, injection drug users with HIV disease present special treatment challenges. These include the existence of an array of complicating co-morbid 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 *[269-271]*.

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 non-sterile needle and syringe use.

These include tuberculosis, 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 *[269-271]*. Successful HIV therapy for injection drug users often rests upon acquiring familiarity with and providing care for these co-morbid conditions**.**

Injection drug users often have decreased access to HIV care and are less likely to receive antiretroviral therapy than other populations *[272, 273]*. 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 *[272, 273]*. 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 *[274]*. 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 co-existing mental illness, further complicates the relationship between health care workers and injection drug users.

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 injection drug users 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*. While 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, is often a critical component of successful treatment for HIV disease. Essential to this end, as well, are flexible community based HIV care sites characterized by familiarity with, and non-judgmental expertise in, managing the wide array of needs of substance abusers, and the development and use of effective strategies for promoting medication adherence *[270, 271]*. 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 has shown promise in this population *[275]*.

IDU/HIV Drug Toxicities and Interactions.
Injection drug users 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 injection drug users. 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 cytochrome P450 isoenzymes 3A4 and 2D6, pharmacologic effects and interactions with antiretrovirals may commonly occur *[276]*. These may diminish the effectiveness of either or both therapies by causing opiate withdrawal or overdose and/or increase in toxicity or decrease in 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 appear 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% *[276]*, with 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 *[277]*. 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 *[278]*. Both

efavirenz and nevirapine, potent inducers of p450 enzymes, 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 seven 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 p450 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 results in a significant decrease in methadone levels *[279, 280]*. Whereas amprenavir 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 and not ritonavir component *[281]*. Another study indicates a lack of pharmacokinetic interaction among atazanavir and methadone *[282]*.

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 injection drug users 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 providing 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 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 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 *[145]*.

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 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 co-administered. 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 pre-conception 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 prevention of mother-to-child transmission (PMTCT) and to maternal and fetal safety, timing of initiation of treatment and selection of regimens may be different from non-pregnant 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 less than 1,000 copies/mL and use of antiretroviral therapy appear to have an independent effect on reduction of perinatal transmission *[144, 283, 284]*.

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 and 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 28**.)

Based on available data, recommendations related to drug choices have been developed by the US Public Health Service Task Force and can be found in **Table 29**.

Current pharmacokinetic studies in pregnancy, although not completed for all agents, suggest no need for dosage modification for NRTIs and nevirapine. Nelfinavir, given as 1,250mg twice daily achieves optimal blood levels, but 750mg three times daily dosing does not, thus, the 1,250mg twice daily dosing should be used in all pregnant women *[117]*. 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, this agent should be used with close monitoring of virologic response *[109]*.

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:

1. 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 *[95]*.
2. The combination of ddI and d4T should be avoided during pregnancy because of several reports of fatal and non-fatal but serious lactic acidosis with hepatic steatosis and/or pancreatitis after prolonged use of regimens containing these two nucleoside analogues in combination *[147]*. This combination should be used during pregnancy only when other NRTI drug

combinations have failed or have caused unacceptable toxicity or side effects.

3. Nevirapine has been associated with a 12-fold increased risk of symptomatic hepatotoxicity in women with pre-nevirapine CD4$^+$ T cell 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 *[285]*. 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$^+$ T cell counts >250 cells/mm^3, nevirapine should not be initiated as a component of a combination regimen unless the benefit clearly outweighs the risk. If nevirapine is used, close clinical and laboratory monitoring, especially during the first 18 weeks of treatment, is strongly advised.
4. The oral liquid formulation of amprenavir contains high level of propylene glycol and should not be used in pregnant women.

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, non-experimental 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* *[145]*.

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

Discontinuation of Antiretroviral Therapy Post-Partum. 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 *[286]*. 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 Co-Infections

Hepatitis B (HBV)/HIV Co-Infection

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

- Emtricitabine, lamivudine, and tenofovir each shows activity against both HIV and HBV. The discontinuation of these drugs may potentially cause serious hepatocellular damage resulting from a flare of HBV *[280]*;

- Lamivudine resistance by HBV is about 40% at two years when used as monotherapy for chronic HBV and is about 90% at four years when used as the only active drug for HBV in co-infected patients *[281-284]*;

- Immune reconstitution is associated with deterioration in liver function tests, possibly because HBV is primarily an immune-mediated disease *[287]*;

- Patients who have immune reconstitution may have loss of hepatitis B early antigen (HBeAg) that is associated with a hepatitis flare *[167]*; and

- All PIs and NNRTIs are associated with relatively high rates of increases in transaminase levels. The rate and magnitude of these increases are higher with HBV co-infection *[288, 289]*. The cause and consequences of these changes in liver function tests are unclear, because continuation of therapy may be accompanied by resolution of the changes. Nevertheless, it is commonly recommended to suspend the implicated agent when the ALT is increased 5-10 times the upper limit of normal. However, in HBV co-infected persons, increases in transaminase levels can herald HBeAg sero-conversion, so the cause of the elevations must be investigated prior to discontinuation of medications.

TREATMENT RECOMMENDATIONS FOR HBV/HIV CO-INFECTED PATIENTS

- All patients with HBV should be advised to avoid alcohol; should receive hepatitis A vaccine, if found not to be immune at baseline (i.e., absence of hepatitis A antibody); should be advised on methods to prevent HBV transmission; and should be evaluated for the extent of HBV infection.

- Need to treat HIV and not HBV: The combination of tenofovir + emtricitabine or tenofovir + lamivudine can be used as the NRTI backbone of an antiretroviral regimen. Lamivudine, tenofovir, or emtricitabine should not be the only agents with anti-HBV activity in a regimen, to avoid development of HBV-resistant mutants.

- Need to treat HIV and HBV: The combination of tenofovir + lamivudine or tenofovir + emtricitabine should be considered as first-choice NRTI backbones. Additional options include entecavir alone or in combination with one of the three nucleosides with activity against both viruses. The use of lamivudine, emtricitabine, or tenofovir as the only active anti-HBV agent should be avoided because of the risk of resistance.

- Treatment of HBV and not HIV: Pegylated interferon-alpha is an option that does not lead to development of drug-resistant HIV or HBV mutants. Entecavir is a nucleoside analogue that is not active against HIV, so it is another option in this situation. Adefovir dipivoxil is active against HBV but not against HIV at the 10mg dose; however, a theoretical risk for development of HIV mutants exists, because it is related to tenofovir. The use of emtricitabine, lamivudine, or tenofovir without a full HAART regimen should be avoided because of the rapid development of drug-resistant HIV mutations.

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

Hepatitis C (HCV)/HIV Co-Infection

Long-term studies of patients with chronic HCV infection show that between 2%-20% develop cirrhosis in 20 years *[290]*. This rate of progression increases with older age, alcoholism, and HIV infection *[290-292]*. A meta-analysis demonstrated that the rate of progression to cirrhosis with HIV/HCV co-infection was about threefold higher when compared with patients who are seronegative

for HIV *[291]*. This accelerated rate is magnified in patients with low CD4$^+$ cell counts. Chronic HCV infection also complicates HIV treatment by the increased frequency of antiretroviral-associated hepatotoxicity *[168]*. Multiple studies show poor prognosis for HCV/HIV co-infection in the era of combination antiretroviral therapy. It is unclear if HCV adversely affects the rate of HIV progression *[293, 294]* or if this primarily reflects the impact of injection drug use (See **Injection Drug Users** section.), which is strongly linked to HCV infection *[294-296]*. It is also unclear if antiretroviral therapy improves the attributable morbidity/mortality for untreated HCV.

Assessment of HCV/HIV Co-Infection. Patients with HIV/HCV infection 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 co-infection, 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 co-morbidities, 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 co-infection 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 *[297, 298]*. These data are based on experience almost exclusively in carefully selected patients with CD4$^+$ T cell counts over 200 cells/mm^3 *[298-300]*.

Treatment of HCV/HIV Co-Infection. Based on these observations, treatment of HCV is recommended according to standard guidelines *[301] with* preference for those with higher CD4 cell 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 Co-Infection . Differences in HCV therapy management in the presence of HIV co-infection include:

- Ribavirin should not be given with didanosine because of the potential for drug-drug interactions leading to pancreatitis and lactic acidosis *[149]*;
- Some NRTIs and all NNRTIs and PIs are potentially hepatotoxic so that monitoring of serum transaminase levels is particularly important *[302]*;
- 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 Co-Infection)

> *Panel's Recommendations:*
> - *The treatment of tuberculosis in patients with HIV infection should follow the same principles for persons without HIV infection (AI).*
> - *Presence of active tuberculosis requires immediate initiation of treatment (AI).*
> - *In antiretroviral-naïve patients, delay of antiretroviral therapy for 4-8 weeks after initiation of tuberculosis treatment permits a better definition of causes of adverse reactions and paradoxical reactions (BIII).*
> - *Directly observed therapy is strongly recommended for HIV/TB co-infected patients (AII).*
> - *Rifampin/rifabutin-based regimens should be given at least three times weekly in patients with CD4$^+$ T cell count <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 anti-retroviral therapy, with dosage adjustment as necessary (AII).*
> - *Paradoxical reaction should be treated with continuation of treatment for tuberculosis and HIV, along with use of non-steroidal 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 tuberculosis by approximately 100-fold *[303]*. The CD4$^+$ T cell count influences both the

frequency and clinical expression of active tuberculosis *[304, 305]*. Tuberculosis also negatively impacts HIV disease. It is associated with a higher HIV viral load and more rapid progression of HIV disease *[303, 304]*. Important issues with respect to the use of antiretroviral drugs in patients with tuberculosis co-infection 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 tuberculosis (paradoxical reactions).

Scenarios for Treating TB/HIV Co-Infection. The treatment of tuberculosis should follow the general principles for tuberculosis in persons without HIV (**AI**). Below are various scenarios:

- **Patients on Antiretroviral Therapy**. Patients receiving antiretroviral treatment at the time tuberculosis treatment is started will require assessment of the antiretroviral regimen with changes that will permit use of the optimal tuberculosis 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 *[306, 307]*. Active tuberculosis 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 tuberculosis and HIV should be avoided, with the possible exception of patients who have CD4$^+$ T cell 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 tuberculosis. Treatment of drug-susceptible tuberculosis should consist of the standard regimen outlined in treatment guidelines, which consist of isoniazid (INH), rifampin or rifabutin (RIF), pyrazinamide (PZA), and ethambutol (EMB) or streptomycin (SM) given two months followed by INH + RIF for 4-7 months *[308]* (**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 tuberculosis, therapy should be prescribed based on susceptibility, preferably in consultation with tuberculosis experts.

Directly Observed Therapy (**DOT**). DOT is strongly recommended for patients with HIV/TB co-infection (**AII**). Once- or twice-weekly dosing has been associated with increased rates of rifamycin resistance in patients with advanced HIV *[309, 310]*. 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$^+$ T cell count <100 cells/mm^3 *[308]* (**AII**). In general, daily directly observed therapy (DOT) is recommended for the first 2 months and then three times weekly DOT for the continuation phase (**BII**).

Anti-tuberculosis/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-tuberculous 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 tuberculosis but are also associated with frequent drug interactions with PIs and NNRTIs because of their effects as inducers of the hepatic cytochrome P-450 enzyme system. Despite these interactions, rifamycin should be included in the tuberculosis treatment regimen in patients receiving antiretroviral agents *[311]* (**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** *[312]*.

Some patients treated for tuberculosis 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 tuberculosis and HIV and with non-steroidal anti-inflammatory agents (**BIII**). Occasional severe cases have been managed with high-dose prednisone (1mg/kg for 1-2 weeks followed by tapering doses) *[306, 307]* (**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:

- 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/desires concerning childbearing at intervals throughout care and refer women who are interested in getting pregnant for 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 *[313]*.

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 is well known. Guidelines are only a starting point for medical decision-making. They can identify some of the boundaries of high care quality, 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

Rating Scheme for Clinical Practice

Strength of Recommendation

A: Strong

B: Moderate

C: Optional

D: Should usually not be offered

E: Should never be offered

Quality of Evidence for Recommendation

I: At least one randomized trial with clinical results

II: Clinical trials with laboratory results

III: Expert opinion
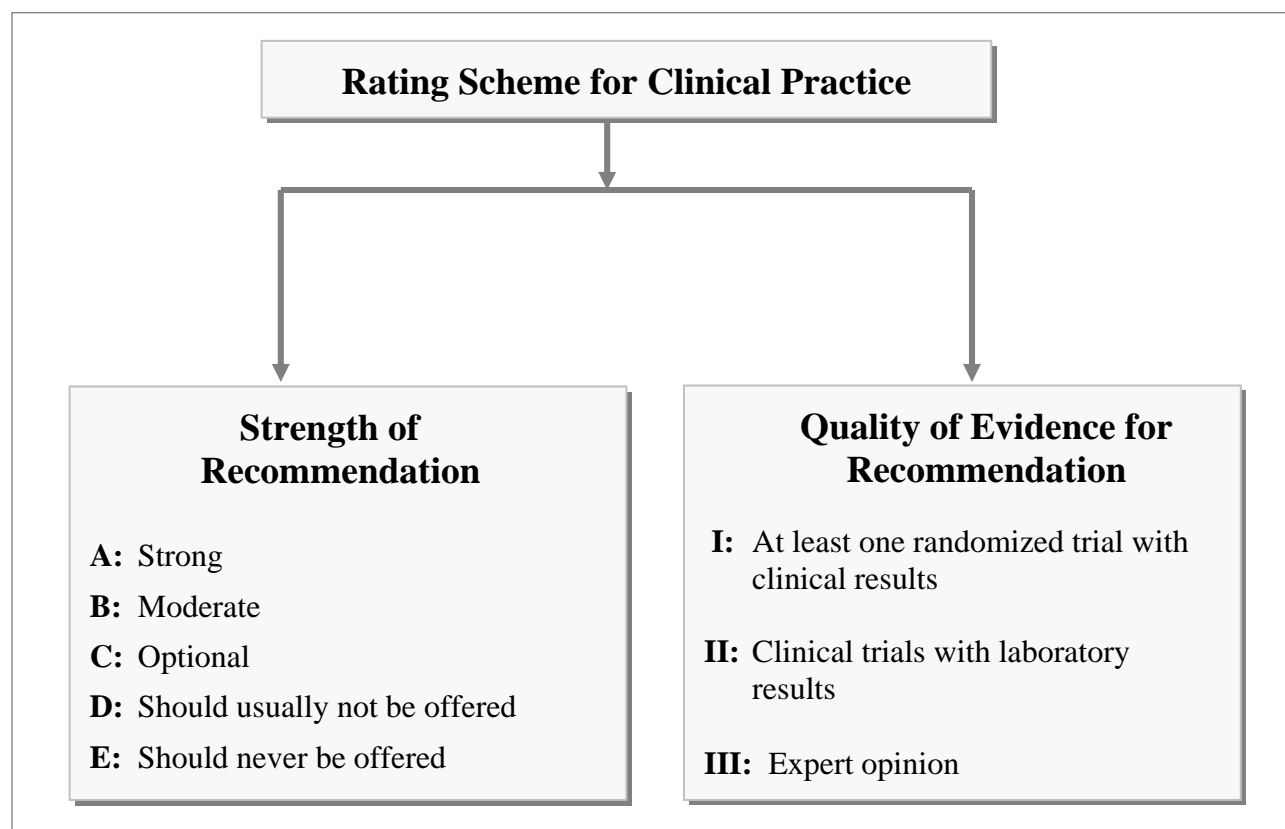
Table 2. Indications for Plasma HIV RNA Testing[*]

Clinical Indication	Information	Use
Syndrome consistent with acute HIV infection (See **Table 27.**)	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$^+$ T cell 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$^+$ T cell 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: <u>If the decision is made to initiate</u> therapy at this time, testing is recommended prior to initiation of treatment **(BIII).** A genotypic assay is generally preferred **(BIII).** <u>If treatment is deferred,</u> resistance testing at this time should still be considered **(CIII)**.	Drug resistance testing will determine if drug-resistant virus was transmitted and will help to design initial or changed (if therapy was initiated prior to test results) regimens accordingly. Earlier testing may be considered because of the potentially greater likelihood that transmitted resistance-associated mutations will be detected earlier in the course of HIV infection.
In chronic HIV infection: Drug resistance testing is recommended prior to initiation of therapy **(BIII)**. A genotypic assay is generally preferred **(BIII)**. Resistance testing earlier in the course of HIV infection may be considered **(CIII)**.	Transmitted HIV with baseline resistance to at least one drug may be seen in 6%-16% of patients. Suboptimal virologic responses may be seen in patients with baseline resistant mutations. Earlier testing may be considered because of the potentially greater likelihood that transmitted resistance-associated mutations will be detected earlier in the course of HIV infection.
With virologic failure during combination antiretroviral therapy **(BII)**	Determine the role of resistance in drug failure and maximize the number of active drugs in the new regimen, if indicated.
With suboptimal suppression of viral load after antiretroviral therapy initiation **(BIII)**	Determine the role of resistance and maximize the number of active drugs in the new regimen, if indicated.
Drug resistance assay not usually recommended	
After discontinuation 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; patients/providers may incur charges and not receive results.

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

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

Predicted risk (%) at current CD4 cell count (x 10^6 cells/l)[a]

Viral load (copies/mL)	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

The optimal time to initiate therapy is unknown among persons with asymptomatic disease and CD4^{+} T cell count of >200 cells/mm^3. This table provides general guidance rather than absolute recommendations for an individual patient. All decisions regarding initiating therapy should be made on the basis of prognosis as determined by the CD4^{+} T cell count and level of plasma HIV RNA indicated in table 4, the potential benefits and risks of therapy, and the willingness of the patient to accept therapy.

Clinical Category	CD4^{+} Cell Count	Plasma HIV RNA	Recommendation
AIDS-defining illness or severe symptoms* (AI)	Any value	Any value	Treat
Asymptomatic** (AI)	CD4^{+} T cells < 200/mm^3	Any value	Treat
Asymptomatic (BII)	CD4^{+} T cells > 200/mm^3 but ≤ 350/mm^3	Any value	Treatment should be offered following full discussion of pros and cons with each patient (See text.)
Asymptomatic (CII)	CD4^{+} T cells > 350/mm^3	≥ 100,000	Most clinicians recommend deferring therapy, but some clinicians will treat (See text.)
Asymptomatic (DII)	CD4^{+} T cells > 350/mm^3	< 100,000	Defer therapy

* AIDS-defining illness per Centers for Disease Control, 1993. Severe symptoms include unexplained fever or diarrhea > 2-4 weeks, oral candidiasis, or > 10% unexplained weight loss.

** Clinical benefit has been demonstrated in controlled trials only for patients with CD4^{+} T cells < 200/mm³, however, the majority of clinicians would offer therapy at a CD4^{+} T cell threshold < 350/mm³. A collaborative analysis of data from 13 cohort studies from Europe and North America found that lower CD4 count, higher HIV viral load, injection drug use, and age over 50 were all predictors of progression to AIDS or death in antiretroviral-naïve patients beginning combination antiretroviral therapy. These data indicate that the prognosis is better for patients who initiate therapy at > 200 cells/mm^3, but risk after initiation of therapy does not vary considerably at > 200 cells/mm^3 (For additional information, see "**When to Treat - Indications for Antiretroviral Therapy**")

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 NRTI.
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 co-morbid 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) (co-formulated)	**Preferred Components** **tenofovir/emtricitabine[3]** (co-formulated) (AII); or **zidovudine/lamivudine[3]** (co-formulated) (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) (co-formulated)	**Alternative to Preferred Components** **abacavir/lamivudine[3]** (co-formulated) (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 child-bearing 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 *[106]*. 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%) *[114]*.

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

[4] Nevirapine should not be initiated in women with CD4+ T cell count >250 cells/mm³ or in men with CD4+ T cell count >400 cells/mm³ 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 (co-formulated) 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	• Most experience with pregnant patients with good tolerability and adequate pharmacokinetic data
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 Components Not Recommended as Initial Therapy

Antiretroviral drugs or components (in alphabetical order)	Reasons for not recommending as initial therapy
Darunavir (ritonavir-boosted) **(DIII)**	• Lack of 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
Zalcitabine + zidovudine **(DII)**	• Inferior virologic efficacy • Higher rate of adverse effects than other dual-NRTI alternatives

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 non-response 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		
Amprenavir oral solution (EIII) in: • pregnant women; children <4 yr old; patients with renal or hepatic failure; and patients on metronidazole or disulfiram	• Oral liquid contains large amount of the excipient propylene glycol, which may be toxic in the patients at risk	• No exception
Amprenavir + fosamprenavir (EII)	• Amprenavir is the active antiviral for both drugs, combined use have no benefit and may increase toxicities	• No exception
Amprenavir oral solution + ritonavir oral solution (EIII)	• The large amount of propylene glycol used as a vehicle in amprenavir oral solution may compete with ethanol (the vehicle in oral ritonavir solution) for the same metabolic pathway for elimination. This may lead to accumulation of either one of the vehicles.	• No exception
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)**
Didanosine + zalcitabine (EIII)	• Additive peripheral neuropathy	• No exception
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
Lamivudine + Zalcitabine (EIII)	• In vitro antagonism	• 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 <u>single</u> protease inhibitor (EIII)	• Poor oral bioavailability (4%) • Inferior antiretroviral activity when compared with other protease inhibitors	• No exception
Stavudine + zalcitabine (EIII)	• Additive peripheral neuropathy	• 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 conc. & greater antiviral effect • Once daily dosing	Potentially more adverse effect on lipids than unboosted atazanavir
	Fosamprenavir (unboosted) (fAPV)	• No food effect	• Skin rash
	Fosamprenavir/ ritonavir (fAPV/r)	• Twice daily dosing resulted in comparable efficacy as LPV/r • RTV-boosting: higher trough fAPV conc. & 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)	• Co-formulated 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

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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)	• Favorable safety and pharmacokinetic profile for pregnant women when compared with other PIs	• Diarrhea • Higher rate of virologic failure when compared with other PIs (LPV/r & fAPV) and EFV in clinical trials • Food requirement
	Saquinavir + ritonavir(SQV/r)	• RTV boosting causes higher trough SQV conc. & 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 non-inferior to ZDV+ 3TC as dual-NRTI backbone • Once-daily dosing • Co-formulation (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
		• Co-formulated 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 • Co-formulated as Combivir® • No food effect	• Bone marrow suppression with zidovudine • Gastrointestinal intolerance
	emtricitabine (in place of lamivudine)	• Long half-life than lamivudine • Once daily dosing • Co-formulation w/ TDF (Truvada™) & w/ EFV/TDF (Atripla™)	• Hyperpigmentation/skin discoloration
Triple-NRTI regimen	Abacavir (ABC) + zidovudine (ZDV) + lamivudine (3TC) only	• Co-formulated 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 *[136]*

Arm	Regimen	N	Baseline CD4 Count*	Baseline Viral Load*	% Subjects with plasma HIV RNA (ITT) <500	<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) *[137]*

Arm	Regimen	N	Baseline CD4 Count#	Baseline Viral Load#	% Subjects with plasma HIV RNA (ITT) <400	<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 *[82, 88]*

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

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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) [93]

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	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 [125]

Arm	Regimen	N	Baseline CD4 Count[#]	Baseline Viral Load[#]	% Subjects with plasma HIV RNA (ITT)		Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
					<200	<20			
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 [86]

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	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

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

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

AACTG 5095 [89]

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) [123]

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) [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 + 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.

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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 [91]

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) [105]

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 + fAPV/r (BID)	434	188	5.1 log$_{10}$	73	66	6.1%	Arm A is non-inferior to Arm B.	fAPV/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) [106]

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 + 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) [112]

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 + fAPV (1400mg bid)	166	214	4.82 log$_{10}$	66	58	6	Arm A virologically superior to Arm B (P<0.001)	fAPV superior to NFV with ABC/3TC backbone.
B	ABC + 3TC + NFV	83	212	4.85 log$_{10}$	51	42	5		

SOLO - APV 30002 (GSK) [113]

Arm	Regimen	N	Baseline CD4 Count[*]	Baseline Viral Load[*]	% Subjects with plasma HIV RNA (ITT)		Adverse Effects Dropout %	Statistical Significance	Comments & Conclusion
					<400	<50			
A	ABC + 3TC + r/fAPV (200mg/1400mg qd)	322	166	4.8 log$_{10}$	68	56	9	Arms A and B were not different in performance.	Daily r/fAPV 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) [110]

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 + 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) [314]

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 + 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) [126]

Arm	Regimen	N	Baseline CD4 Count[*]	Baseline Viral Load[*]	% Subjects with plasma HIV RNA (ITT)		Adverse Effects Dropout %	Statistical Significance	Comments & Conclusion
					<400	<50			
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) [30]

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	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 [85]

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	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 [119]

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	TDF + FTC + EFV	255	233	5.0 $\log_{10}$	81	77	4	Arm A was non-inferior 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 [315]

Arm	Regimen	N	Baseline CD4 Count[#]	Baseline Viral Load[#]	% Subjects with plasma HIV RNA (ITT)		Adverse Effects Dropout %	Premise and Statistical Significance	Comments & Conclusion
					<500	<50			
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 [316]

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 + 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) [317]

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	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
[Antiretroviral Dosage Comparison Studies (continued)]

AI454-152 (BMS) [318]

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	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) [319]

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	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) [320]

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	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) [114]

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	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

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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 which 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 14**)	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 14**) 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 ; **Epizicom**®- w/ ABC **Trizivir**®- w/ ZDV+ABC ;	Epivir® 150mg and 300mg tablets or 10mg/mL oral solution Combivir®- 3TC 150mg + ZDV 300mg Epizicom® - 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 Epizicom® - 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 14**) 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)

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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 14**)	• 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 14**) 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)
Zalcitabine (ddC) **Hivid**®	0.375, 0.75 mg tablets Anticipated discontinuation of distribution in 2006	0.75 mg three times/day	Take without regard to meals	85%	1.2 hours	N/A	Renal excretion 70% Dosage adjustment in renal insufficiency (See **Table 14**)	• Peripheral neuropathy; • Stomatitis; • Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with use of NRTIs); • Pancreatitis
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 14**) 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 pre-nevirapine $CD4^+$ T cell counts >250 cells/mm^3 or in treatment-naive male patients with pre-nevirapine $CD4^+$ T cell 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.

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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
Amprenavir (APV)/ Agenerase®	50mg capsules, 15 mg/mL oral solution (capsules and solution NOT inter-changeable on mg per mg basis) **Note:** APV 150mg capsule is no longer available; consider using fosamprenavir in these patients.	1400mg two times/day (oral solution) **Note:** APV and RTV oral solution should not be co-administered because of competition of the metabolic pathway of the two vehicles.	High-fat meal decreases blood concentration 21%; can be taken with or without food, but high fat meal should be avoided.	Not determined in humans	7.1–10.6 hours	Cytochrome P450 3A4 inhibitor, inducer, and substrate Dosage adjustment in hepatic insufficiency recommended (See **Table 14**)	Room temperature (up to 25ºC or 77ºF)	• GI intolerance, nausea, vomiting, diarrhea • Rash • Oral paresthesias • Hyperlipidemia • Transaminase elevation • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in pts with hemophilia **Note:** Oral solution contains propylene glycol; contraindicated in pregnant women, children <4 years old, patients with hepatic or renal failure, & patients treated with disulfiram or metronidazole
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 14**)	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 (fAPV)/ Lexiva™	700mg tablet	ARV-naïve patients: • fAPV 1,400mg BID or • (fAPV 1,400 + RTV 200mg) QD or • (fAPV 700mg + RTV 100mg) BID PI-experienced pts (QD not recommended): • (fAPV 700mg + RTV 100mg) BID Coadministration w/ EFV (fAPV boosted only): • (fAPV 700mg + RTV 100mg) BID or • (fAPV 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 14**)	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 14**)	Room temperature 15-30ºC (59-86ºF), 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

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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, fAPV, 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 15-30ºC (59-86ºF)	• 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: • (RTV 100mg + SQV 1,000mg) two times/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 15-30ºC (59-86ºF)	• 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; day 3-5: 400mg two times; day 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 non-fatal intracranial hemorrhages have been reported. Most patients had underlying co-morbidity 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; day 3-5: 400mg two times; day 6-13: 500mg two times; day 14: 600mg two times/day.

Table 14. Characteristics of Entry Inhibitors

Generic Name/ Trade Name	Formulation	Dosing Recommendations	Bio-availability	Serum half-life	Route of Metabolism	Storage	Adverse Events
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 25°C or 77°F) Reconstituted solution should be stored under refrigeration at 2°C to 8°C (36°F to 46°F) and used within 24 hours	• 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

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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 26-50 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 1 tablet q48h < 30 not recommended	No dosage recommendation
Zalcitabine (Hivid®)	0.75 mg PO TID	**CrCl (mL/min)** **Dose** 10-40 0.75 mg BID < 10 0.75 mg qd No data on hemodialysis	No dosage recommendation
Zidovudine[*] (Retrovir®)	300mg PO BID	"Severe" renal impairment or HD – 100mg TID	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

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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			
Amprenavir (Agenerase®) Oral Solution	1,400mg PO BID	Not recommended in patients with renal failure	Not recommended in patients with hepatitic failure
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 txt-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

Creatinine Clearance calculation:
Male: (140-age in yr) x weight (kg)   Female: (140-age in yr) x weight (kg) x 0.85
              72 x S.Cr.   72 x 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

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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 1st 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 T cell 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 co-infection; •Alcoholic liver disease •HIV (-) individuals when NVP is used for post-exposure 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 co-infected 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 1000 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

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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) Move this up one	ABC	<u>Onset of 1st reaction:</u> median onset – 9 days; approximately 90% within 1st 6 weeks <u>Onset of rechallenge reactions:</u> within hours of rechallenge dose <u>Symptoms:</u> 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	<u>Onset:</u> months after initiation of ARV; then dramatic motor weakness occurring within days to weeks <u>Symptom:</u> 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 <u>Laboratory findings may include:</u> • 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, fAPV, ABC, <mark>DRV,</mark> ZDV, ddI, IDV, LPV/r, ATV	<u>Onset:</u> first few days to weeks after initation of therapy <u>Symptoms:</u> *Cutaneous involvement:* • Skin eruption with mucosal ulcerations (may involve oroginival 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% to 1% DLV & EFV: 0.1% 1-2 case reports for ABC, fAPV, ddI, ZDV, IDV, LPV/r, ATV, <mark>DRV</mark>	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) <u>Aggressive symptomatic support may include:</u> • 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 <u>Controversial management strategies:</u> • Corticosteroid • Intravenous immunoglobulin **Do not rechallenge patient with offending agent** ▪ It is unknown whether patients who experienced SJS while NNRTI are more susceptible to SJS from another NNRTI – most experts would suggest avoiding use of this class unless no other option available

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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 bacterial infections because of neutropenia	Anemia -1.1 to 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 co-infected 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 co-infection •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

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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	<u>Onset:</u> IDV – months after therapy TDF – weeks to months after therapy <u>Laboratory and other findings:</u> IDV: ↑ serum creatinine, pyruria; hydronephrosis or renal atrophy TDF: ↑ serum creatinine, proteinuria, hypophosphatemia, glycosuria, hypokalemia, non-anion gap metabolic acidosis <u>Symptoms:</u> 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	<u>Onset:</u> usually weeks to months <u>Laboratory abnormalities:</u> increased serum amylase and lipase <u>Symptoms:</u> post-prandial 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 intracellular 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, fAPV, ATV, DRV TPV/RTV	<u>Onset:</u> within first few days to weeks after initiation of therapy <u>Symptoms:</u> 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	<u>All Grades (severe)</u> <u>NVP:</u> 14.8% (1.5% severe) <u>EFV:</u> 26% (1% grades 3- 4) <u>DLV:</u> 35.4% (4.4% grades 3-4) <u>ABC:</u> <5% in pts w/o HSR <u>APV:</u> 20-27% (1.0% grades 3-4) <u>fAPV:</u> 19% (< 1% grades 3-4) <u>ATV:</u> 21% (<1% severe) <u>DRV:</u> 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 1 study with ethinyl estradiol	● NVP – female, Black, Asian, Hispanic ● fAPV, 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

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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 1000/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 [321] •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

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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 NRTI or concomitant use of other drugs which may cause neuropathy • Advanced HIV disease • High dose or concomitant use of drugs which 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 maybe 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	Didanosine	Cotrimoxazole	Acyclovir (IV, high dose)	Azithromycin	Abacavir	Atovaquone	Cidofovir
Cidofovir	Isoniazid	Didanosine	Adefovir	Clarithromycin	Amprenavir	Clindamycin	Didanosine
Cotrimoxazole	Linezolid	Lamivudine (children)	Aminoglycosides	Delavirdine	Atazanavir	Darunavir	Ethambutol
Cytotoxic Chemotherapy	Stavudine	Pentamidine	Amphotericin B	Efavirenz	Atovaquone	Fos-amprenavir	Linezolid
Dapsone	Zalcitabine	Ritonavir	Cidofovir	Fluconazole	Cotrimoxazole	Lopinavir/ ritonavir	Rifabutin
Flucytosine		Stavudine	Foscarnet	Isoniazid	Dapsone	Nelfinavir	Voriconazole
Ganciclovir		Zalcitabine	Indinavir	Itraconazole	Darunavir	Ritonavir	
Hydroxyurea			Pentamidine	Ketoconazole	Delavirdine	Tipranavir	
Interferon-α			Tenofovir	Neviraprine	Efavirenz		
Linezolid				NRTIs	Fosamprenavir		
Peginterferon-α				PI (esp. Tipranavir)	Nevirapine		
Primaquine				Rifabutin	Sulfadiazine		
Pyrimethamine				Rifampin	Tipranavir		
Ribavirin				Voriconazole	Voriconazole		
Rifabutin							
Sulfadiazine							
Trimetrexate							
Valganciclovir							
Zidovudine							

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

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

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.

Amprenavir (Agenerase®) Oral Solution	• Because of the potential risk of toxicity from substantial amounts of the excipient propylene glycol in Agenerase Oral Solution, it is contraindicated for the following patient populations: children age <4 years; pregnant women; patients with renal or hepatic failure; patients treated with disulfiram or metronidazole • Oral solution should be used only when other protease inhibitors cannot be used.
Atazanavir (Reyataz™)	No box warning.
Darunavir	No box warning.
Delavirdine (Rescriptor®)	No box warning.

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.

Efavirenz (Sustiva®); or in combination product with tenofovir DF and emtricitabine (Atripla™)	No box warning.
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 co-infection. • 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 co-infected patients. • If appropriate, initiation of anti-HBV therapy may be warranted after discontinuation of tenofovir.
Enfuvirtide (Fuzeon)	No box warning.
Fosamprenavir (Lexiva™)	No box warning.
Indinavir (Crixivan®)	No box warning.
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 co-infected 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 co-infection. • 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
Lopinavir/ritonavir (Kaletra®)	No box warning.
Nelfinavir (Viracept®)	No box warning.
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 non-specific prodromes of hepatitis and progress to hepatic failure. • Women with CD4 counts > 250 cells/mm³, 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 non-sedating 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 combination of stavudine and didanosine with other antiretroviral combinations. • Stavudine and didanosine combination should only be used during pregnancy if the potential benefit clearly outweighs the potential risks. • Fatal and non-fatal 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 co-infection 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 co-infected patients. • If appropriate, initiation of anti-HBV therapy may be warranted after discontinuation of tenofovir.
Tipranavir (Aptivus®)	• Tipranavir co-adminstered with ritonavir 200mg twice daily has been associated with reports of both fatal and non-fatal intracranial hemorrhage. • Tipranavir co-adminstered 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 co-infection, as these patients have an increased risk of hepatotoxicity.
Zalcitabine (Hivid®)	• Zalcitabine can cause severe peripheral neuropathy, use with caution among patients with pre-existing neuropathy. • In rare cases, zalcitabine can cause pancreatitis, therapy should be withheld until pancreatitis is excluded. • Rare cases of hepatic failure and death have been reported among patients with underlying hepatitis B infection. • Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination.
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 or NNRTI 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											
Amprenavir[*] and 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
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[⊗]
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	

\# 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 U.S. The manufacturer of cisapride has a limited-access protocol for patients meeting specific clinical eligibility criteria.

* Each mL of amprenavir oral solution has 46 IU vitamin E. Patients should be cautioned to avoid supplemental doses of vitamin E. Multivitamin products containing minimal amounts of vitamin E are acceptable.

⊗ 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

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Table 21a. Drug Interactions Among Antiretrovirals and Other Drugs: Protease Inhibitors (PIs)

Drug Interactions Requiring Dose Modifications or Cautious Use		
Drugs Affected	**Atazanavir (ATV)**	**Fosamprenavir (fAPV)**
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 fAPV/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[ε]	Rifabutin 150mg QOD + fAPV 700/100mg BID, rifabutin unchanged. No data on fAPV level. Dose: No change in fAPV dose; decrease rifabutin to 150mg QD or 300mg 3x/week[ε]. If RTV-boosted fAPV, reduce rifabutin dose to 150mg QOD or 3x/week[ε].
Rifampin	Should not be coadministered.	A substantial decrease in APV AUC (≈ ↓ 82%) is expected based on the interaction with APV. Should not be co-administered.
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 co-administer; 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 fAPV 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 25 mg every 48 hours and monitor for adverse effects.	Sildenafil AUC ↑ 2- to 11-fold with APV. 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=17.5h). Start with a 5 mg 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 mg 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 2.5 mg dose and do not exceed a single 2.5 mg dose in 24 hours. Do not exceed 2.5 mg in 72 hours if administered with RTV.	No data, but vardenafil AUC may be substantially increased. Start with a 2.5 mg dose and do not exceed a single 2.5 mg dose in 24 hours. Do not exceed 2.5 mg 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 co-administer. 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 fAPV 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, Cmax, or Cmin, regardless of whether fAPV was given with or without ritonavir.

ε Rifabutin: At least 3x/week is recommended if CD4 cell count is <100/mm³

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

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; co-administration 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.ᵉ IDV 1,000mg Q8H.If RTV boosted, rif 150mg QOD or 3x/weekᵉ 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/weekᵉ; 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 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	Co-administration 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 25 mg 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 5 mg dose; do not exceed a single dose of 10mg q72h.	Tadalafil AUC ↑ 124% when co-administered 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 2.5 mg in 72h if administered w/RTV.	No data, but vardenafil AUC may be substantially increased. Do not exceed a single 2.5 mg 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 co-administered 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

ᵉ   Rifabutin: At least 3x/week is recommended if CD4 cell count is <100/mm³.

*   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.

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

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 co-administered 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.[ℰ] NFV 1,250mg BID.	Levels: Rifabutin ↑ 4X. Dose: ↓ rifabutin to 150mg QOD or dose 3x/week.[ℰ] 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 co-administered 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 25 mg 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 5 mg dose, and do not exceed a single dose of 10mg every 72 hours.	Tadalafil AUC ↑ 124%. Start with a 5 mg 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 2.5 mg dose and do not exceed a single 2.5 mg dose in 24 hours. Do not exceed 2.5 mg in 72 hours if administered with RTV.	Vardenafil AUC ↑ 49 fold. RTV AUC ↓ 20%. Dose: Vafdenafil: Start with a 2.5 mg dose and do not exceed a single 2.5 mg 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).

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

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

Drug Interactions Requiring Dose Modifications or Cautious Use		
Drugs Affected	**Saquinavir[†] (SQV)**	**Tipranavir + Ritonavir (TPV/RTV)**
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.
Ketoconazole	Levels: SQV ↑ 3X. Dose: No dosage adjustment necessary.	No data. Use with caution; do not exceed 200mg ketoconazole daily.
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.
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.
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.
Rifabutin	Levels: SQV ↓ 40%. Contraindicated unless SQV/RTV. Dose: Rifabutin 150mg qod or 3x/week.[ȼ]	Levels: Rifabutin AUC ↑ 2.9-fold. 25-O-desacetyl metabolite ↑ 20.7-fold. Dose: Decrease rifabutin dose to 150mg QOD or 3x/week.[ȼ] Single-dose study, thus the effect of multiple doses of rifabutin on TPV/r PK was not assessed.
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 non-serious rash. Used as hormone replacement therapy, monitor clinically for signs of estrogen deficiency.
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.
Pravastatin	Levels: 50% ↓ when administered with SQV/RTV combination. No dose adjustment needed. Dose: Pravastatin dosage adjustment based on lipid response.	No data.
Simvastatin Lovastatin	Levels: Potential for large increase in statin levels. Avoid concomitant use.	Potential for large increase in statin levels. Avoid concomitant use.
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.
METHADONE	Methadone AUC ↓ 20% when co-administered 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 co-administered with TPV/r.
ERECTILE DYSFUNCTION AGENTS		
Sildenafil	Sildenafil AUC ↑ 2-fold. Use a 25 mg starting dose of sildenafil.	No data. Starting dose should not exceed 25 mg sildenafil within 48 hours.
Tadalafil	Concomitant administration will result in substantial increase in tadalafil AUC and half-life (normal = 17.5 h). Start with a 5 mg 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.
Vardenafil	No data, but vardenafil AUC may be substantially increased. Start with a 2.5 mg dose and do not exceed a single 2.5 mg dose in 24 hours. Do not exceed a single 2.5 mg dose in 72 hours if administered with RTV.	No data. Starting dose should not exceed 2.5 mg vardenafil every 72 hours.
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.

[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 co-administered, 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 co-administered 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 25 mg every 48 hours and monitor for adverse effects. Vardenafil: No data, but vardenafil AUC may be substantially increased. Start with a 2.5 mg dose and do not exceed a single 2.5 mg 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 5 mg 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 co-administered 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	Fos-amprenavir	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 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 1000/100mg bid.‡ **Dose: Should not be co-administered, as doses are not established.**	No data.
Fosamprenavir (fAPV)	•	Levels: With fAPV/ATV 1,400/400 QD, ATV AUC & Cmin ↓ 33% and 57%, resp. fAPV AUC and Cmin ↑ 78% and 283%, respectively. With fAPV/r 700/100mg BID + ATV 300mg QD, ATV AUC and Cmax ↓ 22% and 24%, resp; fAPV unchanged. Dose: Insufficient data.for dose recommendation.	Levels: With coadministration of fAPV 700mg BID and LPV/r capsules 400/100mg BID, fAPV 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: fAPV AUC and Cmin ↑100% and 400%, respectively, with 200mg RTV. Dose: fAPV 1,400 + RTV 200mg QD; or fAPV 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 fAPV, 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 co-administered, 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 co-administered, as doses are not established.**
Ritonavir (RTV)	•	Levels: ATV AUC ↑238%. Dose: ATV 300mg QD + RTV 100mg QD.	Lopinavir is co-formulated 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 co-administered, 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

Drug Affected	Delavirdine	Efavirenz	Nevirapine
Fosamprenavir (fAPV)	Levels: Presumably, similar PK effects as APV: APV AUC ↑ 130%, and DLV AUC ↓ 61%. Dose: Coadministration not recommended.	Levels: fAPV Cmin ↓ 36% (when dosed at 1,400mg QD with 200mg RTV). Dose: fAPV 1,400mg + RTV 300mg QD; or fAPV 700mg + RTV 100mg BID.	No data.
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.
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.
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.
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.
Nelfinavir (NFV)	Levels: NFV ↑ 2 times. DLV ↓50%. Dose: No data.	Levels: NFV ↑ 20%. Dose: Standard.	Levels: NFV ↑ 10%. NVP no effect. Dose: Standard.
Nevirapine (NVP)	No data.	Levels: NVP-no effect. EFV AUC ↓ 22%.	•
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.
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.
Tipranavir	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]

‡ 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. Summary of Guidelines for Changing an Antiretroviral Regimen for Suspected Treatment Regimen Failure

Patient Assessment (AIII)

- Review antiretroviral treatment history.
- Assess for evidence of clinical progression.(e.g., physical exam, laboratory and/or radiologic tests)
- Assess adherence, tolerability, and pharmacokinetic issues.
- Distinguish between limited, intermediate, and extensive prior therapy and drug resistance.
- Perform resistance testing while patient is taking therapy (or within 4 weeks after regimen discontinuation).
- Identify active drugs and drug classes to use in designing the new regimen

Patient Management: Specific Clinical Scenarios

- *Limited or intermediate prior treatment with low (but not suppressed) HIV RNA level (e.g., up to 5000 copies/mL):* The goal of treatment is to re-suppress HIV RNA to below the level of assay detection. Consider intensifying with one drug (e.g., tenofovir) **(BII)** or pharmacokinetic enhancement (use of ritonavir boosting of a protease inhibitor) **(BII)**, perform resistance testing if possible, or most aggressively, change two or more drugs in the regimen **(CIII)**. If continuing the same treatment regimen, HIV RNA levels should be followed closely because ongoing viral replication will lead to accumulation of additional resistance mutations.

- *Limited or intermediate prior treatment with resistance to one drug:* Consider changing the one drug **(CIII)**, pharmacokinetic enhancement (few data available) **(BII)**, or, most aggressively, change two or more drugs in the regimen **(BII)**.

- *Limited or intermediate prior treatment with resistance to more than one drug:* The goal of treatment is to suppress viremia to prevent further selection of resistance mutations. Consider optimizing the regimen by changing classes (e.g., PI-based to NNRTI-based and vice versa) and/or adding new active drugs **(AII)** (See **Table 25**: *Treatment options following virologic failure on initial recommended therapy regimens.*)

- *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., 2–4 weeks) to determine if a resistant viral strain emerges on treatment **(CIII).**

- *Extensive prior treatment and drug resistance:* In patients with active antiretroviral agents available (e.g., an active ritonavir-boosted PI and enfuvirtide), the goal of therapy is suppression of viremia. In patients without active antiretroviral agent available and with ongoing viremia, the goal of therapy is preservation of immune responses and delay of clinical progression. It is reasonable to continue the same antiretroviral regimen if there are few or no treatment options **(CIII)**. In general, avoid adding a single active drug because of the risk for the rapid development of resistance to that drug. In advanced HIV disease with a high likelihood of clinical progression (e.g., CD4 cell count <100 cells/mm^3), adding a single drug may reduce the risk of immediate clinical progression **(CIII)**. In this complicated scenario, expert advice should be sought (See **Table 24**: *Novel strategies to consider for treatment-experienced patients with few available active treatment options.*)

- *Immunologic failure (or blunted CD4 response) with virologic suppression:* Immunologic failure (or blunted CD4 cell response) may not warrant a change in therapy in the setting of suppressed viremia. Assess for other causes of immunosuppression (e.g., HIV-2, HTLV-1, drug toxicity). The combination of didanosine and tenofovir has been associated with CD4 cell declines or blunted CD4 cell responses. In the setting of immunologic failure (or blunted CD4 response), it would be reasonable to change one of these drugs **(BIII)**. Intensifying with additional antiretroviral drugs or the use of immune-based therapies (e.g., interleukin-2) to improve immunologic responses remain unproven strategies and generally should not be offered **(DII).**

Table 24. Novel Strategies to Consider for Treatment-Experienced Patients With Few Available Active Treatment Options

- **Pharmacokinetic enhancement** with ritonavir may increase drug concentrations of most PIs (except nelfinavir) and may overcome some degree of drug resistance **(CII)**.

- **Therapeutic Drug Monitoring** may be considered (See **Therapeutic Drug Monitoring (TDM) for Antiretroviral Agents** section).

- **Re-treating with prior medications** may be useful, particularly if they were discontinued previously for toxicities that can now be better addressed **(BII)**. Reusing prior medications (even with documented drug resistance) may provide some degree of partial antiretroviral activity. Continued drug therapy and maintenance of drug-resistant virus may compromise viral fitness, but it is not known if this has clinical applicability.

- **The use of empiric multi-drug regimens** (including up to 3 PIs and/or 2 NNRTIs) has been advocated by some *[322, 323]*, but may be limited ultimately by complexity, poor tolerability, and unfavorable drug-drug interactions **(CII)**.

- **New antiretroviral drugs** (drugs in existing classes with activity against resistant viral strains, or new drug classes with novel mechanisms of action) including those available on expanded access (**Table 30**) or through clinical trials may be used. For example, the PIs darunavir and tipranavir (in combination with low-dose ritonavir) were approved for use in treatment-experienced patients as part of a combination antiretroviral regimen based on providing superior antiretroviral activity to an investigator-selected comparator PI *[224]*. The first approved HIV-1 entry inhibitor, enfuvirtide (T-20) was approved for use in the treatment-experienced patient with ongoing viremia on the basis of antiretroviral activity in this population *[220, 221]*. Optimally, a new active agent should be used with one or more other active agents in the regimen (e.g., a ritonavir-boosted PI and enfuvirtide) **(BII)**.

Novel Strategy Not Recommended at This Time:
- **Structured treatment interruptions** in the setting of virologic failure have been investigated prospectively, but most trials have shown limited or no virologic benefit *[211, 238, 239]*. The risks of this approach (CD4 cell decline, HIV-related clinical events including death, acute retroviral syndrome) appear to outweigh any possible benefit (decreased HIV RNA levels on the next treatment regimen). Given the seriousness of the risks and the unproven benefits, this strategy cannot be recommended **(DII)**.

Table 25. Treatment Options Following Virologic Failure on Antiretroviral Therapy Regimens

First Virologic Failure:

Regimen Class	Initial Regimen	Recommended Change*
NNRTI	2 NRTIs + NNRTI	• 2 NRTIs (based on resistance testing) + PI (with or without low-dose ritonavir) (**AII**)
PI	2 NRTIs + PI (with or without low-dose ritonavir)	• 2 NRTIs (based on resistance testing) + NNRTI (**AII**) • 2 NRTIs (based on resistance testing) + alternative PI (with low-dose ritonavir; based on resistance testing) (**AII**) • NRTI(s) (based on resistance testing) + NNRTI + alternative PI (with low-dose ritonavir; based on resistance testing) (**AII**)
triple-NRTI	3 nucleosides	• 2 NRTIs (based on resistance testing) + NNRTI or PI (with or without low-dose ritonavir) (**AIII**) • NNRTI + PI (with or without low-dose ritonavir) (**CIII**) • NRTI(s) (based on resistance testing) + NNRTI + PI (with or low-dose ritonavir) (**CII**)

Three-Class (NRTI, NNRTI, PI) Virologic Failure: >1 NRTIs (based on resistance testing) + a newer PI (with low-dose ritonavir; based on resistance testing) +/- enfuvirtide

(note: NNRTIs generally should not be used following the development of NNRTI-resistance because of the risk for selection of additional NNRTI-associated mutations)

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* Antiretroviral therapy regimens should be selected on the basis of treatment history and drug-resistance testing to optimize antiretroviral potency in the second regimen. This is particularly important in selecting NRTIS for an NNRTI-based regimen where drug resistance may occur rapidly to the NNRTI if the NRTIs are not sufficiently potent.

Table 26. Suggested Minimum Target Trough Concentrations for Persons With Wild-Type HIV-1 *[233-235, 237]*

Drug	Concentration (ng/mL)
Amprenavir (Agenerase) or Fosamprenavir (Lexiva)	400 (measured as amprenavir concentration)
Atazanavir (Reyatax)	150
Indinavir (Crixivan)	100
Lopinavir/ritonavir (Kaletra)	1000
Nelfinavir (Viracept) [a]	800
Ritonavir (Norvir) [b]	2100
Saquinavir (Invirase)	100-250
Efavirenz (Sustiva)	1000

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

Table 27. Associated Signs and Symptoms of Acute Retroviral Syndrome and Percentage of Expected Frequency *[252]*

♦ 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 28. Preclinical and Clinical Data Relevant to the Use of Antiretrovirals During 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 non-malignant tumors of liver, thyroid in female rats, and preputial and clitoral gland of mice and rats)	Positive (rodent anasarca and skeletal malformations at 1000mg/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	Unknown	Not completed	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 (rat and monkey)	Positive (hepatic adenomas in female mice at high doses)	Negative (osteomalacia when given to juvenile animals at high doses)
Zalcitabine (HIVID, ddC)	C	Yes (rhesus monkey) [0.30–0.50]	Positive (rodent, thymic lymphomas)	Positive (rodent-hydrocephalus at high dose)
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)	C	Yes (human) [~1.0]	Positive (hepatocellular adenomas and carcinomas in mice and rats)	Negative
Protease inhibitors				
Amprenavir (Agenerase)	C	Unknown	Positive (hepatocellular adenomas and carcinomas in male mice and rats)	Negative (but deficient ossification and thymic elongation in rats and rabbits)
Atazanavir	B	Unknown	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 (humans)	Positive (thyroid adenomas in male rats at highest dose)	Negative (but extra ribs in rodents)
Lopinavir/Ritonavir (Kaletra)	C	Unknown	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 (humans)	Positive (thyroid follicular adenomas and carcinomas in rats)	Negative
Ritonavir (Norvir)	B	Minimal (humans)	Positive (liver adenomas and carcinomas in male mice)	Negative (but cryptorchidism in rodents)
Saquinavir (Fortovase)	B	Minimal (humans)	Negative	Negative
Tipranavir (Aptivus)	C	Unknown	In progress.	Negative (decreased ossification and pup weights in rats at maternally toxic doses)
Fusion inhibitors				
Enfuvirtide (Fuzeon)	B	Unknown	Not done	Negative

† 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.

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Table 29. 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 (AZT 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 dosage change indicated [324].	No evidence of human teratogenicity [325]. 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 dosage change indicated [326].	No evidence of human teratogenicity [325]. 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 dosage change indicated [327].	Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving didanosine and stavudine together [328-330]	Alternate NRTI for dual nucleoside backbone of combination regimens. Didanosine should be used with stavudine only if no other alternatives are available.
Emtricitabine[†]	No 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 [331].	No evidence of human teratogenicity [325]. Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving didanosine and stavudine together [328-330].	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 because of potential for antagonism.
Abacavir[*]	Pharmacokinetics are not significantly altered in pregnancy; no change in dose indicated.	Hypersensitivity reactions occur in ~5-8% of non-pregnant 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[†]	No studies in human pregnancy. Phase I study in late pregnancy in progress.	Studies in monkeys show decreased fetal growth and reduction in fetal bone porosity within two months of starting maternal therapy [332]. Clinical studies in humans (particularly children) show bone demineralization with chronic use; clinical significance unknown [206, 333].	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 studies in human pregnancy.	Rodent studies indicate potential for teratogenicity and developmental toxicity (See **Table 28**).	Given lack of data and concerns regarding teratogenicity in animals, not recommended for use in human pregnancy unless alternatives are not available.

Table 29.   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			
Recommended agents			
Nevirapine	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated *[334]*.	No evidence of human teratogenicity *[325]*. Increased risk of symptomatic, often rash-associated, and potentially fatal liver toxicity among women with CD4$^+$ counts > 250/mm^3 when first initiating therapy *[97, 166]*; 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, because of the increased risk of potentially life-threatening hepatotoxicity in women with high CD4$^+$ counts. Women who enter pregnancy on nevirapine regimens & 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 *[95, 325, 335]*; 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 child bearing 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 studies in human pregnancy.	Rodent studies indicate potential for carcinogenicity and teratogenicity (See **Table 28**).	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).	
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 non-pregnant adults; an increased dose of 4 capsules of lopinavir/ritonavir twice daily starting in the 3rd trimester resulted in adequate lopinavir exposure; by 2 weeks postpartum, standard dosing was again appropriate. Pharmacokinetic studies of the new lopinavir/ritonavir tablet formulation are underway, but data are not yet available.	No evidence of human teratogenicity. 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 underway, 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.
Nelfinavir	Adequate drug levels are achieved in pregnant women with nelfinavir 1250mg, given twice daily *[117]*.	No evidence of human teratogenicity *[325]*. Well-tolerated, short-term safety demonstrated for mother and infant. Nelfinavir dosing at 750mg three times daily produced variable and generally low levels in pregnant women.	Given pharmacokinetic data and extensive experience with use in pregnancy compared with other PIs, preferred PI for combination regimens in pregnant women, particularly if HAART is being given solely for perinatal prophylaxis. In clinical trials of initial therapy in non-pregnant adults, nelfinavir-based regimens had a lower rate of viral response compared with lopinavir/ritonavir or efavirenz-based regimens, but similar viral response compared with atazanavir or nevirapine-based regimens *[106, 107, 111, 125]*.

Table 29. 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 with postpartum, although suppression of HIV RNA was seen [336, 337].	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-SGC/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 with postpartum [338].	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	Pharmacokinetic studies of saquinavir-soft gel capsules (SGC) indicated that inadequate drug levels were observed in pregnant women given 1,200 mg of saquinavir-SGC as a sole PI three times daily [339], but adequate levels were achieved when 800 mg saquinavir-SGC boosted with ritonavir 100 mg was given twice daily [340]. However, saquinavir-SGC are no longer produced. Limited pharmacokinetic data on saquinavir-hard gel capsule (HGC) suggest that 1,000 mg saquinavir-HGC/100 mg ritonavir given twice daily will achieve adequate saquinavir drug levels in pregnant women.	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 in pregnancy. Ritonavir-boosted saquinavir-HGC is an alternative PI for combination regimens in pregnancy, and is an alternative initial antiretroviral recommendation for non-pregnant adults.
Insufficient data to recommend use			
Amprenavir	No 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	No studies in human pregnancy.	Theoretical concern re: increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinemia in the neonate, although transplacental passage of other PIs has been low.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.
Darunavir	No studies in human pregnancy.	No experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.
Fosamprenavir	No studies in human pregnancy.	No experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.
Tipranavir	No studies in human pregnancy.	No experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.

Fusion Inhibitors

Insufficient data to recommend use

Enfuvirtide	No studies in human pregnancy.	No experience in human pregnancy.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.

NRTI = nucleoside reverse transcriptase inhibitor; NtRTI = nucleotide reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; SGC = soft gel capsule; HGC = hard 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 with PI-based HAART regimens. Triple NRTI regimens should be used only when an NNRTI- or PI-based HAART regimen cannot be used (e.g., because of 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 30.   Antiretroviral Agents Available Through Expanded Access Program (EAP)

Drug	TMC-125 (etravirine)	MK-0518
Source	1-866-889-2074 TMC125EAP@i3research.com http://www.tibotec.com/	http://www.earmrk.com
Class	Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)	Integrase Inhibitor
Dose	TMC-125 200mg twice daily + optimized background therapy (based on prior history and resistance testing)	MK-0518 400mg 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 ARV regimens • Unable to use currently approved NNRTIs because of resistance and/or intolerance • Have received licenced oral therapy with each of the 3 major classes (PI, NRTIs, and NNRTI) of ARVs • Have received 2 different PI-based regimens in the past • Primary NNRTI resistance can be included if experienced with at least 2 classes of ARVs (PI, NRTI) • Have not participated in TMC-125 studies in the past • Consult expanded access protocol for list of exclusion criteria.	Inclusion Criteria: • ≥16 years old • Limited or no treatment options available because of resistance (documented resistance to ≥ 1 drug in each of the 3 major classes of PI, NRTI, and NNRTI) or intolerance to multiple antiretroviral regimens • Not achieving adequate virologic suppression on current regimen • Be at risk of immunologic progression • Be clinically stable • Have not received MK-0518 in a clinical trial • Have CrCl >30 mL/min • Consult expanded access protocol for list of exclusion criteria.

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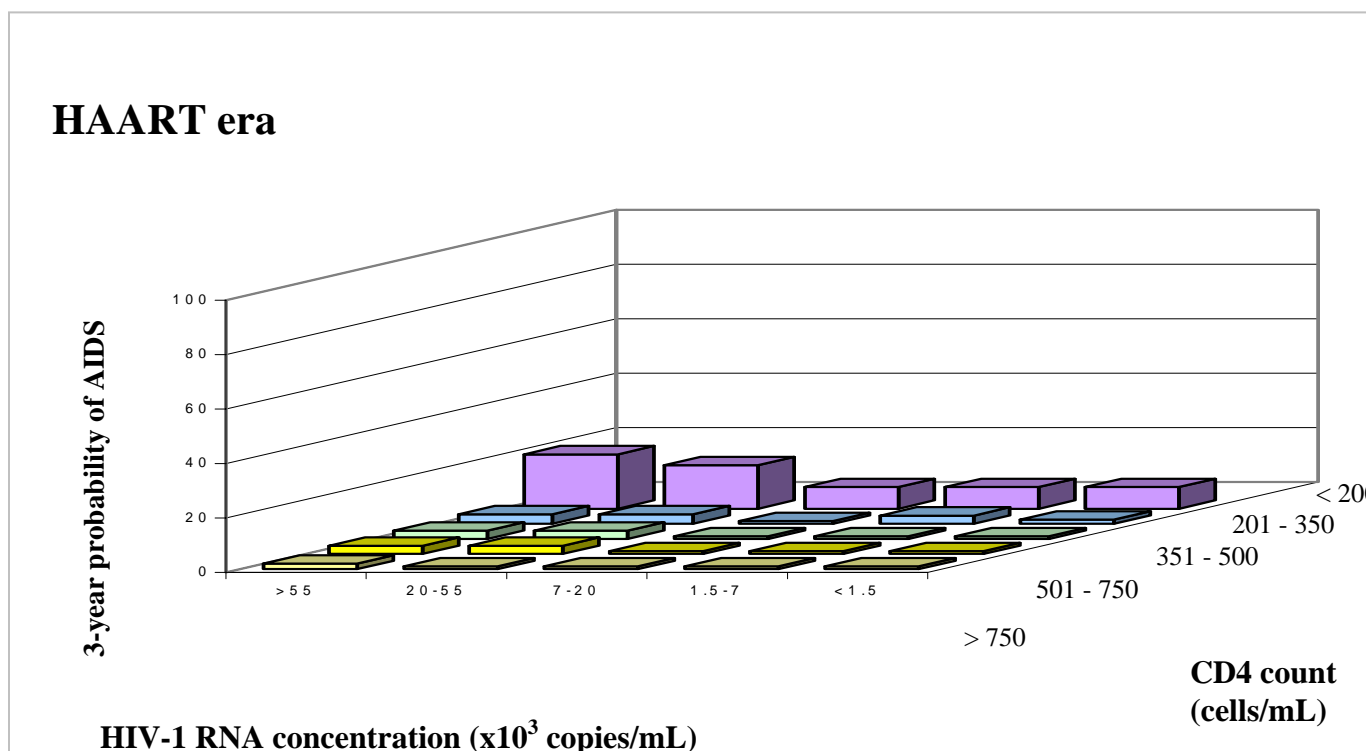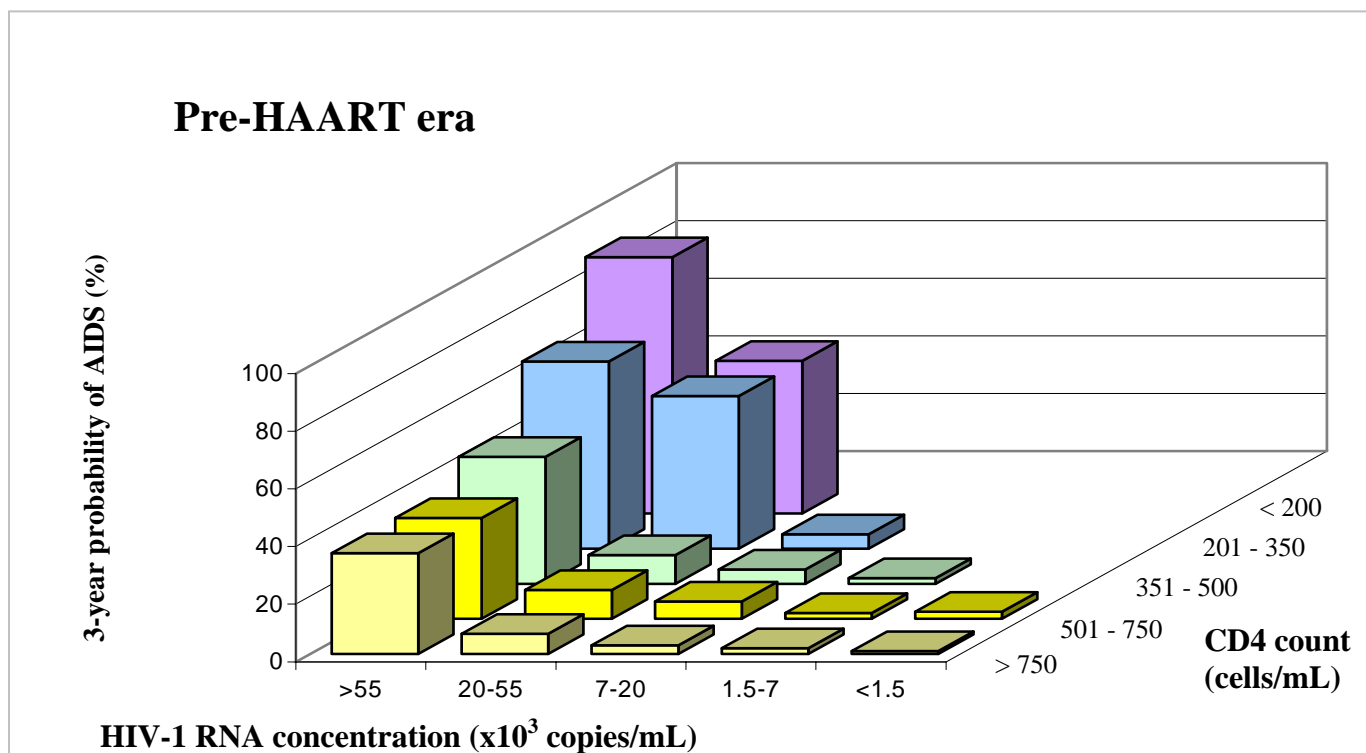
Pre-HAART era

HAART era

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Appendix A: DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents - Financial Conflict of Interest Disclosure – February 2006

Name	Panel Status*	Company	Relationship
Jean Anderson	M	Abbott Agouron/Pfizer Bristol Myers Squibb Glaxo Smith Kline	• Speakers' bureau; unrestricted educational grants • Speakers' bureau, HIV Advisory Board member, research support, unrestricted educational grants, stock holder • Speakers' bureau, unrestricted educational grants • Speakers' bureau, unrestricted educational grants
A. Cornelius Baker	M	Bristol Myers Squibb	• Community Advisory Board
John G. Bartlett	C	Abbott Bristol Myers Squibb Glaxo Smith Kline	• Scientific Advisory Board • Scientific Advisory Board • Scientific Advisory Board
Debra Birnkrant	M	None	N/A
Sam Bozzette	M	Not Reported	Not reported
Victoria Cargill	M	None	N/A
Charles Carpenter	M	None	N/A
Laura Cheever	M	None	N/A
Lawrence Deyton	M	None	N/A
Wafaa El-Sadr	M	None	N/A
Mark Dybul	M	None	N/A
Courtney V. Fletcher	M	Bristol Myers Squibb Glaxo Smith Kline	• Ad-hoc Advisory Boards • Ad-hoc Advisory Boards
Gregg Gonsalves	M	None	N/A
Eric Goosby	M	Gilead Pfizer	• Consultant, grantee, speaker • Grantee
Fred Gordin	M	None	N/A
Roy M. Gulick	M	Abbott Boehringer-Ingelheim Bristol Myers Squibb Gilead Glaxo Smith Kline Merck Monogram Pfizer Schering Tibotec Virco	• Research grant, ad hoc consultant • Research grant, ad hoc consultant • Ad-hoc consultant, speaker honoraria • Ad-hoc consultant, speaker honoraria • Ad-hoc consultant • Research grant • Ad-hoc consultant • Research grant • Research grant, ad-hoc consultant • Research grant, ad-hoc consultant • Ad-hoc consultant

Appendix A: DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents - Financial Conflict of Interest Disclosure – February 2006

Name	Panel Status*	Company	Relationship
Mark Harrington	M	None	N/A
Martin Hirsch	M	Cetek Glaxo Smith Kline Merck Schering Plough	• Advisory Board • Data Safety Monitoring Board • Data Safety Monitoring Board • Ad hoc consultant
Jonathan Kaplan	M	None	N/A
H. Clifford Lane	C	Chiron	• Research support/royalty payment to US Government
Henry Masur	M	None	N/A
John Mellors	M	Abbott Achillon Depomed Emory University Gilead Sciences Merck National Cancer Institute Pharmasset University of California San Diego University of Pittsburgh Virco-Tibotec	• Scientific Advisory Board • Stock Option • Stock holder • Patent • Scientific Advisory Board • Scientific Advisory Board • Patent Pending • Stock Option • Patent • Patent pending • Scientific Advisory Board
Lynne Mofenson	M	None	N/A
Jeffrey Murray	M	None	N/A
Heidi Nass	M	None	N/A
James Neaton	M	Bristol Myers Squibb Chiron Merck	• Data Safety Monitoring Board, consultant • Research grant • Data Safety Monitoring Board, consultant
James Oleske	M	None	N/A
Alice Pau	E	None	N/A
Robert Schooley	M	Achillon Anormed Bristol Myers Squibb Gilead Sciences Glaxo Smith Kline Merck Pfizer Roche Tanox Vertex ViroLogic	• Scientific Advisory Board, stock holder • Scientific Advisory Board, stock holder • Consultant • Consultant • Consultant • Consultant • Consultant • Consultant • Scientific Advisory Board, stock holder • Scientific Advisory Board, stock holder • Scientific Advisory Board, stock holder

Appendix A: DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents – Financial Conflict of Interest Disclosure – February 2006

Name	Panel Status*	Company	Relationship
Renslow Sherer	M	Abbott	• Consultant, Scientific Advisory Board, grant/research support, speakers' bureau
		Agouron	• Consultant, grant/research support, speakers' bureau
		Boehringer-Ingelheim	• Consultant
		Bristol Myers Squibb	• Consultant, grant/research support, speakers' bureau
		Chiron	• Grant/research support, speakers' bureau
		Dupont	• Consultant, grant/research support, speakers' bureau
		Gilead	• Consultant, Scientific Advisory Board, speakers' bureau
		Glaxo Smith Kline	• Consultant, grant/research support, speakers' bureau
		Merck	• Consultant
		Ortho-Biotech	• Consultant, grant/research support, speakers' bureau
		Roxanne	• Speakers' bureau
		Sarawak-Medichem	• Grant/research support, Scientific Advisory Board, speakers' bureau
		Virco-Tibotec	• Consultant
		US Bioscience	• Speakers' bureau
Stephen Spector	M	None	N/A
Sharilyn Stanley	M	None	N/A
Paul Volberding	M	Bristol Myers Squibb	• Advisory Board, honorarium
		Boehringer-Ingelheim	• Advisory Board
		Gilead	• Advisory Board, honorarium
		Glaxo Smith Kline	• Advisory Board, honorarium
		Immune Response	• Stock options
		Merck	• Advisory Board, honorarium
		Ortho Biotech	• Honorarium
		Pfizer	• Advisory Board
		Roche	• Honorarium
Suzanne Willard	M	Abbott	• Clinical Advisory Board

* C = Co-Chair; E = Executive Secretary; M = member
N/A = Not Applicable

Supplement to the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents - October 10, 2006*.

April 30, 2007

Entecavir in Hepatitis B Virus (HBV)/HIV Co-Infected Patients

Previously, the guidelines recommended entecavir as an option for patients who required treatment for Hepatitis B virus (HBV) but not HIV infection. This recommendation was based on in vitro data showing no significant activity of entecavir against HIV-1 *[1]*. A recent case series of three patients who received entecavir without concomitant antiretroviral therapy reported a 1 $\log_{10}$ decline in HIV-RNA levels and emergence of M184V mutations in one patient who was studied in detail *[2]*.

Based on these preliminary findings, the Panel recommends that:

For HBV/HIV co-infected patients, entecavir should not be used for the treatment of HBV infection without concomitant treatment for HIV.

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