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

***July 14, 2003***

**Developed by the Panel on Clinical Practices for Treatment of HIV Infection convened by the Department of Health and Human Services (DHHS)**

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**).

**July 14, 2003**

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*These Guidelines were developed by the Panel on Clinical Practices for Treatment of HIV Infection convened by the Department of Health and Human Services (DHHS).*

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

## SUMMARY

The availability of an increasing number of antiretroviral agents and the rapid evolution of new information has introduced substantial complexity into treatment regimens for persons infected with human immunodeficiency virus (HIV). In 1996, the Department of Health and Human Services and the Henry J. Kaiser Family Foundation convened the Panel on Clinical Practices for the Treatment of HIV to develop guidelines for clinical management of HIV-infected adults and adolescents (CDC Report of the NIH Panel To Define Principles of Therapy of HIV Infection and Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. MMWR 1998;47[RR-5]:1–41). The following issues were discussed.

1. using testing for plasma HIV ribonucleic acid levels (i.e., viral load) and $CD4^+$ T cell count;
2. using testing for antiretroviral drug resistance;
3. considerations for when to initiate therapy;
4. adherence to antiretroviral therapy;
5. considerations for therapy in antiretroviral naïve patients;
6. therapy-related adverse events;
7. interruption of therapy;
8. considerations for changing therapy and available therapeutic options;
9. treatment for acute HIV infection;
10. considerations for antiretroviral therapy among adolescents;
11. considerations for antiretroviral therapy among pregnant women; and
12. concerns related to transmission of HIV to others.

Antiretroviral regimens are complex, have serious side effects, pose difficulty with adherence, and carry serious potential consequences from the development of viral resistance because of nonadherence to the drug regimen or suboptimal levels of antiretroviral agents. Patient education and involvement in therapeutic decisions is critical. Treatment should usually be offered to all patients with symptoms ascribed to HIV infection. Recommendations for offering antiretroviral therapy among asymptomatic patients require analysis of real and potential risks and benefits. Treatment should be offered to persons who have $\leq$350 $CD4^+$ T cells/$mm^3$ or plasma HIV ribonucleic acid (RNA) levels of >55,000 copies/mL (by b-deoxyribonucleic acid [bDNA] or reverse transcriptase-polymerase chain reaction [RT-PCR] assays). The recommendation to treat asymptomatic patients should be based on the willingness and readiness of the person to begin therapy; the degree of existing immunodeficiency as determined by the $CD4^+$ T cell count; the risk for disease progression as determined by the $CD4^+$ T cell count and level of plasma HIV RNA; the potential benefits and risks of initiating therapy in an asymptomatic person; and the likelihood, after counseling and education, of adherence to the prescribed treatment regimen.

Treatment goals should be maximal and durable suppression of viral load, restoration and preservation of immunologic function, improvement of quality of life, and reduction of HIV-related morbidity and mortality. Results of therapy are evaluated through plasma HIV RNA levels, which are expected to indicate a 1.0 $\log_{10}$ decrease at 2–8 weeks and no detectable virus (<50 copies/mL) at 4–6 months after treatment initiation. Failure of therapy at 4–6 months might be ascribed to nonadherence, inadequate potency of drugs or suboptimal levels of antiretroviral agents, viral resistance, and other factors that are poorly understood. Patients whose therapy fails in spite of a high level of adherence to the regimen should have their regimen changed; this change should be guided by a thorough drug treatment history and the results of drug-resistance testing. Because of limitations in the available alternative antiretroviral regimens that have documented efficacy, optimal changes in therapy might be difficult to achieve for patients in whom the preferred regimen has failed. These decisions are further confounded by problems with adherence, toxicity, and resistance. For certain patients, participating in a clinical trial with or without access to new drugs or using a regimen that might not achieve complete suppression of viral replication might be preferable. Because concepts regarding HIV management are evolving rapidly, readers should check regularly for additional information and updates here:

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

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

## INTRODUCTION

This report was developed by the Panel on Clinical Practices for Treatment of HIV (the Panel), which was convened by the Department of Health and Human Services (DHHS) and the Henry J. Kaiser Family Foundation in 1996. The goal of these recommendations is to provide evidence-based guidance for clinicians and other health-care providers who use antiretroviral agents in treating adults and adolescents* infected with human immunodeficiency virus (HIV), including pregnant women. Although the pathogenesis of HIV infection and the general virologic and immunologic principles underlying the use of antiretroviral therapy are similar for all HIV-infected persons, unique therapeutic and management considerations exist for HIV-infected children. Therefore, guidance for antiretroviral therapy for pediatric HIV infection is not contained in this report. A separate document addresses pediatric-specific issues related to antiretroviral therapy, and is available at (http://*AIDSinfo*.nih.gov/guidelines).

These guidelines serve as a companion to the therapeutic principles from the National Institutes of Health (NIH) Panel to Define Principles of Therapy of HIV Infection *[1]*. Together, the reports provide pathogenesis-based rationale for therapeutic strategies as well as guidelines for implementing these strategies. Although the guidelines represent the state of knowledge regarding the use of antiretroviral agents, this is an evolving science and the availability of new agents or new clinical data regarding the use of existing agents will change therapeutic options and preferences. Because this report needs to be updated periodically, a subgroup of the Panel on Clinical Practices for Treatment of HIV Infection, the Antiretroviral Working Group, meets monthly to review new data. Recommendations for changes are then submitted to the Panel and incorporated as appropriate.§ These recommendations are not intended to supercede the judgment of clinicians who are knowledgeable in the care of HIV-infected persons. Furthermore, the Panel recommends that, when possible, the treatment of HIV-infected patients should be directed by a clinician who has extensive experience in the care of these patients. When this is not possible, the patient should have access to such clinical experience through consultations.

Each recommendation is accompanied by a rating that includes a letter and a Roman numeral (Table 1) and is similar to the rating schemes used in previous guidelines concerning prophylaxis of opportunistic infections (OIs) issued by the U.S. Public Health Service and the Infectious Diseases Society of America *[2]*. The letter indicates the strength of the recommendation, which is based on the opinion of the Panel, and the Roman numeral reflects the nature of the evidence supporting the recommendation (Table 1). Thus, recommendations made on the basis of data from clinical trials with clinical results are differentiated from those made on the basis of laboratory results (e.g., $CD4^+$ T lymphocyte count or plasma HIV ribonucleic acid [RNA] levels). When clinical trial data are unavailable, recommendations are made on the basis of the opinions of persons experienced in the treatment of HIV infection and familiar with the relevant literature.

Copies of this document and all updates are available from the

*AIDSinfo* Web site: http://*AIDSinfo*.nih.gov
Phone:1–800–448–0440
TTY: 1–888–480–3739
Fax: 1-301–519–6616

* In this report, an adolescent is defined as a person in late puberty or stage V of the Tanner growth chart (i.e., sexually mature).

§ The panel's reports and updates are available from the *AIDSinfo* service. They are also available from the National Prevention Information Network (NPIN) Internet site at http://www.cdcnpin.org.

# TESTING FOR PLASMA HIV RNA LEVELS AND CD4$^{+}$ T CELL COUNT TO GUIDE DECISIONS REGARDING THERAPY

Decisions regarding initiation or changes in antiretroviral therapy should be guided by monitoring the laboratory parameters of plasma HIV RNA (viral load) and CD4$^{+}$ T cell count in addition to the patient's clinical condition. Results of these laboratory tests provide clinicians with key information regarding the virologic and immunologic status of the patient and the risk for disease progression to acquired immunodeficiency syndrome (AIDS) *[3, 4]*. Three HIV viral load assays have been approved by the Food and Drug Administration (FDA) for determining prognosis and for monitoring the response to therapy. These include:

1. the HIV-1 reverse transcriptase polymerase chain reaction assay (Amplicor HIV-1 Monitor® Test, version 1.5, Roche Diagnostic),
2. in vitro nucleic amplification test for HIV-RNA (NucliSens® HIV-1 QT, Organon Teknika), and
3. in vitro signal amplification nucleic acid probe assay [VERSANT® HIV-1 RNA 3.0 Assay (bDNA)].

The former two assays were approved for a lower limit of detection at 50 copies/mL, where the approved lower limit of detection for the bDNA assay was 75 copies/mL. Because there are significant variability in the techniques and quantitative measurements among the three assays, clinicians are advised to use the same assay in monitoring the plasma viral load responses for an individual patient. Multiple analyses among >5,000 patients who participated in approximately 18 trials with viral load monitoring indicated a statistically significant dose-response–type association between decreases in plasma viremia and improved clinical outcome on the basis of standard results of new AIDS-defining diagnoses and survival. This relationship was observed throughout a range of patient baseline characteristics, including pretreatment plasma RNA level, CD4$^{+}$ T cell count, and previous drug experience.

Thus, viral load testing is an essential parameter in deciding to initiate or change antiretroviral therapies. Measurement of plasma HIV RNA levels (i.e., viral load) by using quantitative methods should be performed at the time of diagnosis and every 3–4 months thereafter for the untreated patient (AIII) (Table 2). CD4$^{+}$ T cell counts should be measured at the time of diagnosis and every 3–6 months thereafter (AIII). These intervals between tests are recommendations only, and flexibility should be exercised according to the circumstances of each patient. Plasma HIV RNA levels should also be measured immediately before and again at 2–8 weeks after initiation of antiretroviral therapy (AIII). This second measurement allows the clinician to evaluate initial therapy effectiveness because, for the majority of patients, adherence to a regimen of potent antiretroviral agents should result in a substantial decrease (~1.0 $\log_{10}$) in viral load by 2–8 weeks. A patient's viral load should continue to decline during the following weeks and, for the majority of patients, should decrease below detectable levels (i.e., defined as <50 RNA copies/mL by the Amplicor HIV-1 Monitor® test or Nuclisens® assay; or < 75 copies/mL by VERSANT HIV-1 RNA 3.0 Assay) by 16–24 weeks. Rates of viral load decline below the limit of detection are affected by the baseline CD4$^{+}$ T cell count, the initial viral load, potency of the regimen, adherence to the regimen, previous exposure to antiretroviral agents, and the presence of any OIs.

These differences must be considered when monitoring the effect of therapy. However, the absence of a virologic response of the magnitude discussed previously should prompt the clinician to reassess patient adherence, rule out malabsorption or drug interactions, consider repeat RNA testing to document lack of response, or consider a change in drug regimen. After the patient is on therapy, HIV RNA testing should be repeated every 3–4 months to evaluate the continuing effectiveness of therapy (AII). With optimal therapy, viral levels in plasma at 24 weeks should be below the limit of detection *[5]*. Data from clinical trials demonstrate that lowering plasma HIV RNA to <50 copies/mL (or <75 copies/mL by VERSANT® HIV-1 RNA 3.0 Assay) is associated with increased duration of viral suppression, compared with reducing HIV RNA to levels of 50–500 copies/mL *[6]*. If HIV RNA remains detectable in plasma after 16–24 weeks of therapy, the plasma HIV RNA test should be repeated to confirm the result and a change in therapy should be considered (Consideration for Treatment - Regimen Failure) (BIII).

When deciding on therapy initiation, the CD4$^{+}$ T lymphocyte count and plasma HIV RNA measurement should be performed twice to ensure accuracy and consistency of measurement (BIII). However, among patients with advanced HIV disease, antiretroviral therapy should be initiated after the first viral load measurement is obtained to prevent a potentially deleterious delay in treatment. The requirement for two measurements of viral load might place a substantial financial burden on patients or payers. Nonetheless, the Panel believes that two measurements of viral load will provide the clinician with the best information for subsequent patient follow-up. Plasma HIV RNA levels should not be measured during or within the 4 weeks after successful treatment of any intercurrent infection, resolution of symptomatic illness, or immunization. Because differences exist among commercially available tests, confirmatory plasma HIV RNA levels should be measured by using the same laboratory and the same technique to ensure consistent results.

A minimal change in plasma viremia is considered to be a threefold or 0.5-$\log_{10}$ increase or decrease. A substantial decrease in $CD4^+$ T lymphocyte count is a decrease of >30% from baseline for absolute cell numbers and a decrease of >3% from baseline in percentages of cells *[7]*. Discordance between trends in $CD4^+$ T cell numbers and plasma HIV RNA levels was documented among 20% of patients in one cohort studied *[8]*. Such discordance can complicate decisions regarding antiretroviral therapy and might be caused by factors that affect plasma HIV RNA testing. Viral load and trends in viral load are believed to be more informative for decision-making regarding antiretroviral therapy than are $CD4^+$ T cell counts; however, exceptions to this rule do occur (see Consideration for Treatment - Regimen Failure). In certain situations, consultation with a specialist should be considered.

## DRUG-RESISTANCE TESTING

Testing for HIV resistance to antiretroviral drugs is a useful tool for guiding antiretroviral therapy *[9]*. Studies of treatment-experienced patients have reported strong associations between the presence of drug resistance identified by genotyping or phenotyping resistance assays and failure of the antiretroviral treatment regimen to suppress HIV replication *[10-13]*. Furthermore, when combined with a detailed drug history and efforts to maximize drug adherence, these assays have been shown to improve the short term virologic response to antiretroviral therapy.

Genotyping assays detect drug resistance mutations that are present in the relevant viral genes (i.e., reverse transcriptase and protease). Certain genotyping 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. Genotyping 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 IAS-USA maintains a list of significant resistance-associated mutations in the reverse transcriptase, protease, and envelope genes (see www.iasusa.org/resistance_mutations). Various techniques such as rules-based algorithms and “virtual phenotype” are now available to assist the provider in interpreting genotyping test results *[10, 14-16]*. Consultation with a specialist in HIV drug resistance is encouraged and can facilitate interpretation of genotyping results; the benefit of such consultation has been demonstrated *[17]*.

Phenotyping assays measure a virus's ability to grow in different concentrations of antiretroviral drugs. Automated, recombinant phenotyping assays are commercially available with results available in 2-3 weeks; however, phenotyping assays are more costly to perform than genotyping assays. Recombinant phenotyping 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 phenotyping 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 *[18-20]*. Again, consultation with a specialist can be helpful for interpreting test results.

Further limitations of both genotyping and phenotyping 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 critical when interpreting data regarding susceptibility to drugs that the patient has taken in the past but that are not part of the current antiretroviral regimen. If drug resistance had developed to a drug that was subsequently discontinued, the drug-resistant virus can become a minor species because its growth advantage is lost *[21-23]*. Consequently, resistance assays should be performed while the patient is taking his or her antiretroviral regimen, and data suggesting the absence of resistance should be interpreted cautiously in relation to the previous treatment history.

## Using Resistance Assays in Clinical Practice

Resistance assays are useful for patients experiencing virologic failure while on antiretroviral therapy (Table 3). 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 genotyping assays, phenotyping assays, or both *[10-13, 17, 24-28]*. In general, these studies indicated that the short-term virologic response to therapy was increased when results of resistance testing were available, compared to 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). Similar rationale applies to the potential use of resistance testing for patients with suboptimal viral load reduction (see Changing Antiretroviral Therapy for Virologic Failure) (BIII). Virologic failure in the setting of combination antiretroviral therapy is, for certain patients, associated with resistance to one component of the regimen only *[29-31]*; in that situation, substituting individual drugs in a failing regimen might be possible, although this concept will require clinical validation (see Consideration for Treatment - Regimen Failure). No prospective data exist to support using one type of resistance assay over another (i.e., genotyping versus phenotyping) in different clinical situations. Therefore, one type of assay is recommended per sample; however, for patients with a complex treatment history, both assays might provide critical and complementary information.

Transmission of drug-resistant HIV strains has been documented and has been associated with a suboptimal virologic response to initial antiretroviral therapy *[32]*. If the decision is made to initiate therapy in a person with acute HIV infection, it is likely that resistance testing at baseline will optimize virologic response, although this strategy has not been tested in prospective clinical trials (BIII). Because of its more rapid turnaround time, using a genotyping assay might be preferred in this situation. Since some resistance-associated mutations are known to persist in the absence of drug pressure, it may be reasonable to extend this strategy for 1–2 years post-seroconversion.

Using resistance testing before initiation of antiretroviral therapy in patients with chronic HIV infection is less straightforward. Available resistance assays might fail to detect drug-resistant species that were transmitted when primary infection occurred but, with the passage of time, became a minor species in the absence of selective drug pressure. As with acute HIV infection, prospective evaluation of "baseline" resistance testing in this setting has not been performed. It may be reasonable to consider such testing, however, when there is a significant probability that the patient was infected with a drug-resistance virus, i.e., if the patient is thought to have been infected by a person who was receiving antiretroviral drugs (CIII). A recent study suggested that baseline testing may be cost-effective when the prevalence of drug resistance in the relevant drug-naïve population is ≥5% *[33]*, but such data are infrequently available.

In pregnant women, the purpose of antiretroviral therapy is to reduce HIV plasma RNA to below the limit of detection, for the benefit of both mother and child. In this regard, recommendations for resistance testing during pregnancy are the same as for nonpregnant persons.

# CONSIDERATIONS FOR PATIENTS WITH ESTABLISHED HIV-1 INFECTION

Patients with established HIV infection are discussed in two arbitrarily defined clinical categories:

1. asymptomatic infection or
2. symptomatic disease (i.e., wasting, thrush, or unexplained fever for >2 weeks) including AIDS, as classified by CDC in 1993 *[34]*.

All patients in the second category should be offered antiretroviral therapy (AI). Initiating antiretroviral therapy among patients in the first category is complex and, therefore, discussed separately. Before therapy for any patient is initiated, however, the following evaluation should be performed:

- Complete history and physical (AII)
- Complete blood count, chemistry profile, including serum transaminases and lipid profile (AII)
- $CD4^+$ T lymphocyte count (AI)
- Plasma HIV RNA Measurement (AI)

Additional evaluation should include routine tests relevant to preventing OIs, if not already performed (e.g., rapid plasma reagin or Venereal Disease Research Laboratory test; tuberculin skin test; toxoplasma immunoglobulin G serology; hepatitis B and C serology; and gynecologic exam, including Papanicolaou smear). Other tests are recommended, if clinically indicated (e.g., chest radiograph and ophthalmologic exam) (AII). Cytomegalovirus serology can be useful for certain patients *[2]* (BIII).

# CONSIDERATIONS FOR INITIATING THERAPY FOR THE PATIENT WITH ASYMPTOMATIC HIV-1 INFECTION

Although randomized clinical trials provide strong evidence for treating patients with <200 $CD4^+$ T cells/$mm^3$ (AI) *[35-37]*, the optimal time to initiate antiretroviral therapy among asymptomatic patients with $CD4^+$ T cell counts >200 cells/$mm^3$ is unknown. For persons with >200 $CD4^+$ T cells/$mm^3$, the strength of the recommendation for therapy must balance the readiness of the patient for treatment, consideration of the prognosis for disease-free survival as determined by baseline $CD4^+$ T cell count and viral load levels, and assessment of the risks and potential benefits associated with initiating antiretroviral therapy.

Regarding a prognosis that is based on the patient's $CD4^+$ T cell count and viral load, data are absent concerning clinical endpoints from randomized, controlled trials for persons with >200 $CD4^+$ T cells/$mm^3$ to guide the decision on when to initiate therapy. Despite their limitations, however, observational cohorts of HIV-infected persons either treated or untreated with antiretroviral therapy provide key data to assist in risk assessment for disease progression.

Observational cohorts have provided critical data regarding the prognostic influence of viral load and $CD4^+$ T cell count in the absence of treatment. These data indicate a strong relationship between plasma HIV RNA levels and $CD4^+$ T cell counts in terms of risk for progression to AIDS for untreated persons and provide potent support for the conclusion that therapy should be initiated before the $CD4^+$ T cell count declines to <200 cells/$mm^3$ (Figure 1 and Tables 4, 5). In addition, these studies are useful for the identification of asymptomatic persons at high risk who have $CD4^+$ T cell counts >200 cells/$mm^3$ and who might be candidates for antiretroviral therapy or more frequent $CD4^+$ T cell count monitoring. Regarding $CD4^+$ T cell count monitoring, the Multicenter AIDS Cohort Study (MACS) demonstrated that the 3-year risk for progression to AIDS was 38.5% among patients with 201–350 $CD4^+$ T cells/$mm^3$, compared with 14.3% for patients with $CD4^+$ T cell counts >350 cells/$mm^3$. However, the short-term risk for progression also was related to the level of plasma HIV RNA, and the risk was relatively low for those persons with <20,000 copies/mL. An evaluation of 231 persons with $CD4^+$ T cell counts of 201–350 cells/$mm^3$ demonstrated that the 3-year risk for progression to AIDS was 4.1% for the 74 patients with HIV RNA <20,000; 36.4% for those 53 patients with HIV RNA 20,001–55,000 copies/mL; and 64.4% for those 104 patients with HIV RNA >55,000 copies/mL. Similar risk gradations by viral load are evident for patients with $CD4^+$ T cell counts >350 cells/$mm^3$ (Figure 1 and Table 5) *[38]*. These data indicate that for certain patients with $CD4^+$ T cell counts >200 cells/$mm^3$, the 3-year risk for disease progression to AIDS in the absence of treatment is substantially increased. Thus, although observational studies of untreated persons cannot assess the effects of therapy and, therefore, cannot determine the optimal time to initiate therapy, these studies do provide key guidance regarding the risks for progression in the absence of therapy on the basis of a patient's $CD4^+$ T cell count and viral load.

Data from observational studies of HAART-treated cohorts also provide critical information to guide the use of antiretroviral therapy among asymptomatic patients *[39-42]*. A collaborative analysis of data from 13 cohort studies from Europe and North America demonstrates that among drug-naïve patients without AIDS-defining illness and a viral load <100,000 copies/mL, the 3-year probability of progression to AIDS or death was 15.8% among those who initiated therapy with $CD4^+$ T cell counts of 0–49 cells/$mm^3$; 12.5% among those with $CD4^+$ T cell counts of 50–99 cells/$mm^3$; 9.3% among those with $CD4^+$ T cell counts of 100–199 cells/$mm^3$; 4.7% among those with $CD4^+$ T cell counts of 200–349 cells/$mm^3$; and 3.4% among those with $CD4^+$ T cell counts of 350 cells/$mm^3$ or higher *[42]*. These data indicate that the prognosis might be better for patients who initiate therapy at >200 cells/$mm^3$; but risk after initiation of therapy does not vary considerably at >200 cells/$mm^3$. Risk for progression also was related to plasma HIV RNA levels in this study. A substantial increase in risk for progression was evident among all patients with a viral load >100,000 copies/mL. In other cohort studies, an apparent benefit in terms of disease progression was reported among persons who began antiretroviral therapy when $CD4^+$ T cell counts were >350 cells/$mm^3$ compared to those who deferred therapy *[43, 44]*. For example, in the Swiss cohort study, an approximate 7-fold decrease occurred in disease progression to AIDS among persons who initiated therapy with a $CD4^+$ T cell count >350 cells/$mm^3$ compared with those who were monitored without therapy during a 2-year period *[44]*. However, a substantial incidence of adverse treatment effects occurred among patients who initiated therapy; 40% of patients had more than one treatment changes because of adverse effects, and 20% were no longer receiving treatment after two years *[44]*. Unfortunately, observational studies of persons treated with HAART also have limitations regarding the ability to determine an optimal time to initiate therapy. The relative risks for disease progression for persons with $CD4^+$ T cell counts 201–350 and >350 cells/mm$^3$ cannot be precisely compared because of the low level of disease progression among these patients during the follow-up period. In addition, groups might differ in key known and unknown prognostic factors that bias the comparison.

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 or delayed therapy initiation for the asymptomatic patient should be considered by the clinician and patient Table 4.

***Potential benefits of early therapy include:***

1. earlier suppression of viral replication;
2. preservation of immune function;
3. prolongation of disease-free survival;
4. lower risk of resistance with complete viral suppression; and
5. possible decrease in the risk for viral transmission.

***Potential risks of early therapy include:***

1. the adverse effects of the drugs on quality of life
2. the inconvenience of some of the available regimens, leading to reduced adherence;
3. development of drug resistance because of suboptimal suppression of viral replication;
4. limitation of future treatment options as a result of premature cycling of available drugs;
5. the risk of transmission of virus resistant to antiretroviral drugs;
6. serious toxicities associated with certain antiretroviral drugs; and
7. the unknown durability of effect of available therapies.

***Potential benefits of delayed therapy include:***

1. avoidance of treatment-related negative effects on quality of life and drug-related toxicities;
2. preservation of treatment options; and
3. delay in the development of drug resistance.

***Potential risks of delayed therapy include:***

1. the possibility that damage to the immune system, which might otherwise be salvaged by earlier therapy, is irreversible;
2. the possibility that suppression of viral replication might be more difficult at a later stage of disease; and
3. the increased risk for HIV transmission to others during a longer untreated period.

Finally, for certain persons, ascertaining the precise time at which the $CD4^+$ T cell count will decrease to a level where the risk for disease is high might be difficult, and time might be required to identify an effective, tolerable regimen. This task might be better accomplished before a patient reaches a $CD4^+$ T cell count of 200 cells/mm$^3$.

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, many specialists in this area believe that the evidence supports initiating therapy in asymptomatic HIV-infected persons with a $CD4^+$ T cell count of <350 cells/mm$^3$ or a viral load >55,000 copies/mL (by RT-PCR or b-deoxyribonucleic acid [bDNA] assays) (BII). For asymptomatic patients with $CD4^+$ T cell counts >350 cells/mm$^3$, rationale exists for both conservative and aggressive approaches to therapy. The conservative approach is based on the recognition that robust immune reconstitution still occurs in the majority of patients who initiate therapy with $CD4^+$ T cell counts in the 200–350 cells/mm$^3$range, and that toxicities and adherence challenges might outweigh the benefits of initiating therapy at $CD4^+$ T cell counts >350 cells/mm$^3$. In the conservative approach, increased levels of plasma HIV RNA (i.e., >55,000 by RT-PCR or bDNA assays) are an indication that more frequent monitoring of $CD4^+$ T cell counts and plasma HIV RNA levels is needed, but not necessarily for initiation of therapy. In the aggressive approach, asymptomatic patients with $CD4^+$ T cell counts >350 cells/mm$^3$ and levels of plasma HIV RNA >55,000 copies/mL would be treated because of the risk for immunologic deterioration and disease progression (CII). The aggressive approach is supported by the observation in multiple studies that suppression of plasma HIV RNA by antiretroviral therapy is easier to achieve and maintain at higher $CD4^+$ T cell counts and lower levels of plasma viral load *[6, 45-48]*. However, long-term clinical outcome data are not available to fully endorse this approach.

Data regarding sex-specific differences in viral load and $CD4^+$ T cell counts are conflicting (See Considerations for Antiretroviral Therapy in Women). Certain studies *[49-55]*, although not others *[56-59]*, have concluded that after adjustment for $CD4^+$ T cell counts, levels of HIV RNA are lower in women than in men. In those studies that have indicated a possible sex difference in HIV RNA levels, women have had RNA levels that ranged from 0.13 to 0.28 $\log_{10}$ lower than levels observed among men. In two studies of HIV seroconverters, HIV RNA copy numbers were substantially lower in women than men at seroconversion, but these differences decreased with time, and median viral load in women and men became similar within 5–6 years after seroconversion *[50, 51, 55]*. Other data indicate that $CD4^+$ T cell counts might be higher in women than in men *[60]*. Importantly however, rates of disease progression do not differ in a sex-dependent manner *[53, 55, 61, 62]*. Taken together, 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. Clinicians might consider lower plasma HIV RNA thresholds for initiating therapy in women with $CD4^+$ T cell counts >350 cells/$mm^3$, although insufficient data exist to determine an appropriate threshold. In patients with $CD4^+$ T cell counts <350 cells/$mm^3$, limited sex-based differences in viral load have been observed; therefore, no changes in treatment guidelines for women are recommended for this group.

In summary, the decision to begin therapy for the asymptomatic patient with >200 $CD4^+$ T cells/$mm^3$ is complex and must be made in the setting of careful patient counseling and education. Factors that must be considered in this decision are:

1. the willingness, ability, and readiness of the person to begin therapy;
2. the degree of existing immunodeficiency as determined by the $CD4^+$ T cell count;
3. the risk of disease progression as determined by the $CD4^+$ T cell count and level of plasma HIV RNA *[1]*); (Figure 1; and Tables 5 and 6**)**;
4. the potential benefits and risks of initiating therapy for asymptomatic persons, including short-and-long-term adverse drug effects; (Table 4); and
5. the likelihood, after counseling and education, of adherence to the prescribed treatment regimen.

Regarding adherence, 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 nonadherence. Rather, the likelihood of patient adherence to a long-term, complex 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: intensive patient education and support regarding the critical need for adherence should be provided; specific goals of therapy should be established and mutually agreed upon; and a long-term treatment plan should be developed with the patient. Intensive follow-up should occur to assess adherence to treatment and to continue patient counseling for the prevention of sexual and drug-injection–related transmission (see Adherence to Potent Antiretroviral Therapy).

# CONSIDERATIONS FOR DISCONTINUING THERAPY

As recommendations evolve, patients who had begun active antiretroviral therapy at $CD4^+$ T cell counts >350/mm³ might consider discontinuing treatment. No clinical data exist addressing whether this should be done or if it can be accomplished safely. Potential benefits include reduction of toxicity and drug interactions, decreased risk for drug-selecting resistant variants, and improvement in quality of life. Risks include rebound in viral replication and renewed immunologic deterioration. If the patient and clinician agree to discontinue therapy, the patient should be closely monitored (CIII).

# ADHERENCE TO POTENT ANTIRETROVIRAL THERAPY

The Panel recommends that certain persons living with HIV, including persons who are asymptomatic, should be treated with HAART for the rest of their lives. Adherence to the regimen is essential for successful treatment and has been reported to increase sustained virologic control, which is critical in reducing HIV-related morbidity and mortality. Conversely, suboptimal adherence has been reported to decrease virologic control and has been associated with increased morbidity and mortality *[63, 64]*. Suboptimal adherence also leads to drug resistance, limiting the effectiveness of therapy *[65]*. The determinants, measurements, and interventions to improve adherence to HAART are insufficiently characterized and understood, and additional research regarding this topic is needed.

## Adherence to Therapy During HIV-1 Disease

Adherence is a key determinant in the degree and duration of virologic suppression. Among studies reporting on the association between suboptimal adherence and virologic failure, nonadherence among patients on HAART was the strongest predictor for failure to achieve viral suppression below the level of detection *[64, 65]*. Other studies have reported that 90%–95% of doses must be taken for optimal suppression, with lesser degrees of adherence being associated with virologic failure *[63, 66]*. No conclusive evidence exists to show that the degree of adherence required varies with different classes of agents or different medications in the HAART regimen.

Suboptimal adherence is common. Surveys have determined that one third of patients missed doses within <3 days of the survey *[67]*. Reasons for missed doses were predictable and included forgetting, being too busy, being out of town, being asleep, being depressed, having adverse side effects, and being too ill *[68]*. One fifth of HIV-infected patients in one urban center never filled their prescriptions. Although homelessness can lead to suboptimal adherence, one program achieved a 70% adherence rate among homeless persons by using flexible clinic hours, accessible clinic staff, and incentives *[69]*.

Predictors of inadequate adherence to HIV medications include

1. lack of trust between clinician and patient;
2. active drug and alcohol use;
3. active mental illness (e.g., depression);
4. lack of patient education and inability of patients to identify their medications *[68]*), and
5. lack of reliable access to primary medical care or medication *[70]*.

Other sources of instability influencing adherence include domestic violence and discrimination *[70]*. Medication side effects can also cause inadequate adherence as can fear of or experiencing metabolic and morphologic side effects of HAART *[71]*.

Predictors of optimal adherence to HIV medications, and hence, optimal viral suppression, include

1. availability of emotional and practical life supports;
2. a patient's ability to fit medications into his or her daily routine;
3. understanding that suboptimal adherence leads to resistance;
4. recognizing that taking all medication doses is critical;
5. feeling comfortable taking medications in front of others *[72]*. and
6. keeping clinic appointments *[46]*.

Measurement of adherence is imperfect and lacks established standards. Patient self-reporting is an unreliable predictor of adherence; however, a patient's estimate of suboptimal adherence is a strong predictor and should be strongly considered *[72, 73]*. A clinician's estimate of the likelihood of a patient's adherence is also an unreliable predictor *[74]*. Aids for measuring adherence (e.g., pill counts, pharmacy records, "smart" pill bottles with computer chips that record each opening [i.e., medication event monitoring systems or MEMS caps]) might be useful, although each aid requires comparison with patient self-reporting *[73, 75]*. Clinician and patient estimates of the degree of adherence have been reported to exceed measures that are based on MEMS caps. Because of its complexity and cost, MEMS caps technology might be used as an adjunct to adherence research, but it is not useful in clinical settings.

Self-reporting should include a short-term assessment of each dose that was taken during the recent past (e.g., <3 days) and a general inquiry regarding adherence since the last visit, with explicit attention to the circumstances of missed doses and possible measures to prevent further missed doses. Having patients bring their medications and medication diaries to clinic visits might be helpful also.

## Approaching the Patient

### *Patient-related strategies*

The first principle of patient-related strategies is to negotiate a treatment plan that the patient understands and to which he or she commits Tables 7–10 *[76, 77]*. Before writing the first prescription, clinicians should assess the patient's readiness to take medication, which might take two or three office visits and patience. Patient education should include the goals of therapy, including a review of expected outcomes that are based on baseline viral load and $CD4^+$ T cell counts (e.g., MACS data from the Guidelines [4]), the reason for adherence, and the plan for and mechanics of adherence. Patients must understand that the first HAART regimen has the best chance for long-term success *[1]*. Clinicians and health teams should develop a plan for the specific regimen, including how medication timing relates to meals and daily routines. Centers have offered practice sessions and have used candy in place of pills to familiarize the patient with the rigors of HAART; however, no data exist to indicate if this exercise improves adherence. Daily or weekly pillboxes, timers with alarms, pagers, and other devices can be useful. Because medication side effects can affect treatment adherence, clinicians should inform patients in advance of possible side effects and when they are likely to occur. Treatment for side effects should be included with the first prescription, as well as instructions on appropriate response to side effects and when to contact the clinician. Low literacy is also associated with suboptimal adherence. Clinicians should assess a patient's literacy level before relying on written information, and they should tailor the adherence intervention for each patient. Visual aids and audio or video information sources can be useful for patients with low literacy *[78]*.

Education of family and friends and their recruitment as participants in the adherence plan can be useful. Community interventions, including adherence support groups or the addition of adherence concerns to other support group agendas, can aid adherence. Community-based case managers and peer educators can assist with adherence education and strategies for each patient.

Temporary postponement of HAART initiation has been proposed for patients with identified risks for suboptimal adherence *[79, 80]*. For example, a patient with active substance abuse or mental illness might benefit from psychiatric treatment or treatment for chemical dependency before initiating HAART. During the 1–2 months needed for treatment of these conditions, appropriate HIV therapy might be limited to OI prophylaxis, if indicated, and therapy for drug withdrawal, detoxification, or the underlying mental illness. In addition, readiness for HAART can be assessed and adherence education can be initiated during this period. Other sources of patient instability (e.g., homelessness) can be addressed during this time. Patients should be informed and in agreement with plans for future treatment and time-limited treatment deferral.

Selected factors (e.g., sex, race, low socioeconomic status or education level, and past drug use) are not reliable predictors of suboptimal adherence. Conversely, higher socioeconomic status and education level and a lack of past drug abuse do not predict optimal adherence *[81]*. No patient should automatically be excluded from antiretroviral therapy simply because he or she exhibits a behavior or characteristic judged by the clinician to indicate a likelihood of nonadherence.

### *Clinician and health team-related strategies*

Trusting relationships among the patient, clinician, and health team are essential Table 8. Clinicians should commit to communication between clinic visits, ongoing adherence monitoring, and timely response to adverse events or interim illness. Interim management during clinician vacations or other absences must be clarified with the patient.

Optimal adherence requires full participation by the health-care team, with goal reinforcement by more than 2 team members. Supportive and nonjudgmental attitudes and behaviors will encourage patient honesty regarding adherence and problems. Improved adherence is associated with interventions that include pharmacist-based adherence clinics *[81]*, street-level drop-in centers with medication storage and flexible hours for homeless persons *[82]*, adolescent-specific training programs *[83]*, and medication counseling and behavioral intervention *[84]*; Table 9. For all health-care team members, specific training regarding HAART and adherence should be offered and updated periodically.

Monitoring can identify periods of inadequate adherence. Evidence indicates that adherence wanes as time progresses, even among patients whose adherence has been optimal, a phenomenon described as pill fatigue or treatment fatigue *[79, 85]*. Thus, monitoring adherence at every clinic encounter is essential. Reasonable responses to decreasing adherence include increasing the intensity of clinical follow-up, shortening the follow-up interval, and recruiting additional health team members, depending on the problem *[80]*. Certain patients (e.g., chemically dependent patients, mentally retarded patients in the care of another person, children and adolescents, or patients in crisis) might require ongoing assistance from support team members from the outset.

New diagnoses or symptoms can influence adherence. For example, depression might require referral, management, and consideration of the short- and long-term impact on adherence. Cessation of all medications at the same time might be more desirable than uncertain adherence during a 2–month exacerbation of chronic depression.

Responses to adherence interventions among specific groups have not been well-studied. Evidence exists that programs designed specifically for adolescents, women and families, injection-drug users, and homeless persons increase the likelihood of medication adherence *[81, 83, 86, 87]*. The incorporation of adherence interventions into convenient primary care settings; training and deployment of peer educators, pharmacists, nurses, and other health-care personnel in adherence interventions; and monitoring of clinician and patient performance regarding adherence are beneficial adherence. *[82, 88, 89]*. In the absence of data, a reasonable response is to address and monitor adherence during all HIV primary care encounters and incorporates adherence goals in all patient treatment plans and interventions. This might require the full use of a support team, including bilingual providers and peer educators for non-English–speaking populations, incorporation of adherence into support group agendas and community forums, and inclusion of adherence goals and interventions in the work of chemical-dependency counselors and programs.

### *Regimen-related strategies*

Regimens should be simplified as much as possible by reducing the number of pills and therapy frequency and by minimizing drug interactions and side effects. For certain patients, problems with complex regimens are of lesser importance, but evidence supports simplified regimens with reduced pill numbers and dose frequencies *[90, 91]*. With the effective options for initial therapy noted in this report and the observed benefit of less frequent dosing, twice-daily dosing of HAART regimens is feasible for the majority of patients. Regimens should be chosen after review and discussion of specific food requirements and patient understanding of and agreement to such restrictions. Regimens requiring an empty stomach multiple times daily might be difficult for patients with a wasting disorder, just as regimens requiring high fat intake might be difficult for patients with lactose intolerance or fat aversion. However, an increasing number of effective regimens do not have specific food requirements.

### *Directly observed therapy*

Directly observed therapy (DOT), in which a health-care provider observes the ingestion of medication, has been successful in tuberculosis management, specifically among patients whose adherence has been suboptimal. DOT, however, is labor-intensive, expensive, intrusive, and programmatically complex to initiate and complete; and unlike tuberculosis, HIV requires lifelong therapy. Pilot programs have studied DOT among HIV patients with preliminary success. These programs have studied once-daily regimens among prison inmates, methadone program participants, and other patient cohorts with a record of repeated suboptimal adherence. Modified DOT programs have also been studied in which the morning dose is observed and evening and weekend doses were self-administered. The goal of these programs is to improve patient education and medication self-administration during a limited period (e.g., 3–6 months); however, the outcome of these programs, including long-term adherence after DOT completion, has not been determined *[92-95]*.

## THERAPY GOALS

Eradication of HIV infection cannot be achieved with available antiretroviral regimens, chiefly because the pool of latently infected $CD4^+$ T cells is established during the earliest stages of acute HIV infection *[96]* and persists with a long half-life, even with prolonged suppression of plasma viremia to <50 copies/mL *[97-100]*. The primary goals of antiretroviral therapy are maximal and durable suppression of viral load, restoration and preservation of immunologic function, improvement of quality of life, and reduction of HIV-related morbidity and mortality (Table 10). In fact, adoption of treatment strategies recommended in this report has resulted in substantial reductions in HIV-related morbidity and mortality *[101-103]*.

Plasma viremia is a strong prognostic indicator in HIV infection *[3]*. Furthermore, reductions in plasma viremia achieved with antiretroviral therapy account for substantial clinical benefits *[104]*. Therefore, suppression of plasma viremia as much as possible for as long as possible is a critical goal of antiretroviral therapy, but this goal must be balanced against the need to preserve effective treatment options. Switching antiretroviral regimens for any detectable level of plasma viremia can rapidly exhaust treatment options; reasonable parameters that can prompt a change in therapy are discussed in Consideration for Treatment - Regimen Failure.

HAART often leads to increases in the $CD4^+$ T cell count of $\geq$100–200 cells/$mm^3$/year, although patient responses are variable. $CD4^+$ T cell responses are usually related to the degree of viral load suppression *[105]*. Continued viral load suppression is more likely for those patients who achieve higher $CD4^+$ T cell counts during therapy *[106]*. A favorable $CD4^+$ T cell response can occur with incomplete viral load suppression and might not indicate an unfavorable prognosis *[107]*. Durability of the immunologic responses that occur with suboptimal suppression of viremia is unknown; therefore, although viral load is the strongest single predictor of long-term clinical outcome, clinicians should consider also sustained rises in $CD4^+$ T cell counts and partial immune restoration. The urgency of changing therapy in the presence of low-level viremia is tempered by this observation. Expecting that continuing the existing therapy will lead to rapid accumulation of drug-resistant virus might not be reasonable for every patient. A reasonable strategy is maintenance of the regimen, but with redoubled efforts at optimizing adherence and increased monitoring.

Partial reconstitution of immune function induced by HAART might allow elimination of unnecessary therapies (e.g., therapies used for prevention and maintenance against OIs). The appearance of naïve T cells *[108, 109]*, partial normalization of perturbed T cell receptor Vβ repertoires *[110]*, and evidence of residual thymic function in patients receiving HAART *[111, 112]* demonstrate that partial immune reconstitution occurs in these patients. Further evidence of functional immune restoration is the return during HAART of in vitro responses to microbial antigens associated with opportunistic infections *[113]* and the lack of Pneumocystis carinii pneumonia among patients who discontinued primary Pneumocystis carinii pneumonia prophylaxis when their $CD4^+$ T cell counts rose to >200 cells/$mm^3$ during HAART *[114-116]*. Guidelines include recommendations concerning discontinuation of prophylaxis and maintenance therapy for certain OIs when HAART-induced increases in $CD4^+$ T cell counts occur *[2]*.

## Tools To Achieve the Goals of Therapy

Combination therapy with at least three antiretroviral agents has been shown to have a significant effect upon morbidity and mortality in HIV disease *[117]*. These positive responses are mediated through suppression of HIV replication, preservation of immune function and reconstitution of specific immune responses *[118]*. Viral load reduction to below limit of detection in a treatment-naïve patient usually occurs within the first 8-24 weeks of therapy. However, maintenance of excellent treatment response is highly variable. (See Testing for Plasma HIV RNA Levels) Predictors of long-term virologic success include:

1. low baseline viremia,
2. higher baseline CD4 cell count *[6, 119]*,
3. brisk reduction of viremia in response to treatment *[119]*, and
4. adherence to treatment regimen *[6, 119]*.

Successful outcomes have not been observed across all patient populations, however. Studies have shown that only approximately 50% of patients in urban clinic settings have consistently achieved viral suppression. The reasons for such variability are complex, but include inadequate adherence due to multiple social issues that confront the patients *[46, 120, 121]*. Patient factors clearly associated with the risk of decreased adherence, including depression and lack of social support, need to be addressed with patients before and during initiation of antiretroviral therapy *[78, 122]*. Careful research has demonstrated that the demographic characteristics of patients, such as race/ethnicity, sex, age, and socioeconomic status are generally not predictive of medication adherence *[123]*. (See "Adherence to Potent Antiretroviral Therapy")

Other methods for maximizing the benefits of antiretroviral therapy include the sequencing of drugs and the preservation of future treatment options for as long as possible. Three types of combination regimens may be employed as initial therapy. These include:

1. NNRTI-based regimens that are PI sparing,
2. PI-based regimens that are NNRTI sparing, and
3. triple NRTI regimens that are both PI-and NNRTI-sparing.

The goal of a class-sparing regimen is to "save" one or more classes of drugs for later use and potentially avoids or delays certain class specific side effects. Table 11 summarizes the advanatage and disadvantages of each of these approaches. Recommended individual antiretroviral regimens for the initiation of therapy, with the attendant advantages and disadvantages of different agents or components can be found in Tables 12a and 12b.

It is known that the presence of drug resistant virus in treatment-experienced patients is a strong predictor of virologic failure. Resistance testing to guide the choice of therapy in a patient failing a particular regimen has been shown to be of benefit in some patients *[12, 124]*.

The increased transmission of drug resistant virus presents unique, additional challenges, however *[11]*. Resistance testing in treatment-naïve, chronically infected patients is generally not recommended except in cases where there is a significant probability that the patient was infected with a drug-resistant virus. ("See Drug-Resistance Testing" for details)

# INITIATING THERAPY FOR THE HIV–INFECTED PATIENT, PREVIOUSLY UNTREATED WITH ANTIRETROVIRAL THERAPY

## Introduction

Since the introduction of PIs and potent combination antiretroviral therapy (previously referred to as highly active antiretroviral therapy or HAART) in 1995, a substantial, (though well acknowledged as incomplete,) body of clinical data has been amassed that helps the selection of initial therapy for the previously untreated patient. There are now 19 approved antiretroviral agents with which to design regimens of three or more agents.

Accordingly, Table 12a has been re-formatted to provide clinicians with a selection of potential antiretroviral combination regimens for initiation of therapy. This table provides a listing of three categories of regimens – "one NNRTI + two NRTIs"; "one or two PIs + two NRTIs"; and "three NRTIs". Potential advantages and disadvantages for each regimen component are listed in Table 12b to guide prescribers in choosing the regimen best suited for an individual patient. Regimens that are preferred by the Panel for initial use are highlighted. Only regimens judged to meet criteria for optimal performance in initial use are included.

In its deliberations for the Guidelines, the Panel reviews published clinical trials in the literature and in abstract form. Few of these trials have enough follow-up data to include clinical endpoints (such as development of AIDS-defining illness or death). Thus, assessment of regimen efficacy and potency were mostly based on surrogate marker (i.e., HIV-RNA) endpoints. Such endpoints in prospective, randomized trials of antiretrovirals meet the standard for a Category I classification as required by the FDA for approval of antiretroviral drugs. Additionally, the Panel acknowledges that in areas in which available clinical data were incomplete or lacking, expert opinion (Category III) was used to guide the recommendations. The text that follows will review the studies that were used to make these recommendations.

Only regimens for which adequate clinical trial data support their use are included in Table 12a. The first criterion for selection was potency in a randomized, prospective clinical trial with an adequate sample size, as measured by durable viral suppression and immunologic enhancement (as evidenced by increased $CD4^+$ T-lymphocyte counts). In addition, tolerability and drug toxicity were assessed by incident adverse effect rates and discontinuation rates, both due to toxicity and overall, as well as pill size and burden, dosing frequency, food requirements, and potential for drug-drug interactions. Where available, data on regimen adherence were also considered. Finally, given the paucity of head-to-head trials of the numerous potential antiretroviral combinations, inferences were drawn across numerous clinical trials with all potential factors considered in the determination for inclusion in Table 12a, and in the designation of "preferred regimens."

The Panel affirms that regimen selection should be individualized, on the basis of the advantages and disadvantages of each regimen and the consideration of numerous other factors, and that head-to-head, randomized, prospective clinical trials, when available, provide the best information regarding the relative performance of antiretroviral regimens. Factors to consider when starting antiretroviral therapy include:

1. the patients' willingness and readiness to begin therapy;
2. the assessment of adherence potential;
3. the patients' preference regarding pill burden, dosing frequency, and food and fluid considerations;
4. severity of HIV disease according to the baseline $CD4^+$ T-lymphocyte count, viral load, and presence or history of AIDS-defining conditions;
5. potential adverse drug effects;
6. co-morbidity or conditions such as tuberculosis, liver disease, depression or mental illness, cardiovascular disease, chemical dependency, pregnancy, and family planning status; and
7. and potential drug interactions with other medications.

The recent availability of potent antiretroviral therapy administered once daily is an additional new consideration, though there is no evidence to date of clinical, virological, or immunological superiority of once-daily over multiple-daily dosing regimens. (See Once Daily Therapy)

The most extensive clinical trial data are available for the three types of regimens shown in Table 12a, i.e. one NNRTI + two NRTIs, one or two PIs + two NRTIs, or three NRTIs. New data regarding "backbone" NRTI pairs have emerged that have led to revisions in NRTI recommendations in Table 12a. The rationale for recommendation of these combination regimens is discussed in the following sections. At present, the data are insufficient to recommend alternative combinations such as triple class regimens, i.e. NRTI + NNRTI + PI combinations; NRTI-sparing regimens such as two drug combination containing only dual full-dose PIs, and PI + NNRTI combinations; regimens containing five or more active agents; and other novel regimens in treatment-naïve patients. A listing of characteristics (dosing, pharmacokinetics, and common adverse effects) of individual antiretroviral agents can be found in Tables 14-17.

## RECOMMENDED COMBINATION ANTIRETROVIRAL REGIMENS
(Table 12a)

### Nonnucleoside Reverse Transcriptase Inhibitor–Based Regimens

***The Panel recommends:***

- ***Efavirenz + (zidovudine or tenofovir or stavudine) + lamivudine as preferred initial NNRTI-based regimens (except for pregnant women). (AI)***

- ***(Efavirenz + didanosine + lamivudine) (except for pregnant women) <u>or</u> nevirapine-based regimen can be used as an alternative. (BII)***

Three NNRTIs (namely, delavirdine, efavirenz, and nevirapine) are currently marketed for use. Delavirdine is the least potent of these agents and is generally not recommended for use as part of an initial antiretroviral regimen. Both efavirenz-based and nevirapine-based regimens were compared with PI-based and triple NRTI regimens, as well as to each other. The clinical trial experience of efavirenz and nevirapine are summarized below.

## Nevirapine–Based vs PI–Based Regimens

Nevirapine has been compared with PI-based regimens in the Atlantic *[125]* and Combine *[126]* trials. Neither trial was powered to establish equivalence of the PI- and nevirapine-based regimens. In the Atlantic Study, patients were randomized to receive either indinavir or nevirapine in combination with didanosine (ddI) and stavudine (d4T). At 96 weeks, 44% of patients in the indinavir arm and 55% of patients in the nevirapine arm achieved viral load <50 copies/mL *[125]*. In the Combine Study, nevirapine (n=72) was compared to nelfinavir (n=70) in combination with zidovudine (ZDV) and lamivudine (3TC). After 12 months, 75% of nevirapine treated patients and 60% of patients in nelfinavir arm had a viral load <200 copies/mL (p=0.06) *[126]*. Together in these two studies fewer than 200 patients on the nevirapine and PI-regimen were evaluated.

## Efavirenz– vs PI–Based Regimens

Efavirenz has been compared with PI-based regimens in treatment-naïve individuals in two relatively large studies *[127, 128]*. In the DuPont 006 study, efavirenz and indinavir were compared on a background of ZDV + 3TC with approximately 150 patients in each arm. At 48 weeks, significantly more patients assigned to efavirenz had a viral load <400 copies/mL (70% versus 48% based on the intent-to-treat analysis with treatment discontinuation counted as failures; p<0.001). Efavirenz was better tolerated than indinavir in this study *[127]*.

In the ACTG 384 study, 310 patients were randomly allocated to efavirenz and 310 were allocated to nelfinavir; background NRTI treatments were also randomized in this study using a 2x2 factorial design (ddI+d4T versus ZDV+3TC as the second factor) *[128]*. The primary endpoint of this trial considered virologic failure on the second regimen (nelfinavir for those assigned to efavirenz and efavirenz for those assigned to nelfinavir), toxicity or intolerance, or premature study treatment discontinuation for any reason (including lost to follow-up). Overall, 132 patients (42.6%) assigned efavirenz and 140 (45.2%) assigned nelfinavir experienced the primary endpoint. Examination of rates of failure on the initially assigned regimens demonstrated fewer events on efavirenz than nelfinavir regardless of NRTI combination (100 versus 143 overall). A more favorable benefit was evident for efavirenz compared to nelfinavir among those assigned ZDV+3TC (hazard ratio = 0.40; 95% CI: 0.25 to 0.66) than those assigned ddI+d4T (hazard ratio = 0.88; 95% CI: 0.61 to 1.29). With consideration of both primary and secondary outcomes, this study strongly suggests that the combination of efavirenz + ZDV+3TC is a particularly useful starting regimen.

To date, virologic results from a small number of trials comparing efavirenz with ritonavir-boosted PI regimens have favored efavirenz over the comparator regimens. In the FOCUS trial, an efavirenz-based regimen was compared to boosted saquinavir (1,600 mg soft gel saquinavir and 100 mg ritonavir once daily) in 152 antiretroviral naïve individuals *[129]*. Use of efavirenz resulted in better virologic control at 48 weeks (71% versus 51% with viral load <50 copies/mL) and less toxicity. A ritonavir-boosted amprenavir regimen was compared with an efavirenz-based regimen in a recent trial *[130]*. At 48 weeks, 73% for the ritonavir-boosted amprenavir group and 94% for efavirenz group were reported to have viral load <50 copies/mL.

## Efavirenz– vs Nevirapine–Based Regimens

Two studies have compared the efficacy and tolerability of nevirapine with efavirenz. In one small study, after 48 weeks, 64% of 36 patients assigned to nevirapine and 74% of 31 patients assigned to efavirenz, each with d4T+ddI, had a viral load <50 copies/mL. The 95% CI for the difference (-32% to 12%) was too wide to draw meaningful conclusions about the similarity (or lack thereof) of efficacy *[131]*.

The 2NN study was a much larger study that compared nevirapine with efavirenz, in antiretroviral naïve participants *[132]*. Patients were randomized to nevirapine (400 mg once daily or qd; n= 220), nevirapine (200 mg twice daily or bid; n= 387), efavirenz (600 mg qd; n=400), or nevirapine (400 mg qd) plus efavirenz (800 mg qd) (n=209), together with d4T+3TC.

Treatment failure at 48 weeks was defined as less than one $log_{10}$ decline in the first 12 weeks, virologic failure from week 24 onward (two consecutive viral load measurements >50 copies/mL), switch from assigned treatment drugs, or progression to death or CDC category C event. Secondary outcomes included percent with viral load <50 copies/mL at 48 weeks, changes in CD4+ T-lymphocyte cell count, changes in lipid levels, and adverse events *[133]*. At 48 weeks, 43.7% of patients in the bid nevirapine arm and 37.8% of those in the efavirenz arm experienced treatment failure (95% CI for difference: -0.9 to 12.8%; p=0.095). At this same time point, 65.4% of patients in the bid nevirapine arm and 70.0% of those in the efavirenz arm had viral load <50 copies/mL (95% CI for difference: -1.9% to 11.2%; p=0.17). The CD4+ cell count increase was the same in both groups (160 cells/$mm^3$).

The percent of patients discontinuing treatment due to an adverse event was 21.2% in the bid nevirapine group and 15.5% in efavirenz group (95% CI: 0.3% to 11.1%; p = 0.04). More patients on bid nevirapine than efavirenz experienced a grade 3/4 clinical hepatotoxicity (2.1% versus 0.3%) and a grade 3/4 laboratory hepatobiliary toxicity (7.8% versus 4.5%). Of note, two deaths (due to toxic hepatitis and Steven's-Johnson syndrome) were attributed to bid nevirapine in this study.

Other notable findings from this study are that qd nevirapine was similar in efficacy to bid nevirapine (43.6% versus 43.7% for treatment failure outcome) although more laboratory hepatotoxicities were found with the once-daily than with the twice-daily dose (13.2% versus 7.8%). The combination of nevirapine and efavirenz resulted in a discontinuation rate due to adverse events of 29.7%.

In the design of the 2NN study, a difference between the two treatment groups of 10% in treatment failure at 48 weeks was prespecified to be clinically meaningful. *[133]*. The results of the study indicate that a difference of this magnitude cannot be ruled out (i.e., based on the upper bound of the 95% confidence interval, the advantage of efavirenz over nevirapine at 48 weeks may exceed 10% for major efficacy outcomes). Furthermore, there appears to be more safety concerns (particularly, higher incidence and more serious skin rash and hepatotoxicity) about using nevirapine over efavirenz.

On the basis of the clinical trial results as discussed above, the Panel recommends efavirenz in combination with lamivudine and zidovudine, tenofovir, or stavudine as preferred first-line NNRTI-containing regimens in antiretroviral naïve patients. An exception to this recommendation will be in pregnant women or women at risk for pregnancy, as efavirenz has been associated with significant teratogenic effects in nonhuman primates *[134]*.

## Protease Inhibitor-Based Regimen

***The Panel recommends lopinavir/ritonavir + (zidovudine or stavudine) + lamivudine as preferred PI-based regimens. (AI) Alternative PI-based regimens are listed in Table 12a.***

Seven protease inhibitors (PIs) were marketed in the United States for treatment of HIV infection. The advantages and disadvantages of each of these agents (except for atazanavir), can be found in Table 12b. Atazanavir was recently approved by the FDA after the drafting of the present guidelines revision. An update with the role of atazanavir as initial therapy will appear in the next revision of this document.

PIs in combination with NRTIs have been evaluated in several controlled trials with clinical outcomes *[36, 37, 135, 136]*. Initial studies established the superior efficacy of indinavir *[36]* and ritonavir-based *[37]* regimens compared to nucleoside only regimens for AIDS or death among patients with advanced disease. Later head-to-head studies found that indinavir and nelfinavir were much better tolerated than ritonavir *[135-137]*. The study of nelfinavir versus ritonavir established that nelfinavir was better tolerated than ritonavir and had clinical, immunologic, and virologic efficacy that was nearly as great as ritonavir *[136]*.

As a result of these and other studies, regimens with full dose ritonavir (600mg twice daily) are not recommended due to its poor tolerability. Because indinavir alone has a dosage requirement of every eight hours and has food constraints, its use as a single PI has been more limited because of concerns with adherence. Nelfinavir, which can be taken twice daily, is well tolerated, with the exception of diarrhea. In general, there is substantial clinical experience with both indinavir and nelfinavir. Therefore, resistance patterns, long-term toxicities, and the impact on clinical outcomes are better understood for these two PIs than most other single PI-based regimens.

Low-dose ritonavir can enhance the effect of other protease inhibitors and ritonavir-boosted regimens are being used more often because of convenience in terms of pill burden, scheduling, and elimination of food restrictions (in the case of indinavir). An early study established that 400 mg of ritonavir and saquinavir twice daily was as potent as higher dose ritonavir-boosted saquinavir regimens *[138]*. A study, which established that indinavir was better tolerated than ritonavir *[137]*, a third arm was included that found ritonavir (400 mg) plus saquinavir was as effective as indinavir at 72 weeks, with 51% versus 58% of patients with HIV RNA <20 copies/mL in the indinavir and ritonavir/saquinavir arms respectively. Gastrointestinal sides effects were common for patients on the ritonavir-boosted regimen. As a consequence, recent studies have used lower doses (100-200 mg) of ritonavir *[139-141]*. When saquinavir is used in a ritonavir-boosted regimen, the overall drug exposure is similar regardless of whether the soft gel or hard gel capsule formulation is used. However, the hard gel capsule appears to have much better gastrointestinal tolerance than the soft gel preparation *[142, 143]*.

The largest of the studies evaluating a low-dose ritonavir-boosted regimen is a trial of lopinavir/ritonavir versus nelfinavir (each with 2 NRTIs) involving 653 patients. In this trial 400 mg of lopinavir and 100 mg of ritonavir (as a co-formulated preparation) given twice daily was well tolerated and was superior to nelfinavir (750 mg thrice daily) 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). Overall adverse event rates and study discontinuation rates due to adverse events were similar in the two groups, although average triglycerides elevations were greater among those assigned lopinavir/ritonavir compared to nelfinavir (125 mg/dl versus 47 mg/dl increase; p<0.001) *[139]*.

Another trial found that at 48 weeks, virologic response of 306 patients 39% of whom were PI–naïve randomly assigned to either boosted saquinavir (1,000 mg saquinavir plus 100 mg ritonavir twice a day) or boosted indinavir (800 mg indinavir plus 100 mg ritonavir twice a day) were comparable (p = 0.84), but that when switches were considered failures boosted saquinavir was superior (p = 0.01). The greater number of switches on boosted indinavir was attributed to poorer tolerability of that regimen. Boosted indinavir also resulted in greater lipid increases than boosted saquinavir (p<0.05) *[140]*. Data on other ritonavir-boosted regimens is more limited. With the exception of the study mentioned above *[140]*, ritonavir-boosted indinavir regimens have not been evaluated in randomized trials for antiretroviral treatment-naïve individuals.

Although there are limited data on the comparative efficacy of lopinavir/ritonavir with other ritonavir-boosted regimens and with efavirenz-based regimens, on the basis of 48-week trial data for virologic potency, patient tolerance, and pill burden the Panel considers lopinavir/ritonavir to be a useful starting PI-based regimen. Of note, there is little experience with the use of lopinavir/ritonavir in pregnant women. Among all the currently marketed PIs, nelfinavir has the most safety experience in this population (See section on “Pregnant Women and Women of Reproductive Age”).

## Triple NRTI Regimen

***The Panel recommends that a 3-NRTI regimen consisting of abacavir + (zidovudine or stavudine) + lamivudine may be used as an alternative to an NNRTI-based or a PI–based regimen in antiretroviral-naïve patients (CII). This regimen should not be initiated in patients with baseline viral load >100,000 copies/mL (DII).***

Another approach to antiretroviral therapy is to use a triple (3)-NRTI combination. Potential advantages of the 3-NRTI strategy are to save PIs and NNRTIs for later use, to avoid certain PI- or NNRTI-associated adverse effects *[144]*, and minimal drug-drug interactions. Some clinicians, however, have concerns over the potency of this single-class regimen as well as the potential of development of more NRTI mutations and limitation of future treatment options.

Abacavir was approved by the FDA based on two randomized, controlled trials comparing a combination of abacavir/zidovudine/lamivudine (ABC/ZDV/3TC) to a PI-based regimen containing indinavir (IDV/ZDV/3TC) *[145, 146]* in treatment-naïve patients. The overall virologic responses at 48 weeks for the 3-NRTI-based and PI-based regimens were equivalent (51% in each group; 95% confidence interval for difference: -9% to 8%) based on pre-specified criteria (+/- 12%) for a viral load <400 copies/mL. When a viral load cutoff of 50 copies/mL was considered, a sustained response was obtained for 40% of patients assigned ABC/ZDV/3TC and 46% of patients assigned IDV/ZDV/3TC and treated patients (95% confidence interval for difference: -15% to 2%). However, this difference was greater for those with baseline plasma HIV RNA >100,000 copies/mL (31% versus 45%; 95% CI: -27% to 0%) *[145]*.

The ACTG A5095 trial is a randomized, double-blinded, placebo-controlled Phase III trial that compared three PI-sparing regimens in antiretroviral naïve patients [ABC/ZDV/3TC versus efavirenz

(EFV)/ZDV/3TC versus EFV/ABC/ZDV/3TC]. After an average of 32 weeks of therapy, the unblinded results showed a higher incidence of, and earlier time to, virologic failure (defined as an HIV-RNA value > 200 copies/mL at least four months after starting treatment) in the ABC/ZDV/3TC arm compared to the pooled EFV-based arms (p<0.001). This difference was evident regardless of whether the baseline HIV-RNA levels were greater than or less than 100,000 copies/mL. These results led to the premature closure of the ABC/ZDV/3TC arm of the study *[147]*.

The CLASS study compared the virologic efficacy of an NNRTI-based (EFV regimen), a boosted PI-based (ritonavir + amprenavir regimen), and a 3-NRTI (d4T-based) regimen, all combined with ABC and 3TC as backbone NRTIs *[130]*. Preliminary 48-week data based on intent-to-treat analysis showed superiority of the EFV-based regimen (76% with HIV-RNA <50 copies/mL) over the ritonavir-boosted amprenavir and the 3-NRTI arms (59% and 62% respectively).

In the Atlantic study *[133]* the virologic and immunologic efficacy of stavudine (d4T) plus didanosine (ddI) in combination with either nelfinavir, nevirapine, or 3TC in antiretroviral-naïve subjects were evaluated. The virologic responses of both the PI- and the NNRTI-based regimens were found to be superior to the d4T/ddI/3TC combination at 96 weeks. Several other combination studies comparing 3-NRTI with various PI-based or NNRTI-based regimens are currently underway

The available clinical trial results to date have demonstrated that triple NRTI regimens (ABC/ZDV/3TC or ABC/d4T/3TC) are inferior to an efavirenz-based regimen in virologic responses at 32 to 48 weeks regardless of baseline viral load. This regimen has similar efficacy to an indinavir-based or ritonavir-boosted amprenavir-based regimen in patients with baseline viral load of <100,000 copies/mL, but is less efficacious than indinavir-based regimen in patients with baseline viral load >100,000 copies/mL.

On the basis of the above data, the Panel recommends that a triple NRTI regimen consisting of ABC/ZDV/3TC or ABC/d4T/3TC may be used as an alternative to an NNRTI-based or a PI-based regimen in treatment-naïve patients where the other options may be less desirable due to concerns over toxicities, drug interaction, or regimen complexity (CII). Additionally, the Panel would not recommend initiation of a 3-NRTI regimen in patients with baseline viral load >100,000 copies/mL (DII).

## Selection of Two Nucleosides as Part of Combination Therapy

***The Panel recommends a combination of lamivudine with zidovudine as the 2-NRTI combination of choice as part of a combination regimen (AI). Combination of lamivudine with stavudine (AII) or tenofovir (AII) may be used as alternative***.

Eight nucleoside/nucleotide HIV-1 reverse transcriptase inhibitors (NRTIs) are currently marketed in the U.S. Emtricitabine received FDA approval after the drafting of this guideline revision. Discussion regarding the utility of this agent in combination antiretroviral therapy will be deferred until the next guideline revision.

Dual nucleoside combinations are by far the most commonly utilized "backbone" of combination antiretroviral regimens upon which additional third or fourth agents confer sufficient potency for long-term efficacy. The choice of the specific two nucleosides is made on the basis of potency, short-and long-term toxicities, drug-drug interactions, the propensity to select for resistance mutations, and dosing convenience. Any of the most common two-drug combinations allows for convenient once-or twice-daily administration with low pill burdens. The fixed-dose formulation of zidovudine and lamivudine allows single pill, twice-daily dosing. Highest regimen simplicity is possible with once-daily drugs (currently including tenofovir, lamivudine, didanosine, and emtricitabine) although regimens based on these agents are generally less fully validated in prospective clinical trials. Until recently, most dual nucleoside regimens included one thymidine-based drug, specifically zidovudine or stavudine. More recent trials, however, have shown promising results with a dual regimen backbone including tenofovir *[145]*, didanosine *[148]*, or abacavir *[130]* along with a second drug, usually lamivudine. These approaches are being explored to avoid side effects considered associated with thymidine analogs that may represent mitochondrial DNA damage. Lamivudine is a common second agent in these combinations given its near-absent toxicity and the capacity of maintenance of susceptibility to thymidine analogs despite high-level resistance following a single M184V mutation *[149]*. Certain members of this drug class should not be used in combination. These include

1. zidovudine with stavudine *[150]* - given pharmacologic interaction that may result in antagonism in vitro as well as in vivo; and,
2. stavudine with didanosine which should be avoided in pregnant women due to the reports of serious including fatal lactic acidosis with pancreatitis or hepatic steatosis *[151]*.

Perhaps more generally, combination of stavudine and didanosine should be avoided because of excess toxicity *[128, 152, 153]*. An early nucleoside analog, zalcitabine, is less convenient and more toxic and should rarely if ever be recommended.

Of the many available two-drug nucleoside regimens, the Panel currently favors zidovudine with lamivudine as a convenient and reasonably potent co-formulation with an acceptable toxicity profile and extensive clinical experience *[128]*. Tenofovir and lamivudine have been shown to be highly and durably (up to 96 weeks) effective in combination with efavirenz *[154]*. Because tenofovir and lamivudine have not been studied as initial therapy in a PI-based regimen, however, no recommendation can be made for such combination at this time. The combination of stavudine with lamivudine is also widely used but may be more frequently associated with dyslipidemia, lipoatrophy, and mitochondrial toxicities *[155, 156]*. Once-daily combinations of existing or extended-release formulations of nucleoside agents are of great interest and may allow for greater adherence in some patients.

## Antiretroviral Components Not Recommended as Part of An Initial Regimen in an Antiretroviral–Naïve Patient

Based on the criteria used in selection of initial antiretroviral regimens as discussed earlier, the Panel does not endorse a number of antiretrovirals or antiretroviral components as part of an initial regimen in an antiretroviral-naïve patient. The reasons for not recommending their use as initial therapy are as follows:

1. ***Modest antiviral activities***
   - delavirdine *[157]*
   - combination of zidovudine plus zalcitabine *[158]*
2. ***High pill burden***
   - amprenavir (16 capsules per day) as sole PI
   - saquinavir soft gel capsule (18 capsules per day) as sole PI
   - combination of nelfinavir and saquinavir (16-22 capsules per day) as dual PI
3. ***High incidence of toxicities***
   - ritonavir used as sole PI (600 mg twice daily)-gastrointestinal side effects *[159, 160]*.
   - combination of stavudine and didanosine - increased peripheral neuropathy *[128]* and/or hyperlactatemia *[152, 153]*.

# SPECIAL CONSIDERATIONS IN SELECTION OF ANTIRETROVIRAL REGIMENS

## Once–Daily Therapy

***The panel recommends once-daily therapy with NRTIs that have pharmacokinetic profiles that justify once-daily use (didanosine, lamivudine, tenofovir, and efavirenz) (AI). Alternative options are ritonavir-boosted saquinavir (BII), ritonavir-boosted amprenavir (BII), and nevirapine (CII).***

Once-daily therapy is desired for patient convenience and adherence. This applies not only to treatment of any chronic disease but also to HIV. However, it may be more important with HIV disease due to the risk of development of drug resistance caused by nonadherence *[161]*.

A number of antiretroviral drugs are currently FDA-approved for once-daily administration, including efavirenz, didanosine, tenofovir, lamivudine, stavudine extended release, emtricitabine, atazanavir, and amprenavir + ritonavir. Other agents that have the potential for once daily administration based on pharmacokinetic data, but are not yet FDA-approved for use in this fashion include abacavir, nevirapine, and several ritonavir-boosted PI regimens.

One major concern with once-daily therapy is the paucity of long-term trials with comparison to potent twice daily regimens. Several studies demonstrated the efficacy of drugs that are FDA-approved for once daily therapy, but these are usually studied in regimens where other components of the regimen are given twice daily. A second concern is the consequence of a missed dose. The outcome of missing doses is highly dependent on the pharmacology of the active antiretroviral drug (i.e. Cmin, elimination half-life, intracellular drug concentrations, and the IC50 of an individual patient's HIV-1 isolate). The greater the Cmin:IC50 ratio and the longer the half-life of the drug, the more likely it would be for the Cmin to remain over the HIV-isolate's IC50 despite missing one dose. On the contrary, when an antiretroviral agent with a low Cmin:IC50 ratio and a relatively short half-life is given as once-daily dosing, missing one dose may result in inadequate drug exposure over a defined period of time leading to a higher probability of development of drug resistance.

The Panel endorses once-daily regimens, but only with NRTIs that have pharmacokinetic profiles that justify once-daily use (AI) plus efavirenz (AI). Other agents with once-daily potential include nevirapine (CII) and ritonavir-boosted PIs with established once-daily efficacy (BII). To date, the ritonavir-boosted PIs with the most clinical data are ritonavir + saquinavir *[162]* and ritonavir + amprenavir *[130]*. Clinical trial data with longer follow-up are needed to support the routine use of these less conventional dosing strategies.

## Drug Interactions

Potential drug-drug interactions should be taken into consideration when selecting an antiretroviral regimen. Thorough review of current medications can help to design a regimen with the least propensity of causing undesirable interactions. Moreover, review of drug interaction potential should be undertaken when any new drug is to be added to an existing antiretroviral combination. A list of significant drug interactions with different antiretroviral agents and suggested recommendations on contraindication, dose modification, and alternative agents can be found in Tables 19-21.

Most drug interactions with antiretrovirals are mediated through inhibition or induction of hepatic drug metabolism *[163]*. 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 other conditions, such as lipid-lowering agents (the "statins"), benzodiazepines, immunosuppressants (such as cyclosporine, and tacrolimus), neuroleptics, sildenafil, ergotamine, rifamycins, azole antifungals, macrolides, oral contraceptive, St. John's Wort, and methadone.

All PIs are substrates and inhibitors of CYP3A4, with ritonavir having the most pronounced effect and saquinavir having the least potent inhibitory effect. The NNRTIs are also substrates of CYP3A4, and can be an inducer (nevirapine), an inhibitor (delavirdine), or a mixed inducer and inhibitor (efavirenz). Thus, these antiretroviral agents can interact with each other and with other drugs commonly prescribed for other concomitant diseases.

Use of a CYP3A4 substrate with 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 it is added to a PI, such as amprenavir, indinavir, lopinavir, or saquinavir *[164]*. Lower-than-therapeutic doses of ritonavir are commonly used in clinical practice as a pharmacokinetic enhancer to increase the trough concentration (Cmin) and prolong the $t_{1/2}$ of the active PIs *[165]*. The higher Cmin allows for a greater Cmin: IC50 ratio, reducing the chance for development of drug resistance as a result of suboptimal drug exposure; whereas the longer $t_{1/2}$ allows for less frequent dosing,

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 CYP 3A4 inducers that can significantly reduce plasma concentrations of most PIs and NNRTIs *[166, 167]*. 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 the wider experience with rifampin when used for this indication *[168]*. Dosage recommendations for concomitant use of rifamycins and other CYP3A4 inducers and PIs and NNRTIs are listed in Table 20.

Unlike PIs and NNRTIs, NRTIs do not undergo hepatic transformation through the CYP metabolic pathway. Significant pharmacodynamic interactions of NRTI and other drugs have been reported including, increases in intracellular drug levels and toxicities when didanosine is used in combination with hydroxyurea *[169, 170]* or ribavirin *[171]*; or additive bone marrow suppressive effects of zidovudine and ganciclovir *[172]*. 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 and tenofovir *[173, 174]*. A list of significant interactions with NRTIs can be found in Table 20.

# WOMEN OF REPRODUCTIVE AGE AND PREGNANT WOMEN

***When initiating antiretroviral therapy for the woman of reproductive age, the indications for initiation of therapy and the goals of treatment are the same as for other adults and adolescents. (AI) For the woman who is pregnant, an additional goal of therapy is prevention of mother-to-child transmission (MTCT). (AI) Special considerations in regimen selection for these two groups of women are discussed below.***

## Women of Reproductive Age

In women of reproductive age, 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 risk of efavirenz-containing regimens (see below) should pregnancy occur. These regimens should be avoided in women who are trying to conceive or are not using effective and consistent contraception. This counseling should be provided on a routine basis after initiation of therapy as well.

## Pregnant Women

Pregnancy should not preclude the use of optimal therapeutic regimens. However, because of considerations related to prevention of MTCT and to maternal and fetal safety, timing of initiation of treatment and selection of regimens are different than for the nonpregnant adults or adolescents.

Prevention of MTCT: Antiretroviral therapy is recommended in all pregnant women, regardless of virologic, immunologic, or clinical parameters, for the purpose of prevention of MTCT. (AI) Reduction of HIV-RNA levels to below 1,000 copies/mL and use of antiretroviral therapy appear to have an independent effect on reduction of perinatal transmission *[175-177]*.

Standard combination antiretroviral therapy (HAART) is recommended for pregnant women who meet the clinical, immunologic, or virologic criteria for initiating therapy (AI). HAART should also be recommended and offered to pregnant women who do not meet criteria outlined for initiation of therapy in nonpregnant adults, but who have HIV-RNA levels >1,000 copies/mL (AIII). These regimens should be chosen from among those recommended for non-pregnant adults and adolescents, but should also include the three-part ZDV chemoprophylaxis regimen used in the PACTG 076 study whenever possible. This regimen has shown the greatest reductions in MTCT in clinical trial settings.

D4T-containing regimens are not recommended as initial regimens for antiretroviral-naïve women in pregnancy because of pharmacologic antagonism with ZDV. However, regimens containing d4T may be considered in women unable to tolerate ZDV; regardless of the antepartum antiretroviral regimen, the intrapartum and neonatal components of the ZDV chemoprophylaxis regimen are still recommended.

For pregnant women with HIV-RNA levels <1,000 copies/mL on no therapy, acceptable options include standard combination therapy with HAART, dual NRTI therapy with ZDV+ 3TC, or ZDV monotherapy, all including the three-part ZDV chemoprophylaxis regimen. Although use of less-than-standard therapy during pregnancy is controversial, possible advantages include reduction in potential maternal and/or fetal/infant toxicity and other adverse effects; improved adherence; maintenance of benefit in reduction of MTCT; and low expected rates of resistance due to low viral replication and time-limited administration of drug(s) during the second and third trimesters of pregnancy.

## Maternal and Fetal/Infant Safety and Toxicity

In antiretroviral-naïve pregnant women initiation of antiretroviral therapy may be delayed until after 10–12 weeks gestation, to avoid the period of greatest vulnerability of the fetus to potential teratogenic effects and because nausea and vomiting in early pregnancy may affect optimal adherence and absorption of antiretroviral medications (CIII). However, if clinical, virologic, or immunologic indications for initiation of therapy in nonpregnant individuals exist, many experts would recommend initiating therapy regardless of gestational age (CIII).

There are insufficient data to support or refute teratogenic risk of antiretroviral drugs in humans when administered during the first trimester of pregnancy. However, efavirenz-containing regimens should be avoided in pregnancy because significant teratogenic effects were seen in primate studies at drug exposures similar to those representing human exposure. In addition, single case of myelomeningocele has now been reported after early human gestational exposure to efavirenz *[178]*.

The combination of ddI and d4T should be avoided as first-line therapy during pregnancy because of reports of several maternal deaths secondary to lactic acidosis with prolonged use of regimens containing these two nucleoside analogues in combination *[151]*. In general, antiretroviral combination should be used during pregnancy only when other NRTI drug combinations have failed or have caused unacceptable toxicity or side effects.

Lastly, the oral liquid formulation of amprenavir contains high level of propylene glycol and should not be used in pregnant women. For more information, see Considerations for Antiretroviral Therapy in HIV-Pregnant Women and http://www.aidsinfo.nih.gov.

## ANTIRETROVIRAL REGIMENS OR COMPONENTS THAT SHOULD NOT BE OFFERED AT ANY TIME (Table 13)

Some agents or combinations of agents are generally contraindicated due to suboptimal antiviral potency, unacceptable toxicity, or pharmacological concerns. These are summarized as follows:

- **Monotherapy:** All single-drug regimens are considered contraindicated because none have demonstrated potent and sustained antiviral activity. The rare exception is ZDV monotherapy as part of the PACTG 076 ZDV regimen for a pregnant woman who does not meet clinical, immunologic, or virologic criteria for initiation of therapy and who has an HIV RNA <1,000 copies/mL. The goal of therapy is to prevent perinatal HIV-1 transmission. ZDV monotherapy should be discontinued immediately after delivery or combination antiretroviral therapy can be initiated if clinical indicated.

- **Dual nucleoside therapy:** These regimens are not currently recommended as initial therapy because none have demonstrated potent and sustained antiviral activity as compared to three-drug combination regimens. For patients previously given this treatment, it is reasonable to continue if viral suppression to less than the limit of detection is achieved and sustained.

- **D4T + ddI in pregnancy:** The combination of ddI and d4T was associated with several maternal deaths secondary to severe lactic acidosis with or without hepatic steatosis and pancreatitis after prolonged use of regimens containing these two agents in combination *[151]*. This antiretroviral combination should be used during pregnancy only when other NRTI drug combinations have failed or have caused unacceptable toxicities.

- **Efavirenz in pregnancy:** Efavirenz was associated with significant teratogenic effects in primates at drug exposures similar to those representing human exposure. A single case of myelomeningocele has now been reported after early human gestational exposure to efavirenz *[178]*. Efavirenz should be avoided in pregnancy and in women who are trying to conceive or who are not using effective and consistent contraception, unless no other antiretroviral options are available. In this situation, therapy should be interrupted in early pregnancy or delayed until after the first trimester when feasible, to minimize teratogenic risk.

- **Zidovudine plus stavudine:** Combination regimens containing these two NRTIs should be avoided due to the demonstration of antagonism in vitro *[179]* and in vivo *[180]*.

- **Saquinavir hard gel capsule (Invirase®) as a single PI:** The hard gel formulation of saquinavir is contraindicated as a single PI due to poor bioavailability that averages only 4% even with a concurrent high-fat meal *[181]*.

- **Zalcitabine plus stavudine or zalcitabine plus didanosine:** These combinations are contraindicated due to increased rates and severity of peripheral neuropathy *[182, 183]*.

- **Hydroxyurea:** This agent appears to enhance the antiviral activity of didanosine *[184]*. However, it also promotes the toxicity of didanosine with increased rates of peripheral neuropathy *[185]* and pancreatitis *[169]*. An additional concern is the lack of CD4 response with hydroxyurea that presumably reflects the drug's cytotoxic effect *[186]* (See "Hydroxyurea").

## HAART-ASSOCIATED ADVERSE CLINICAL EVENTS

Potential adverse events associated with antiretroviral agents are outlined in Tables 14-17. A summary of FDA Box warnings is provided in Table 18. A list of overlapping toxicities can be found in Table 22. Drug interactions of concern are listed in Tables 19-21.

## Lactic Acidosis/Hepatic Steatosis

Chronic compensated hyperlactatemia can occur during treatment with NRTIs *[187, 188]*. Although cases of severe decompensated lactic acidosis with hepatomegaly and steatosis are rare (estimated incidence of 1.3 cases/1,000 person-years of NRTI exposure), this syndrome is associated with a high mortality rate *[189-192]*. Severe lactic acidosis with or without pancreatitis, including three fatal cases, were reported during the later stages of pregnancy or among postpartum women whose antiretroviral therapy during pregnancy included stavudine and didanosine in combination with other antiretroviral agents *[191, 193, 194]*. Other risk factors for experiencing this toxicity include obesity, being female, and prolonged use of NRTIs, although cases have been reported with risk factors being unknown *[191]*.

The mitochondrial basis of NRTI-induced lactic acidosis and hepatic steatosis is one possible mechanism of cellular injury because NRTIs also inhibit deoxyribonucleic acid (DNA) polymerase gamma, which is the enzyme responsible for mitochondrial DNA synthesis. The ensuing mitochondrial dysfunction might also result in multiple other adverse events (e.g., pancreatitis, peripheral neuropathy, myopathy, and cardiomyopathy *[195]*. Certain features of lipodystrophy syndrome have been hypothesized as being tissue-specific mitochondrial toxicities caused by NRTI treatment *[196-198]*.

The initial clinical signs and symptoms of patients with lactic acidosis syndrome are variable and can include nonspecific gastrointestinal symptoms without substantial elevation of hepatic enzymes *[199]*. Clinical prodromes can include otherwise unexplained onset and persistence of abdominal distention, nausea, abdominal pain, vomiting, diarrhea, anorexia, dyspnea, generalized weakness, ascending neuromuscular weakness, myalgias, paresthesias, weight loss, and hepatomegaly *[200]*. In addition to hyperlactatemia, laboratory evaluation might reveal an increased anion gap (Na - [Cl + $CO_2$] >16), elevated aminotransferases, creatine phosphokinase, lactic dehydrogenase, lipase, and amylase *[190, 199, 201]*. Echotomography and computed tomography (CT) scans might indicate an enlarged fatty liver, and histologic examination of the liver might reveal microvesicular steatosis *[199]*. Because substantial technical problems are associated with lactate testing, routine monitoring of lactate level is not usually recommended. Clinicians must first rely on other laboratory abnormalities plus symptoms when lactic acidosis is suspected. Measurement of lactate requires a standardized mode of sample handling, including prechilled fluoride-oxalate tubes, which should be transported immediately on ice to the laboratory and processed within 4 hours after collection; blood should be collected without using a tourniquet, without fist-clenching, and if possible, without stasis *[202, 203]*. When interpreting serum lactate, levels of 2–5 mmol/dL are considered elevated and need to be correlated with symptoms. Levels >5 mmol/dL are abnormal, and levels >10 mmol/dL indicate serious and possibly life-threatening situations. Certain persons knowledgeable in HIV treatment also recommend monitoring of serum bicarbonate and electrolytes for the early identification of an increased anion gap every 3 months.

For certain patients, the adverse event resolves after discontinuation of NRTIs *[199, 204]*, and they tolerate administration of a revised NRTI-containing regimen *[199, 205]*; however, insufficient data exist to recommend this strategy versus treatment with an NRTI-sparing regimen. If NRTI treatment is continued, for certain patients, progressive mitochondrial toxicity can produce severe lactic acidosis manifested clinically by tachypnea and dyspnea. Respiratory failure can follow, requiring mechanical ventilation. In addition to discontinuation of antiretroviral treatment and intensive therapeutic strategies that include bicarbonate infusions and hemodialysis *[206]* (AI), clinicians have administered thiamine *[207]* and riboflavin *[193]* on the basis of the pathophysiologic hypothesis that sustained cellular dysfunctions of the mitochondrial respiratory chain cause this fulminant clinical syndrome. However, efficacy of these latter interventions requires clinical validation. Antiretroviral treatment should be suspended if clinical and laboratory manifestations of the lactic acidosis syndrome occur (BIII).

## Hepatotoxicity

Hepatotoxicity, which is defined as a 3–5 times increase in serum transaminases (e.g., aspartate aminotransferase, alanine aminotransferase, or gamma-glutamyltransferase) with or without clinical hepatitis, has been reported among patients receiving HAART. All marketed NNRTIs and PIs have been associated with serum transaminase elevation. The majority of patients are asymptomatic, and certain cases resolve spontaneously without therapy interruption or modification *[208]*. Hepatic steatosis in the presence of lactic acidosis is a rare but serious adverse effect associated with the nucleoside analogs (see more detailed discussion in Lactic Acidosis and Hepatic Steatosis).

Among the NNRTIs, nevirapine has the greatest potential for causing clinical hepatitis. An incidence of 12.5% of hepatotoxicity among patients initiating nevirapine has been reported, with clinical hepatitis diagnosed for 1.1% of these patients *[209]*. In an African randomized trial where stavudine was the backbone NRTI, and either nevirapine or efavirenz was added to emtricitabine or lamivudine, 9.4% of the nevirapine-treated patients experienced grade 4 liver enzyme elevation as compared with none of the efavirenz-treated patients. Two of these patients died of liver failure. The incidence among female patients was twice that observed among male patients (12% versus 6%; p = 0.05) *[210]*. Nevirapine-associated hepatitis might also be present as part of a hypersensitivity syndrome, with a constellation of other symptoms (e.g., skin rash, fever, and eosinophilia). Approximately two thirds of the cases of nevirapine-associated clinical hepatitis occur within the first 12 weeks. Fulminant and even fatal cases of hepatic necrosis have been reported. Patients might experience nonspecific gastrointestinal and flu-like symptoms with or without liver enzyme abnormalities. The syndrome can progress rapidly to hepatomegaly, jaundice, and hepatic failure within days *[211]*. A two-week lead-in dosing with 200 mg once daily before dose escalation to twice daily might reduce the incidence of hepatotoxicity. Because of the potential severity of clinical hepatitis, certain clinicians advise close monitoring of liver enzymes and clinical symptoms after nevirapine initiation (e.g., every 2 weeks for the first month; then monthly for first 12 weeks, and every 1–3 months thereafter). Patients who experience severe clinical hepatotoxicity while receiving nevirapine should not receive nevirapine therapy in the future.

Unlike the early-onset hepatotoxicity observed with nevirapine, PI-associated liver enzyme abnormalities can occur any time during the treatment course. In a retrospective review, severe hepatotoxicity (defined as a >5 times increase over baseline aspartate aminotransferase or alanine aminotransferase) was observed more often among patients receiving ritonavir- or ritonavir/saquinavir-containing regimens than those receiving indinavir, nelfinavir, or saquinavir *[212]*. Coinfection with hepatitis C virus is reported to be a major risk factor for development of hepatotoxicity after PI initiation *[213, 214]*. HAART-induced immune reconstitution rather than direct liver toxic effects of the PIs have been indicated as the cause of liver decompensation among hepatitis C or hepatitis B coinfected patients. Other potential risk factors for hepatotoxicity include hepatitis B infection *[208, 213, 215]*, alcohol abuse *[214]*, baseline elevated liver enzymes *[216]*, stavudine use *[215]*, and concomitant use of other hepatotoxic agents.

## Hyperglycemia

Hyperglycemia, new-onset diabetes mellitus, diabetic ketoacidosis, and exacerbation of preexisting diabetes mellitus have been reported among patients receiving HAART *[217-219]*. These metabolic derangements are strongly associated with PI use *[220]*, though they can occur independently of PI use *[221]*. The incidence of new onset hyperglycemia was reported as 5% in a 5-year historical cohort analysis of a population of 221 HIV-infected patients. PIs were independently associated with hyperglycemia, and the incidence did not vary substantially by PIs *[222]*. Viral load suppression and increase in body weight did not reduce the magnitude of the association with PIs. The pathogenesis of these abnormalities has not been fully elucidated; however, hyperglycemia might result from peripheral and hepatic insulin resistance, relative insulin deficiency, an impaired ability of the liver to extract insulin, and a longer exposure to antiretroviral medications *[223, 224]*. Hyperglycemia with or without diabetes has been reported among 3%–17% of patients in multiple retrospective studies. In these reports, symptoms of hyperglycemia were reported at a median of approximately 60 days (range: 2–390 days) after initiation of PI therapy. Hyperglycemia resolved for certain patients who discontinued PI therapy; however, the reversibility of these events is unknown because of limited data. Certain patients continued PI therapy and initiated treatment with oral hypoglycemic agents or insulin. Clinicians are advised to monitor closely their HIV-infected patients with preexisting diabetes when PIs are prescribed and to be aware of the risk for drug-related new-onset diabetes among patients without a history of diabetes (BIII). Patients should be advised of the warning signs of hyperglycemia (i.e., polydipsia, polyphagia, and polyuria) and the need to maintain a recommended body weight when these medications are prescribed. Certain clinicians recommend routine fasting blood glucose measurements at 3–4–month intervals during the first year of PI treatment for patients with no previous history of diabetes (CIII). Routine use of glucose tolerance tests to detect this complication is not recommended (DIII). Because pregnancy is an independent risk factor for impaired glucose tolerance, closer monitoring of blood glucose levels should be done for pregnant women receiving PI–containing regimens. No data are available to aid in the decision to continue or discontinue drug therapy among patients with new-onset or worsening diabetes; however, the majority of experienced clinicians recommend continuation of HAART in the absence of severe diabetes (BIII). Studies have attempted to examine the potential of reversing insulin resistance after switching from PI-containing HAART regimens to NNRTI-based regimens, but results have been inconclusive.

## Fat Maldistribution

HIV infection and antiretroviral therapy have been associated with unique fat distribution abnormalities. Generalized fat wasting is common in advanced HIV disease, and localized fat accumulations have been reported with NRTI monotherapy *[225]*. However, the recognition and observation of fat maldistribution syndromes have increased in the era of combination antiretroviral therapy characterized by fat wasting (lipoatrophy) or fat accumulation (hyperadiposity). Fat maldistribution is often referred to as lipodystrophy, and in combination with metabolic abnormalities, such as insulin resistance and hyperlipidemia, is referred to as lipodystrophy syndrome. The absence of a commonly used case definition for the different forms of lipoatrophy or fat accumulation, often collectively called lipodystrophy, has led to different prevalence estimates (range: 25%–75%) *[226-229]*. Although the lack of defining criteria has also impeded investigation into the pathogenic mechanisms of these abnormalities, the spectrum of morphologic abnormalities might indicate multifactorial causation related to specific antiretroviral exposure and underlying host factors. Lipodystrophy might be associated with serum dyslipidemias, glucose intolerance, or lactic acidosis *[229-231]*.

Fat accumulation might be seen in the abdomen, the dorsocervical fat pad, and, among both men and women, the breasts. Prevalence increases with duration of antiretroviral therapy *[232]*. Although available evidence indicates that an increased risk for fat accumulation exists with PIs, whether specific drugs are more strongly associated with this toxicity is unclear. The face and extremities are most commonly affected by fat atrophy, and variability exists in severity. Prevalence of this toxicity has been reported to increase with long-term NRTI exposure *[233]*. Although stavudine has been frequently reported in cases of lipoatrophy, this might be a marker of longer term treatment exposure *[198, 233-236]*.

No clearly effective therapy for fat accumulation or lipoatrophy is known. In the majority of persons, discontinuation of antiretroviral medications or class switching has not resulted in substantial benefit; however, among a limited number of persons, improvement in physical appearance has been reported *[237]*. Preliminary results from limited studies indicate a reduction in accumulated fat and fat redeposition with the use of certain agents *[238]*. Data are inconclusive, however, and recommendations cannot be made.

## Hyperlipidemia

HIV infection and antiretroviral therapy are associated with complex metabolic alterations, including dyslipidemia. Cachexia, reduced total cholesterol, and elevated triglycerides were reported before the availability of potent antiretroviral therapy *[239, 240]*. HAART is associated with elevation of total serum cholesterol and low-density lipoprotein and in additional increases in fasting triglycerides *[228, 241]*. The magnitude of changes varies substantially and does not occur among all patients. Dyslipidemias primarily occur with PIs; however, a range from an increased association with ritonavir to limited or no association with a newer investigational compound indicates that hyperlipidemia might be a drug-specific toxicity rather than a class-specific toxicity *[242]*. Frequently, antiretroviral-associated dyslipidemias are sufficiently severe enough to consider therapeutic intervention. Although data remain inconclusive, lipid elevations might be associated with accelerated atherosclerosis and cardiovascular complications among HIV-infected persons.

Indications for monitoring and intervention in HIV therapy-associated dyslipidemias are the same as among uninfected populations *[243]*. No evidence-based guidelines exist for lipid management specific to HIV infection and antiretroviral therapy. However, close monitoring of lipid levels among patients with additional risks for atherosclerotic disease might be indicated *[244]*. Low-fat diets, regular exercise, control of blood pressure and smoking cessation are critical elements of care. Hypercholesterolemia might respond to b-hydroxy-b-methylglutaryl-CoA reductase inhibitors (statins). However, recognizing the interactions of certain statins with PIs that can result in increased statin levels is critical (Table 19). Usually, agents that are less affected by the inhibitory effect of PIs via the cytochrome P450 system are preferred (e.g. pravastatin). Atorvastatin, which is at least partially metabolized by this pathway, can also be used with PIs. Atorvastatin should be used with caution and at reduced doses, however, because higher concentrations of atorvastatin are expected *[245]*. Monotherapy with fibrates is less effective, but fibrates can be added to statin therapy; additional monitoring is needed because of the increased risk of rhabdomyolysis and hepatotoxicity. Isolated triglyceride elevations respond best to low-fat diets, fibrates, or statins *[245, 246]*. Lipid elevations might require modifications in antiretroviral regimens if they are severe or unresponsive to other management strategies. Numerous trials, variably well-controlled, have demonstrated modest reductions in lipid elevations when an NNRTI replaces a PI or when an abacavir-containing triple NRTI regimen replaces a PI-containing regimen *[247-249]*. Improvement in lipid levels tends to be more substantial with nevirapine than with efavirenz in studies regarding switching therapies.

## Increased Bleeding Episodes Among Patients with Hemophilia

Increased spontaneous bleeding episodes among patients with hemophilia A and B have been observed with PI use *[250]*. Reported episodes have involved joints and soft tissues; however, serious bleeding episodes, including intracranial and gastrointestinal bleeding, have been reported. Bleeding episodes occurred a median of 22 days after initiation of PI therapy. Certain patients received additional coagulation factor while continuing PI therapy.

## Osteonecrosis, Osteopenia, and Osteoporosis

Avascular necrosis and decreased bone density are now recognized as emerging metabolic complications of HIV infection that might be linked to HAART regimens. Both of these bone abnormalities have been reported among adults and children with HIV infection who are now surviving longer with their disease in part because of HAART *[251-253]*.

Avascular necrosis involving the hips (known as Legg-Calvé-Perthes disease) was first described among HIV-infected adults and more recently among HIV-infected children. Diagnoses of osteonecrosis are usually made by CT scan or magnetic resonance imaging (MRI), when these studies are performed in response to patient's complaints of pain in an affected hip or spine. However, asymptomatic disease with MRI findings can occur among 5% of HIV patients *[254]*. Avascular necrosis is not associated with a specific antiretroviral regimen among HIV-infected adults, but it has been linked to corticosteroids use among certain patients *[254, 255]*. Factors associated with osteonecrosis include alcohol abuse, hemoglobinopathies, corticosteroid treatment, hyperlipidemia, and hypercoagulability states. Occurrence of hyperlipidemia indicates an indirect link between antiretroviral therapy and the occurrence of osteonecrosis among HIV-infected patients; however, prospective clinical studies are required to establish this association. No accepted medical therapy exists for avascular necrosis, and surgery might be necessary to treat disabling symptoms.

Decreases in bone mineral density (BMD), both moderate (osteopenia) and severe (osteoporosis), are a reflection of the competing effects of bone reabsorption by osteoclast and bone deposition by osteoblast and are measured by bone densitometry. Before HAART, marginal decreases in BMD among HIV-infected persons were reported *[256]*. This evidence for decreased bone formation and turnover has been demonstrated with more potent antiretroviral therapy, including PIs *[257]*. Studies of bone demineralization among a limited number of patients receiving HAART have reported that <50% of patients receiving a PI-based regimen experienced osteopenia, compared with 20% of patients who are untreated or receiving a non-PI–containing regimen *[258]*. Other studies have reported that patients with lipodystrophy with extensive prior PI therapy had associated findings of osteopenia (28%) or osteoporosis (9%), respectively*[259]*. Preliminary observations of increased serum and urinary markers of bone turnover among patients on protease-containing HAART who have osteopenia support the possible link of bone abnormalities to other metabolic abnormalities observed among HIV-infected patients *[260, 261]*. Presently, no recommendation can be made for routine measurement of bone density among asymptomatic patients by dual energy X-ray absorptiometry (DEXA) or by such newer measurements as quantitative ultrasound (QUS). Specific prophylaxis or treatment recommendations to prevent more substantial osteoporosis have not been developed for HIV-infected patients with osteopenia.

On the basis of experience in the treatment of primary osteoporosis, recommending adequate intake of calcium and vitamin D and appropriate weight-bearing exercise is reasonable. When fractures occur or osteoporosis is documented, more specific and aggressive therapies with bisphosphonates, raloxifene, or calcitonin might be indicated *[262]*. Hormone replacement therapy including estrogen may be considered in the setting of substantially decreased bone density among postmenopausal women on HAART.

## Skin Rash

Skin rash occurs most commonly with the NNRTI class of drugs. The majority of cases are mild to moderate, occurring within the first weeks of therapy. Certain experienced clinicians recommend managing the skin rash with antihistamine for symptomatic relief without drug discontinuation, although continuing treatment during such rashes has been questioned

*[263]*. More serious cutaneous manifestations (e.g., Stevens-Johnson syndrome [SJS] and toxic epidermal necrosis [TEN]) should result in the prompt and permanent discontinuation of NNRTI or other offending agents. Most reactions resulting in skin rash are confined to cutaneous reactions, however. A severe or even life-threatening syndrome of drug rash with eosinophilia and systemic symptoms (DRESS) has also been described *[264, 265]*. Systemic symptoms can include fever, hematological abnormalities, and multiple organ involvement. Among NNRTIs, skin rash occurs more frequently and with greater severity with nevirapine. Using a 2-week lead-in dose escalation schedule when initiating nevirapine therapy might reduce the incidence of rash. In a case-control multinational study, SJS and TEN were reported among 18 HIV-infected patients. Fifteen of the 18 patients were receiving nevirapine. The median time from initiation of nevirapine to onset of cutaneous eruption was 11 days, with two thirds of the cases occurring during the initial dosing period *[263]*. Female patients might have as much as a sevenfold higher risk for developing grade 3 or 4 skin rashes than male patients *[266, 267]*. The use of systemic corticosteroid or antihistamine therapy at the time of the initiation of nevirapine to prevent development of skin rash has not proven effective *[267, 268]*. In fact, a higher incidence of skin rash has been reported among the steroid-treated or antihistamine-treated patients. At present, prophylactic use of corticosteroids should be discouraged.

Skin rash appears to be a class-adverse reaction of the NNRTIs. The incidence of cross-hypersensitivity reactions between these agents is unknown. In a limited number of reports, patients with prior histories of nevirapine-associated skin rashes had been able to tolerate efavirenz without increased rates of cutaneous reactions *[269, 270]*. The majority of experienced clinicians do not recommend using another NNRTI among those patients who experienced SJS or TEN with one NNRTI. Initiating NNRTI for a patient with a history of mild to moderate skin rash with another NNRTI should be done with caution and close follow-up.

Among the NRTIs, skin rash occurs most frequently with abacavir. Skin rash might be one of the symptoms of abacavir-associated systemic hypersensitivity reaction; in that case, therapy should be discontinued without future attempts to resume abacavir therapy.

Among all PIs, skin rash occurs most frequently with amprenavir, with incidence of <27% in clinical trials. Although amprenavir is a sulfonamide, the potential of cross-reactivity between amprenavir and other sulfa drugs is unknown. As a result, amprenavir should be used with caution in patients with histories of sulfa allergies.

## INTERRUPTION OF ANTIRETROVIRAL THERAPY

Antiretroviral therapy might need to be discontinued temporarily or permanently for multiple reasons. If a need exists to discontinue any antiretroviral medication, clinicians and patients should be aware of the theoretical advantage of stopping all antiretroviral agents simultaneously, rather than continuing one or two agents, to minimize the emergence of resistant viral strains. If a decision is made to interrupt therapy, the patient should be monitored closely, including clinical and laboratory evaluations. Chemoprophylaxis against OIs should be initiated as needed on the basis of $CD4^+$ T cell count.

An interest exists in what is sometimes referred to as structured or supervised treatment interruptions (STI). The concepts underlying STI vary, depending on patient populations, and encompass more than 3 major strategies:

1. STI as part of salvage therapy;
2. STI for autoimmunization and improved immune control of HIV; and
3. STI for the sole purpose of allowing less total time on antiretroviral therapy.

Because of limited available data, none of these approaches can be recommended.

Salvage STI is intended for patients whose virus has developed substantial antiretroviral drug resistance and who have persistent plasma viremia and relatively low $CD4^+$ T cell counts despite receiving therapy. The theoretical goal of STI in this patient population is to allow for the reemergence of HIV that is susceptible to antiretroviral therapy. Although HIV that was sensitive to antiretroviral agents was detected in the plasma of persons after weeks or months of interrupted treatment, the emergence of drug-sensitive HIV was associated with a substantial decline in $CD4^+$ T cells and a substantial increase in plasma viremia, indicating improved replicative fitness and pathogenicity of wild type virus *[271]*. In addition, drug-resistant HIV persisted in $CD4^+$ T cells. The observed decrease in $CD4^+$ T cells is of concern in this patient population, and STI cannot be recommended for these patients.

Autoimmunization STI and STI for the reduction of total time receiving antiretroviral drugs are intended for persons who have maintained suppression of plasma viremia below the limit of detection for prolonged periods of time and who have relatively high $CD4^+$ T cell counts. The theoretical goal of autoimmunization STI is to allow multiple short bursts of viral replication to augment HIV-specific immune responses. This strategy is being studied among persons who began HAART during either the very early stage or chronic stages of HIV infection *[272-274]*. STI for the purpose of spending less time on therapy employs predetermined periods of long- or short-cycle intermittent antiretroviral therapy. The numbers of patients and duration of follow-up are insufficient for adequate evaluation of these approaches. Risks include a decline in $CD4^+$ T cell counts, an increase in transmission, and the development of drug resistance.

Because of insufficient data regarding these situations, STI cannot be recommended for use in general clinical practice. Further research is necessary in each of these areas.

# MANAGEMENT OF THE TREATMENT– EXPERIENCED PATIENT

## Considerations for Treatment Regimen Failure

***Recommendations:*** **Assessing and managing a patient with extensive prior antiretroviral experience and treatment regimen failure is complex and expert advice is critical (BII). After excluding adherence, tolerability, and pharmacokinetic issues, the usual cause of treatment regimen failure is virologic failure (BI). 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 confirmed HIV RNA level >400 copies/mL after suppression of viremia (BII). In managing virologic failure, there needs to be a distinction between limited and extensive prior treatment (AIII). The goal of treatment with limited prior drug exposure is maximum viral suppression (AI), while the goal of treatment with extensive prior drug exposure where viral suppression is difficult to achieve is preservation of immune function and prevention of clinical progression (CIII).**

While there are a number of causes of failure of treatment regimens, many will lead to virologic, immunologic, and/or clinical failure. Virologic failure occurs in as many as 63% of patients in population-based studies *[46, 47]*, but incidence is decreasing: in a recent large cohort study, 72% of subjects on therapy had HIV RNA <500 copies/mL at 6 months *[275]*. Virologic failure occurs less commonly on clinical trials, typically 10%-20% of subjects have HIV RNA >400 copies/mL at 48 weeks *[276]*. In addition, “missing=failure” (i.e. regimen-specific) analyses tend to overestimate failure rates because patients may experience failure on one regimen, but then respond to another *[277, 278]*. 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 antiretroviral regimen *[279]*. In one study, clinical progression (a new AIDS event or death) occurred in 7% of treated patients with suppressed viremia, 9% of treated patients with suppressed viremia followed by viral rebound, and 20% of treated patients who never achieved suppressed viremia over 2.5 years *[47]*. Some patient cohorts demonstrated that suboptimal adherence and toxicity accounted for 28%-40% of treatment regimen discontinuations *[280, 281]*. Treatment regimen failure ultimately increases the risk of clinical progression and should be addressed aggressively.

Although heterogeneous, treatment-experienced patients may be divided into those with (1) limited or (2) extensive prior treatment because the assessment and approach to management will differ for each. Some patients will have intermediate levels of prior treatment experience and strategies of assessment and management from both limited and extensive prior treatment scenarios may apply.

## Definitions and Causes of Treatment Regimen Failure

**Treatment regimen failure** is a broad term that incorporates all possible reasons for failure (e.g., adherence, toxicity, pharmacokinetics, suboptimal virologic potency, resistance, etc.). Treatment regimen failure is often associated with virologic, immunologic, and/or clinical failure.

There are many possible reasons for treatment regimen failure:

1. baseline patient factors: age (some cohorts), year of starting therapy, pretreatment HIV RNA level, pretreatment CD4 cell count, prior AIDS illness, co-morbidities (e.g. depression), active substance use, baseline drug resistance, prior antiretroviral treatment with drug resistance or cross resistance;
2. suboptimal adherence and missed clinic appointments;
3. drug side effects and toxicity;

4. pharmacokinetics (absorption, metabolism, penetration into reservoirs, food/fasting requirements, drug-drug interactions with concomitant medications);
5. potency of the antiretroviral regimen; and
6. other, unknown reasons.

Multiple reasons can occur in one patient. Some factors have not been demonstrated to be associated with treatment failure: gender, race, pregnancy, history of substance use.

***Virologic failure*** refers specifically to incomplete (or lack of) HIV RNA response:

1. ***incomplete virologic response:*** (e.g., not achieving HIV RNA <400 copies/mL by 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 viremia. The timing, pattern, and/or slope of HIV RNA decrease may predict ultimate virologic response *[282]*. 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 *[283-285]*.
2. ***virologic rebound:*** After virologic suppression, repeated detection of viremia.

There is no consensus on the optimal time to change therapy for low-level viremia. 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. Isolated episodes of viremia ("blips", e.g. single levels of 50–1,000 copies/mL) 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 *[286, 287]*.

***Immunologic failure:*** Failure to increase 25–50 cells/mm$^3$ above the baseline CD4 cell count over the first year of therapy or experiencing 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 *[276]*. A lower baseline CD4 cell count may be associated with a reduced CD4 cell response to therapy. For reasons not fully understood, some patients may have initial CD4 cell increases, but then blunted subsequent responses.

***Clinical failure:*** Occurrence or recurrence of HIV-related events (after at least 3 months on an antiretroviral regimen), excluding immune reconstitution syndromes *[288]*.

## Assessment of Treatment Regimen Failure

In general, the cause of treatment regimen failure should be explored by reviewing the medical history and performing a physical examination to assess for signs of clinical progression (AII). Important elements of the medical history include: the course of HIV RNA and CD4 cell count changes; the occurrence of HIV-related clinical events; antiretroviral treatment history and results of prior resistance testing (if any); medication-taking behavior, including the need for food and fasting requirements; adherence; tolerability; concomitant medications (with consideration for drug-drug interactions); and comorbidities (including substance use). In many cases the cause(s) of treatment regimen failure will be readily apparent. In some cases, no obvious cause will be identified.

For more information about approach to treatment regimen failure see Table 23–25.

It is important to distinguish among the reasons for regimen failure (e.g., adherence, tolerability, pharmacokinetics, suboptimal virologic potency, resistance, etc.) because approaches to treatment will differ.

For **adherence**: Identify and address the underlying cause(s) for nonadherence (e.g. access, depression, active substance use). Simplify the regimen (e.g., decrease pill count or increase dosing interval) (AII) (See Adherence section).

For **tolerability**: Assess the side effects. Address the likely duration of side effects: (e.g., the limited duration of gastrointestinal symptoms with some regimens). Management strategies may include:

- use symptomatic treatment (e.g. antiemetics, antdiarrheals);
- change one drug within the same drug class, if needed (e.g. stavudine for zidovudine-related anemia or gastrointestinal symptoms;
- use nevirapine for efavirenz-related central nervous system symptoms);
- or change classes (e.g., from a PI to a NNRTI) if necessary. (AI)

For **pharmacokinetic issues**: Review food/fasting requirements of treatment regimens. Review recent history of gastrointestinal symptoms to assess the likelihood of malabsorption. Review concomitant medications and dietary supplements for possible drug-drug interactions and make appropriate substitutions for antiretroviral agents and/or concomitant medications, as possible. (AII) (See Therapeutic Drug Monitoring.)

***When adherence, tolerability, and pharmacokinetic causes of treatment regimen failure have been considered and ruled out, consider virologic, immunologic, and clinical failure:***

For **virologic, immunologic, or clinical failure**: The overall goal of antiretroviral therapy is to prevent clinical progression and prolong healthy life. Review detailed antiretroviral treatment history: all prior antiretroviral medications with regard to dose and formulation, duration of therapy, adherence, tolerability, and likelihood of drug resistance or cross resistance. Distinguish limited and extensive prior treatment. Confirm a single HIV RNA increase with a two (or more) determinations and confirm CD4 cell count trends with at least 3 determinations. Obtain resistance testing while the patient is taking the failing regimen (See Resistance section).

Some patients demonstrate discordant responses in virologic, immunologic, and clinical parameters *[117]*. In addition, virologic, immunologic, and clinical failure have distinct time courses and may occur independently or simultaneously. In general, virologic failure occurs first, followed by immunologic failure, and finally by clinical failure; these events may be separated by months to years. Although some clinicians have explored the use of immune-based therapies (e.g., interleukin-2) for isolated immunologic failure *[289]*, such therapies remain unproven and generally should not be offered in the setting of discordant responses (DII).

***For patients with limited prior treatment:*** The goal is to re-suppress HIV RNA maximally to below the limit of detection 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. A single drug substitution (made on the basis of resistance testing) can be considered, but is unproven in this setting (CIII). Immunologic or clinical failure may not warrant a change in therapy in the setting of suppressed viremia (BIII).

***For patients with extensive prior treatment (Table 23–25):*** Viral suppression is often difficult to achieve in this population. Thus, the goal is to preserve immunologic function and prevent clinical progression (even with ongoing viremia). Even partial virologic suppression of HIV RNA $\geq$0.5 $\log_{10}$ copies/mL correlates with clinical benefits *[290]*; however, but 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 ongoing viremia and the absence of CD4 responses increases, decreases the risk of disease progression *[22]*. In a patient with a lower CD4 cell count (e.g. <200/$mm^3$), a change in therapy may be critical to preventing clinical progression and is therefore indicated (AII). 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 therapy (even with ongoing viremia) leads to a rapid increase in HIV RNA, a decrease in CD4 cell counts, and increases the risk for clinical progression *[271, 291]* and is therefore not recommended (DII).

## CHANGING ANTIRETROVIRAL THERAPY FOR VIROLOGIC FAILURE

General approach (see Tables 23–25): Ideally, design a regimen with 3 or more active drugs (on the basis of resistance testing or new mechanistic class) (BII) *[12]*. Note that 3 "new" drugs (i.e. drugs the patient has not yet taken) are not sufficient because of cross-resistance within drug classes and that drug potency varies. Drug potency is more important than the number of drugs. The principles are the same for virologic failure in pregnancy (See Perinatal Guidelines).

Early studies of treatment-experienced patients identified factors associated with improved virologic responses to subsequent regimens *[292, 293]*: lower HIV RNA at the time of therapy change, using a new (i.e. not yet taken) class of drugs (e.g. NNRTI, entry inhibitors), and using ritonavir-boosted PIs in PI-experiences patients.

The order of use among some antiretroviral agents may be important. With prolonged use, cross-resistance occurs commonly among NRTIs. Most, if not all, NNRTI-associated resistance mutations confer resistance to the entire NNRTI class of drugs. Novel early mutations to amprenavir, atazanavir, nelfinavir, or 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 (See Resistance section.)

Investigational agents in existing drug classes (e.g., reverse transcriptase and protease inhibitors) currently are under investigation in clinical trials. Some of these agents demonstrate distinct resistance patterns and activity against drug-resistant viruses. Drugs with new mechanisms of action (e.g., the HIV entry inhibitor, enfuvirtide) demonstrate antiretroviral activity, even in patients with extensive prior antiretroviral experience and multidrug resistance *[294, 295]*. However, adding a single active drug to a failing treatment regimen likely will rapidly select for resistance to the new drug. In patients with advanced HIV disease and multidrug-resistant HIV at risk for clinical progression, the advantage (short-term antiretroviral activity) and disadvantages (selection of drug resistance) of this approach must be assessed carefully. (AIII)

For specific clinical scenarios or see Table 22.

# STATEMENT ON THERAPEUTIC DRUG MONITORING (TDM) FOR ANTIRETROVIRAL AGENTS

***Recommendation: Therapeutic drug monitoring (TDM) for antiretroviral agents is not currently recommended for routine use in the management of the HIV-infected adult. (CIII)***

Antiretroviral agents meet most of the characteristics of agents that can be considered candidates for a TDM strategy *[296]*. The argument for TDM arises because of (1) data showing considerable interpatient variability in concentrations among patients who take the same dose and (2) data indicating relationships between the concentration of drug in the body and anti-HIV effect, and in some cases, toxicities. In particular, these concentration-response data exist for PIs and NNRTIs. Relationships between plasma concentrations of NRTIs and their intracellular pharmacologically active moieties have not yet been established; therefore, monitoring of plasma concentrations largely remains a research tool. The data describing relationships between anti-HIV agents and response have been reviewed in various publications *[297-300]*. While there are limitations and unanswered questions in these data, the consensus of U.S. and European clinical pharmacologists is that the data do provide a framework for the potential implementation of TDM for PIs and NNRTIs.

Scenarios in which both data and expert opinion indicate that information on the concentration of an antiretroviral agent may be useful in patient management are listed below. Consultation with an expert clinical pharmacologist may be advisable.

- clinically significant drug-drug or drug-food interactions that may result in reduced efficacy or increased dose-related toxicities;
- 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;
- therapy of treatment-experienced persons who may have viral isolates with reduced susceptibility to antiretroviral agents;
- the use of alternative dosing regimens whose safety and efficacy have not been established in clinical trials;
- concentration-dependent drug-associated toxicities; and
- the lack of expected virologic response in a treatment-naïve person.

There are several challenges and scientific gaps to the implementation of TDM in the clinical setting. The therapeutic range 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. Therefore, the key characteristic of a drug that is a candidate for TDM is knowledge of a therapeutic range of concentrations. Implementation of TDM in a patient requires the quantification of the concentration of the drug, usually in plasma or serum; the 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 published by the Adult AIDS Clinical Trials Group Pharmacology Committee *[297]* and at: http://www.hivpharmacology.com *[301]*.

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. Table 26 presents a synthesis of recommendations *[297-299, 301]* for minimum target trough PI and NNRTI concentrations in persons with wild-type virus. 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. Information on relationships between concentrations and drug-associated toxicities are also sparse, and clinicians using TDM as a strategy to manage these toxicities also should consult the most current literature for specific concentration recommendations.

The most important limiting factor for the implementation of TDM at present is the lack of prospective studies demonstrating that TDM improves clinical outcome. Additional limitations are the lack of widespread availability of laboratories that perform quantitation of antiretroviral drug concentrations under rigorous quality assurance/quality control standards and the shortage of experts in the interpretation of antiretroviral concentration data and application of such data to revise patients' dosing regimens. 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.

## ACUTE HIV-1 INFECTION

An estimated 40%–90% of patients acutely infected with HIV will experience certain symptoms of acute retroviral syndrome (Table 27) and should be considered for early therapy *[302-305]*. However, acute HIV infection is often not recognized by primary care clinicians because of the similarity of the symptom complex with those of influenza or other illnesses. Additionally, acute primary infection can occur asymptomatically. Health-care providers should consider a diagnosis of HIV infection for patients who experience a compatible clinical syndrome (Table 27) and should obtain appropriate laboratory testing. Evidence includes detectable HIV RNA in plasma by using sensitive PCR or bDNA assays combined with a negative or indeterminate HIV antibody test. Although measurement of plasma HIV RNA is the preferable diagnostic method, a test for p24 antigen might be useful when RNA testing is not readily available. However, a negative p24 antigen test does not eliminate acute infection, and a low titer (<10,000 copies/mL), false-positive test can exist with HIV RNA levels. When suspicion for acute infection is high (e.g., in a patient with a report of recent risk behavior in association with the symptoms and signs listed in Table 27, a test for HIV RNA should be performed (BII). Patients with diagnosed HIV infection by HIV RNA testing should have confirmatory testing performed (Table 2).

Information regarding treatment of acute HIV infection from clinical trials is limited. Preliminary data indicate that treatment of primary HIV infection with combination therapy has a beneficial effect on laboratory markers of disease progression *[306-309]*. However, the potential disadvantages of initiating therapy include additional exposure to antiretroviral therapy without a known clinical benefit, which could result in substantial toxicities, development of antiretroviral drug resistance, and adverse effect on quality of life. Ongoing clinical trials are addressing the question of the long-term benefit of potent treatment regimens.

Theoretically, early intervention can

- 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.

The potential risks of therapy for acute HIV infection include

- adverse effects on quality of life resulting from drug toxicities and dosing constraints;
- drug resistance if therapy fails to effectively suppress viral replication, which might limit future treatment options; and
- a need for continuing therapy indefinitely.

These considerations are similar to those for initiating therapy for the asymptomatic patient. (See Considerations for Initiating Therapy for the Patient with Asymptomatic HIV-Infection).

The health-care provider and the patient should be fully aware that therapy for primary HIV infection is based on theoretical considerations, and the potential benefits should be weighed against the potential risks. Certain authorities endorse treatment of acute HIV infection on the basis of the theoretical rationale and limited but supportive clinical trial data.

Apart from patients with acute primary HIV infection, experienced clinicians also recommend consideration of therapy for patients among whom seroconversion has occurred within the previous 6 months (CIII). Although the initial burst of viremia among infected adults usually resolves in 2 months, 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 *[310]*. 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 by using the algorithm discussed in Considerations for Patients with Established HIV Infection (CIII). Except for postexposure prophylaxis with antiretroviral agents *[311]*, no patient should be treated for HIV infection until the infection has been documented. All patients being examined without a formal medical record of a positive HIV test (e.g., those who have a positive result from a home test kit) should undergo enzyme-linked immunosorbent assay and an established confirmatory test (e.g., Western Blot) to document HIV infection (AI).

### Treatment Regimen for Primary HIV-1 Infection

After the clinician and patient have made the decision to use antiretroviral therapy for primary 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; potential combinations of agents available are similar to those used in established infection Table 12a.

These aggressive regimens can be associated with disadvantages, including drug toxicity, pill burden, cost, and the possibility of drug resistance that could limit future options. The latter is probable if virus replication is not adequately suppressed or if the patient has been infected with a viral strain that is already resistant to one or more agents. The patient should be counseled regarding potential limitations, and decisions should be made only after weighing the risks and sequelae of therapy against the theoretical treatment benefits because:

1. the goal of therapy is suppression of viral replication to below the level of detection;
2. the benefits of therapy are based on theoretical considerations; and
3. long-term clinical outcome benefit has not been documented; any regimen that is not expected to maximally suppress viral replication is not appropriate for treating the acutely HIV-infected person (EIII). Additional clinical studies are needed to delineate the role of antiretroviral therapy during the primary infection period.

### Patient Follow-up

Testing for plasma HIV RNA levels and $CD4^+$ T cell count and toxicity monitoring should be performed as described in Testing for Plasma HIV RNA Levels and $CD4^+$ T Cell Count in Guiding Decisions for Therapy (i.e., on initiation of therapy, after 4 weeks, and every 3–4 months thereafter) (AII). However, certain experienced clinicians believe that testing for plasma HIV RNA levels at 4 weeks is not helpful in evaluating the therapy's effect regarding acute infection, because viral loads might be decreasing from peak viremia levels, even in the absence of therapy.

### Duration of Therapy for Primary HIV-1 Infection

After therapy is initiated, experienced clinicians recommend continuing treatment with antiretroviral agents indefinitely because viremia has been documented to reappear or increase after therapy discontinuation (CII). Optimal duration and therapy composition are unknown, but ongoing clinical trials should provide relevant data regarding these concerns. Difficulties inherent in determining the optimal duration and therapy composition initiated for acute infection should be considered when first counseling the patient regarding therapy.

## CONSIDERATIONS FOR ANTIRETROVIRAL THERAPY AMONG HIV-INFECTED ADOLESCENTS

HIV-infected adolescents who were infected through sex or injection-drug use during adolescence follow a clinical course that is more similar to HIV disease among adults than children. In contrast, adolescents who were infected perinatally or through blood products as young children have a unique clinical course that differs from that of other adolescents and long-term surviving adults. The majority of HIV-infected adolescents were infected through sex during the adolescent period and are in an early stage of infection.

Puberty is a time of somatic growth and hormone-mediated changes, with females acquiring additional body fat and males additional muscle mass. Theoretically, these physiologic changes can affect drug pharmacology, including drugs with a narrow therapeutic index that are used in combination with protein-bound medicines or hepatic enzyme inducers or inhibitors. However, no clinically substantial impact of puberty has been reported with NRTI use. Clinical experience with PIs and NNRTIs has been limited. Thus, medication dosages used to treat HIV and OIs among adolescents should be based on Tanner staging of puberty and not specific age. Adolescents in early puberty (Tanner stages I and II) should be administered dosages on the basis of pediatric guidelines, whereas those in late puberty (Tanner stage V) should be administered dosages on the basis of adult guidelines. Youth who are in the midst of their growth spurt (Tanner stage III females and Tanner stage IV males) should be monitored closely for medication efficacy and toxicity when choosing adult or pediatric dosing guidelines.

## CONSIDERATIONS FOR ANTIRETROVIRAL THERAPY AMONG HIV-INFECTED PREGNANT WOMEN

Antiretroviral treatment recommendations for HIV-infected pregnant women are based on the belief that therapies of known benefit to women should not be withheld during pregnancy, unless the risk for adverse effects outweighs the expected benefits for the woman. Combination antiretroviral therapy is the recommended standard treatment for HIV-infected nonpregnant women. Additionally, a three-part regimen of zidovudine, administered orally starting at 14 weeks gestation and continued throughout pregnancy, intravenously during labor and to the newborn for the first 6 weeks of life, reduced the risk for perinatal transmission by 66% in a randomized, double-blind clinical trial (i.e., the Pediatric AIDS Clinical Trials Group [PACTG] protocol 076) *[312]* and is recommended for all pregnant women *[313]*. Pregnancy should not preclude the use of optimal therapeutic regimens. However, recommendations regarding the choice of antiretroviral drugs for treatment of infected women are subject to unique considerations including:

1. potential changes in dosing requirement resulting from physiologic changes associated with pregnancy,
2. potential effects of antiretroviral drugs on a pregnant woman,
3. effect on the risk for perinatal HIV transmission, and;
4. the potential short- and long-term effects of the antiretroviral drug on the fetus and newborn, all of which may not be known for certain antiretroviral drugs *[313]*. (See *Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States*).

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.

Women who are in the first trimester of pregnancy and who are not receiving antiretroviral therapy might wish to consider delaying therapy initiation until after 10–12 weeks gestation. This period of organogenesis is when the embryo is most susceptible to potential teratogenic drug effects, and the risks regarding antiretroviral therapy to the fetus during that period are unknown. However, this decision should be discussed between the clinician and patient and should include an assessment of the woman's health status and the benefits versus risks of delaying therapy initiation for these weeks. If clinical, virologic, or immunologic parameters are such that therapy would be recommended for nonpregnant women, the majority of Panel members recommend initiating therapy regardless of gestational age. Nausea and vomiting during early pregnancy, affecting the woman's ability to take and absorb oral medications, can be a factor in the decision regarding treatment during the first trimester.

Standard combination antiretroviral therapy is recommended as initial therapy for HIV-infected pregnant women whose clinical, immunologic, or virologic status would indicate treatment if not pregnant. When antiretroviral therapy initiation would be considered optional on the basis of current guidelines for treatment of nonpregnant women, but HIV-1 RNA levels are $\geq$1,000 copies/mL, infected pregnant women should be counseled regarding the benefits of standard combination therapy and offered therapy, including the three-part zidovudine chemoprophylaxis regimen (Table 28). Although such women are at low risk for clinical disease progression if combination therapy is delayed, antiretroviral therapy that successfully reduces HIV-1 RNA levels to <1,000 copies/mL substantially lowers the risk for perinatal transmission *[175, 177, 314]* and limits the need to consider elective cesarean delivery as an intervention to reduce transmission risk *[313]*.

Use of antiretroviral prophylaxis has been demonstrated to provide benefit in preventing perinatal transmission, even for infected pregnant women with HIV-1 RNA levels <1,000 copies/mL. In a meta-analysis of factors associated with perinatal transmission among women who had infected infants despite having HIV-1 RNA <1,000 copies/mL at or near delivery, transmission was only 1.0% among women receiving zidovudine prophylaxis compared with 9.8% among those receiving no antiretroviral treatment *[177]*. The time-limited use of zidovudine alone during pregnancy for chemoprophylaxis of perinatal transmission is controversial. Potential benefits of standard combination antiretroviral regimens for treatment of HIV infection should be discussed with and offered to all pregnant HIV-infected women regardless of viral load and is recommended for all pregnant women with HIV-1 RNA levels >1,000 copies/mL. However, a woman might wish to restrict exposure of her fetus to antiretroviral drugs during pregnancy but still wish to reduce the risk for transmitting HIV to her infant. Additionally, for women with HIV-1 RNA levels <1,000 copies/mL, time-limited use of zidovudine during the second and third trimesters of pregnancy is less likely to induce resistance caused by the limited viral replication existing in the patient and the time-limited exposure to the antiretroviral drug. For example, zidovudine resistance was unusual among healthy women who participated in PACTG 076 *[315]*. Use of zidovudine chemoprophylaxis alone during pregnancy might be an appropriate option for these women.

When combination therapy is administrated principally to reduce perinatal transmission and would have been considered optional for treatment if the woman were not pregnant, consideration can be given to discontinuing therapy postnatally, with the decision to reinstitute treatment on the basis of standard criteria for nonpregnant women. If drugs are discontinued postnatally, all drugs should be stopped simultaneously. Discussion regarding the decision to continue or stop combination therapy postpartum should occur before initiation of therapy during pregnancy.

Women already receiving antiretroviral therapy might recognize their pregnancy early enough in gestation that concern for potential teratogenicity can lead them to consider temporarily stopping antiretroviral therapy until after the first trimester. Insufficient data exist to support or refute teratogenic risk regarding antiretroviral drug use among humans when administered during the first 10–12 weeks of gestation. However, treatment with efavirenz should be avoided during the first trimester because substantial teratogenic effects among rhesus macaques occurred at drug exposures similar to those representing human exposure. Hydroxyurea is a potent teratogen among animal species and should be avoided also during the first trimester.

Temporary discontinuation of antiretroviral therapy could result in a rebound in viral levels that theoretically could be associated with increased risk for early in utero HIV transmission or could potentiate disease progression in the woman *[316]*. Although the effects of all antiretroviral drugs on the developing fetus during the first trimester are uncertain, experienced clinicians recommend continuation of a maximally suppressive regimen, even during the first trimester. If antiretroviral therapy is discontinued during the first trimester for any reason, all agents should be stopped simultaneously to avoid drug resistance. After the drugs are reinstituted, they should be introduced simultaneously for the same reason.

Limited data are available on the pharmacokinetics and safety of antiretroviral agents during pregnancy for drugs other than zidovudine.[**] (see Safety and Toxicity of Individual Antireroviral Agents in Pregnancy). In the absence of data, drug choices should be personalized on the basis of discussion with the patient and available data from preclinical and clinical testing of each drug. FDA's pregnancy classification for all currently approved antiretroviral agents and selected other information regarding the use of antiretroviral drugs is available in this report Table 29. The predictive value of in vitro and animal screening tests for adverse effects among humans is unknown. Certain drugs commonly used to treat HIV infection or its consequences can result in positive readings on >1 screening tests. For example, acyclovir is positive on certain in vitro assays for chromosomal breakage and carcinogenicity and is associated with fetal abnormalities among rats; however, data regarding human experience from the Acyclovir in Pregnancy Registry indicate no increased risk for birth defects among human infants with in utero exposure *[317]*.

When combination antiretroviral therapy is administered during pregnancy, zidovudine should be included as a component of antenatal therapy whenever possible. Circumstances might arise where this option is not feasible (e.g., occurrence of substantial zidovudine-related toxicity). Additionally, women receiving an antiretroviral regimen that does not contain zidovudine but who have HIV-1 RNA levels that are consistently low or undetectable have a low risk for perinatal transmission, and addition of zidovudine to the current regimen could compromise regimen

[**] Additional information is available at http://AIDSinfo.nih.gov

adherence. Regardless of the antepartum antiretroviral regimen, intravenous intrapartum zidovudine and the standard 6-week course of zidovudine for the infant is recommended. If the woman has not received zidovudine as a component of her antenatal therapeutic antiretroviral regimen, intravenous zidovudine should still be administered to the pregnant woman during the intrapartum period, when feasible. Additionally, for women receiving combination antiretroviral treatment, the maternal antenatal antiretroviral treatment regimen should be continued on schedule as much as possible during labor to provide maximal virologic effect and to minimize the chance of drug resistance. Zidovudine and stavudine should not be administered together because of potential pharmacologic antagonism; therefore, options for women receiving oral stavudine as part of their antenatal therapy include continuing oral stavudine during labor without intravenous zidovudine or withholding oral stavudine during intravenous administration during labor.

Toxicity related to mitochondrial dysfunction has been reported among HIV-infected patients receiving long-term treatment with nucleoside analogues and can be of concern for pregnant women. Symptomatic lactic acidosis and hepatic steatosis can have a female preponderance *[191]*. Additionally, these syndromes have similarities to the rare but life-threatening syndromes of acute fatty liver of pregnancy and hemolysis, elevated liver enzymes and low platelets (HELLP syndrome) that occur during the third trimester of pregnancy. Certain data indicate that a disorder of mitochondrial fatty acid oxidation in the mother or her fetus during late pregnancy can affect the etiology of acute fatty liver of pregnancy and HELLP syndrome *[318, 319]* and possibly contribute to susceptibility to antiretroviral-associated mitochondrial toxicity.

Whether pregnancy augments the incidence of the lactic acidosis/hepatic steatosis syndrome reported among nonpregnant women receiving nucleoside analogue treatment is unclear. Bristol-Myers Squibb has reported three maternal deaths caused by lactic acidosis, two with and one without accompanying pancreatitis, among women who were either pregnant or postpartum and whose antepartum therapy during pregnancy included stavudine and didanosine in combination with other antiretroviral agents (either a PI or nevirapine) *[194]*. All cases were among women who were receiving treatment with these agents at the time of conception and continued for the duration of pregnancy; all of the women were seen late in gestation with symptomatic disease that progressed to death in the immediate postpartum period. Two women were also associated with fetal demise. Nonfatal cases of lactic acidosis among pregnant women have also been reported.

Because pregnancy itself can mimic certain early symptoms of lactic acidosis/hepatic steatosis syndrome or be associated with other disorders of liver metabolism, clinicians who care for HIV-infected pregnant women receiving nucleoside analogue drugs need to be alert for this syndrome. Pregnant women receiving nucleoside analogue drugs should have hepatic enzymes and electrolytes assessed more frequently during the last trimester of pregnancy, and any new symptoms should be evaluated thoroughly. Additionally, because of reports of maternal mortality secondary to lactic acidosis with prolonged use of the combination of stavudine and didanosine by HIV-infected pregnant women, clinicians should prescribe this antiretroviral combination during pregnancy with caution and only when other nucleoside analogue drug combinations have failed or caused unacceptable toxicity or side effects *[194]*.

The antenatal zidovudine dosing regimen used in the perinatal transmission prophylaxis trial PACTG 076 was zidovudine 100 mg administered five times/day and was selected on the basis of standard zidovudine dosage for adults at the time the study was designed in 1989 (Table 28). However, data indicate that administration of zidovudine three times/day will maintain intracellular zidovudine triphosphate at levels comparable with those observed with more frequent dosing *[320, 321]*. Comparable clinical response also has been observed in clinical trials among persons receiving zidovudine two times/day *[322-324]*. Thus, the standard zidovudine dosing regimen for adults is 200 mg three times/day or 300 mg two times/day. A less-frequent dosing regimen would be expected to enhance maternal adherence to the zidovudine perinatal prophylaxis regimen and, therefore, is an acceptable alternative antenatal dosing regimen for zidovudine prophylaxis.

In a short-course antenatal/intrapartum zidovudine perinatal transmission prophylaxis trial in Thailand, administration of zidovudine 300 mg two times/day for 4 weeks antenatally and 300 mg every 3 hours orally during labor was reported to reduce perinatal transmission by approximately 50%, compared with a placebo *[325]*. The lower efficacy of the short-course two-part zidovudine prophylaxis regimen studied in Thailand compared with the three-part zidovudine prophylaxis regimen used in PACTG 076 and recommended for use in the United States, could result from

1. the shorter antenatal duration of zidovudine,

2. oral rather than intravenous administration during labor;
3. lack of treatment for the infant; or
4. a combination of these factors. In the United States, identification of HIV-infected pregnant women before or as early as possible during the course of pregnancy and use of the full three-part PACTG 076 zidovudine regimen is recommended for prevention of perinatal HIV transmission.

Monitoring and use of HIV-1 RNA for therapeutic decision-making during pregnancy should be performed as recommended for nonpregnant women. Data from untreated and zidovudine-treated infected pregnant women indicate that HIV-1 RNA levels correlate with risk for transmission *[175, 312, 314]*. However, although risk for perinatal transmission among women with HIV-1 RNA below the level of assay quantitation is low, transmission from mother to infant has been reported among women with all levels of maternal HIV-1 RNA. Additionally, antiretroviral prophylaxis is effective in reducing transmission even among women with low HIV RNA levels *[177, 312]*. Although the mechanism by which antiretroviral prophylaxis reduces transmission is probably multifactorial, reduction in maternal antenatal viral load is a key component of prophylaxis. However, pre- and postexposure prophylaxis of the infant is provided by passage of antiretroviral drugs across the placenta, resulting in inhibitory drug levels in the fetus during and immediately after the birth process *[326]*. The extent of transplacental passage varies among antiretroviral drugs (Table 29). Additionally, although a correlation exists between plasma and genital tract viral load, discordance has also been reported *[327-329]*. Further, differential evolution of viral sequence diversity occurs between the peripheral blood and genital tract *[329, 330]*. Studies are needed to define the relationship between viral load suppression by antiretroviral therapy in plasma and levels of HIV in the genital tract and the relationship between these compartment-specific effects and the risk for perinatal HIV transmission. The full zidovudine chemoprophylaxis regimen, including intravenous zidovudine during delivery and zidovudine administration to the infant for the first 6 weeks of life, in combination with other antiretrovirals or alone, should be discussed with and offered to all infected pregnant women regardless of their HIV-1 RNA level.

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. The registry collects observational, nonexperimental data regarding antiretroviral exposure during pregnancy for the purpose of assessing potential teratogenicity. Registry data will be used to supplement animal toxicology studies and assist clinicians in weighing the potential risks and benefits of treatment for each patient. The registry is a collaborative project with an advisory committee of obstetric and pediatric practitioners, staff from CDC and NIH, and staff from pharmaceutical manufacturers. The registry allows the anonymity of patients, and birth outcome follow-up is obtained by registry staff from the reporting clinician. Referrals should be directed to

Antiretroviral Pregnancy Registry
115 North Third Avenue, Suite 306,
Wilmington, NC 28401
Telephone: 910-251-9087 or 1-800-258-4263
FAX: 1-800-800-1052.

## PREVENTION COUNSELING FOR THE HIV-INFECTED PATIENT

Ongoing prevention counseling is an essential component of management for HIV-infected persons *[331]*. Each patient encounter provides an opportunity to reinforce HIV prevention messages. Therefore, each encounter should include assessment and documentation of:
1. the patient's knowledge and understanding of HIV transmission; and
2. the 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. The physician, nurse, or other health-care team member should routinely provide this counseling. Partner notification is a key component of HIV detection and prevention and should be pursued by the provider or by referral services.

Although the core elements of HIV prevention messages are unchanged since the introduction of HAART, key observations regarding the biology of HIV transmission, the impact of HAART on transmission, and personal risk behaviors have been noted. For example, sustained low plasma viremia that results from successful HIV therapy substantially reduces the likelihood of HIV transmission. In one study, for each log reduction in plasma viral load, the likelihood of transmission between discordant couples was reduced 2.5-fold *[332]*. Similarly, mother-to-child

HIV transmission was observed to decline in a linear fashion with each log reduction in maternal delivery viral load *[175, 314, 331]*. Although this relationship is usually linear, key exceptions should be noted. For example, mother-to-child transmission has been reported even among women with very low or undetectable viral loads *[177, 333, 334]*. Similarly, the relationship between viral load in the plasma and the levels in the genital fluid of women and the seminal fluid of men is complex. Studies have demonstrated a rough correlation between plasma HIV levels and genital HIV levels, but key exceptions have been observed *[333]*. Viral evolution can occur in the genital compartment that is distinct from the viral evolution in the plasma, and transmissions have been documented in the presence of an undetectable plasma viral load *[177, 312, 334]*. Thus, although durably effective HAART substantially reduces the likelihood of HIV transmission, the degree of protection is incomplete.

Certain biologic factors other than plasma viral load have also been demonstrated to influence sexual transmission of HIV, including ulcerative and nonulcerative sexually transmitted infections *[335]*, vaginitis (including bacterial vaginosis and candida albicans vaginal infections) *[336]*, genital irritation associated with frequent use of nonoxynol-9 (N-9)–containing products *[337]*; menstruation; lack of circumcision in men *[338-340]*; oral contraceptive use *[341]*; estrogen deficiency *[341]*; progesterone excess *[336]*; and deficiencies of vitamin A *[342]* and selenium *[340]*.

Behavioral changes among HIV-infected persons have been observed during the HAART era that impact prevention. Unfortunately, evidence exists that awareness of the potential benefits of HAART is leading certain persons to relapse into high-risk activities. For example, reports from urban communities of men who have sex with men (MSM) in the United States indicate rising HIV seroprevalence rates, as well as rising rates of unsafe sexual practices, corroborated by the rising rates of other sexually transmitted infections. Recently, an association between knowledge of the benefits of HAART among MSM and relapse to high-risk activity was observed *[343, 344]*.

Women might have unprotected sex because they wish to become pregnant. For women of childbearing potential, desire for pregnancy should be assessed at each encounter; women wishing to pursue pregnancy should be referred for preconception counseling to reduce risks for perinatal transmission and transmission to uninfected sexual partners. Among women of childbearing age who wish to avoid pregnancy, condoms should be encouraged in addition to other forms of contraception for preventing transmission of HIV and other sexually transmitted infections (dual-method use) or used as a single method for pregnancy prevention as well (dual protection). In a randomized placebo-controlled clinical trial of N-9 conducted among commercial sex workers with high rates of sexual activity, N-9 did not protect against HIV infection, resulted in increased vaginal lesions, and possibly caused increased transmission *[336]*. Although these adverse effects might not occur with less frequent use, given current evidence, spermicides containing N-9 should not be recommended as an effective means of HIV prevention.

Optimal adherence to antiretroviral regimens has been directly associated with a lower risk for morbidity and mortality and indirectly with a reduction in risk for HIV transmission because of its association with lower viral loads *[345]*. Suboptimal adherence to HIV medication recently has been demonstrated to be a predictor of suboptimal adherence to HIV prevention strategies *[346]*. More intensive adherence and prevention counseling might be appropriate for persons who demonstrate repeated deficiencies in either area.

Despite the strong association between a reduced risk for HIV transmission and sustained low viral load, the message of HIV prevention for patients should remain simple: After becoming infected, a person can transmit the virus at any time, and no substitute exists for latex or polyurethane male or female condoms, other safer sexual behaviors (e.g., partner reduction or abstinence), and cessation of any sharing of drug paraphernalia. Prevention counseling for patients known to have HIV infection remains a critical component of HIV primary care, including easy access to condoms and other means of prevention. Clinicians might wish to directly address with their patients the risks associated with using viral load outcomes as a factor in considering high-risk behavior. HIV-infected persons who use injection drugs should be advised to enroll in drug rehabilitation programs. If this advice is not followed or if these services are unavailable, the patient should receive counseling regarding risks associated with sharing needles and paraphernalia.

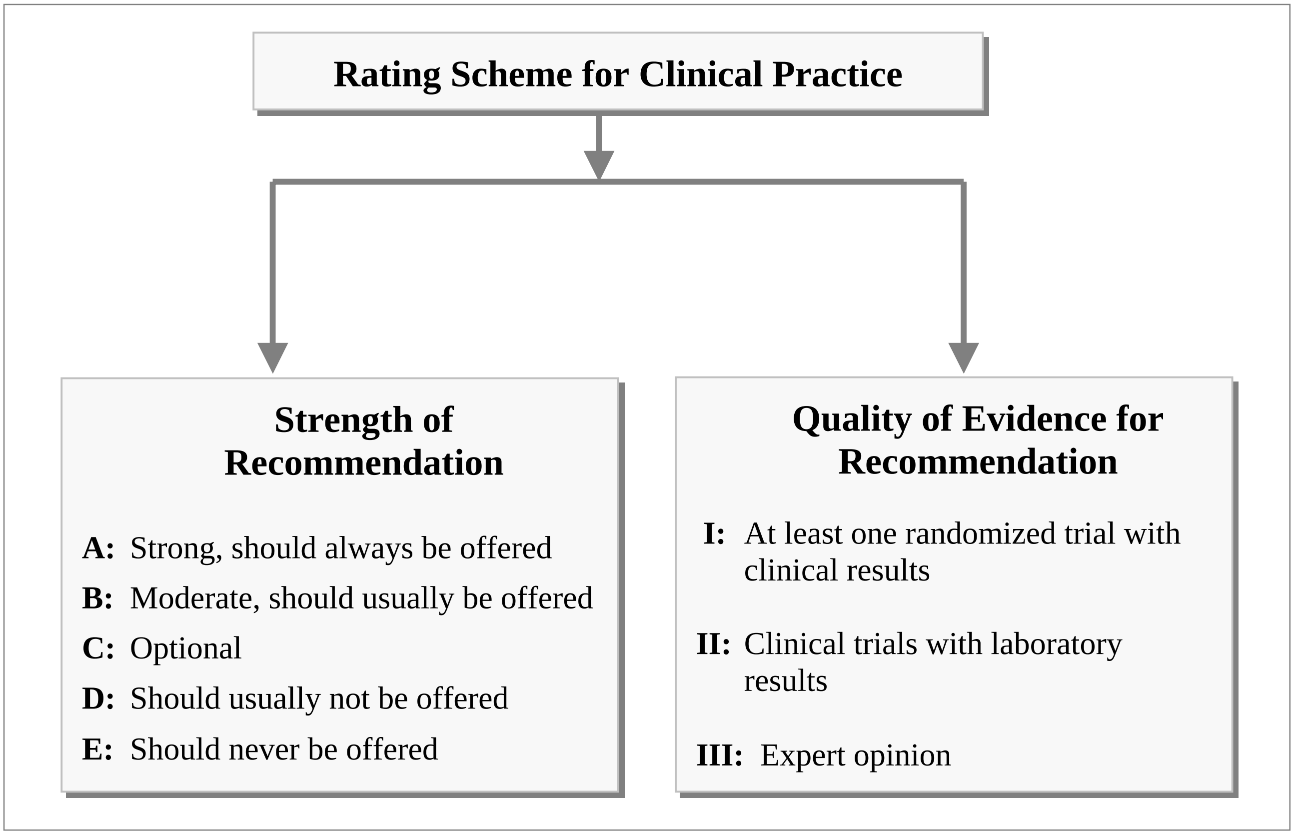
Finally, the most successful and effective prevention messages are those tailored to each patient. These messages are culturally appropriate, practical, and relevant to the person's knowledge, beliefs, and behaviors *[331]*. The message, the manner of delivery, and the cultural context vary substantially, depending on the patient (For additional information regarding these strategies, as well as recommendations on prevention, see HIV Prevention at (http://hivinsite.ucsf.edu/InSite.jsp?page=kb-07).

## CONCLUSION

The Panel has attempted to use the advances in knowledge regarding the pathogenesis of HIV in the infected person to translate scientific principles and data obtained from clinical experience into guidelines that can be used by clinicians and patients to make therapeutic decisions. These guidelines are offered for ongoing discussion between the patient and clinician after having defined specific therapeutic goals with an acknowledgment of uncertainties. Patients should be entered into a continuum of medical care and services, including social, psychosocial, and nutritional services, with the availability of professional referral and consultation. To achieve the maximal flexibility in tailoring therapy to each patient during his or her infection, drug formularies must allow for all FDA-approved NRTIs, NNRTIs, and PIs as treatment options. The Panel urges industry and the public and private sectors to conduct further studies to allow refinement of these guidelines. Specifically, studies are needed to optimize recommendations for primary therapy; to define secondary therapy; and to delineate the reasons for treatment failure. The Panel remains committed to revising these guidelines as new data become available.

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

## Table 1. Rating Scheme for Clinical Practice Recommendations



## Table 2. Indications for Plasma HIV RNA Testing*

| Clinical Indication | Information | Use |
|---|---|---|
| Syndrome consistent with acute HIV infection | Establishes diagnosis when HIV antibody test is negative or indeterminate | Diagnosis† |
| Initial evaluation of newly diagnosed HIV infection | Baseline viral load setpoint | Decision to start or defer therapy |
| Every 3–4 months in patients not on therapy | Changes in viral load | Decision to start therapy |
| 2–8 weeks after initiation of antiretroviral therapy | Initial assessment of drug efficacy | Decision to continue or change therapy |
| 3–4 months after start of therapy | Maximal 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 carinii 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 (e.g., Western blot serology performed 2–4 months after the initial indeterminate or negative test).

## Table 3. Recommendations For Using Drug-Resistance Assays

| Clinical setting/recommendations | Rationale |
|---|---|
| **Drug-resistance assay recommended** | |
| Virologic failure during combination antiretroviral therapy (AI) | Determine the role of resistance in drug failure and maximize the number of active drugs in the new regimen, if indicated. |
| 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. |
| Acute human immunodeficiency virus (HIV) infection, if decision is made to initiate therapy (AIII) | Determine if drug-resistant virus was transmitted and change regimen accordingly. |
| **Drug-resistance assay should be considered** | |
| Chronic HIV infection before therapy initiation (CIII) | Available assays might not detect minor drug-resistant species. However, should consider if significant probability that patient was infected with drug-resistant virus (i.e., if the patient is thought to have been infected by a person receiving antiretroviral drugs). |
| **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. |
| Plasma viral load <1,000 HIV RNA copies/mL (DIII) | Resistance assays cannot be consistently performed because of low copy number of HIV RNA; patients/providers may incur charges and not receive results. |

## Table 4. Potential Benefits and Risks of Early Versus Delayed Therapy Initiation For the Asymptomatic Human Immunodeficiency Virus (HIV)-Infected Patient[*]

### Potential Benefits and Risks of Early Therapy[*]

**Potential benefits of early therapy**

- Earlier suppression of viral replication
- Preservation of immune function
- Prolongation of disease-free survival
- Lower risk of resistance with complete viral suppression
- Possible decrease in the risk of HIV transmission[‡]

**Potential risks of early therapy**

- Drug-related adverse effects on quality of life
- Drug-related serious toxicities
- Early development of drug resistance due to suboptimal viral suppression
- Risk of transmission of virus resistant to antiretroviral drugs (if suboptimal suppression)
- Limitation of future treatment options
- Unknown durability of current available therapy

### Potential Benefits and Risks of Delayed Therapy[*]

**Potential benefits of delayed therapy**

- Avoid negative effects on quality of life
- Avoid drug-related adverse events
- Preserve future treatment options
- Delay in development of drug resistance

**Potential risks of delayed therapy**

- Possible risk of irreversible immune system compromise
- Possible greater difficulty in viral suppression
- Possible increased risk of HIV transmission

* See Table 6 for consensus recommendations regarding when to initiate therapy.

† The risk for viral transmission still exists; antiretroviral therapy cannot substitute for primary HIV prevention measures (e.g., use of condoms and safer sex practices).

## Table 5. Risk for Progression to AIDS-Defining Illness Among a Cohort of Men Who Have Sex with Men, Predicted by Baseline CD4+ T Cell Count and Viral Load*

| CD4 ≤ 200 cells/mm³ Plasma Viral Load (copies/mL) † | | Percentage of AIDS-defining illness ‡ | | | |
|---|---|---|---|---|---|
| **bDNA** | **RT-PCR** | **n** | **3 years** | **6 years** | **9 years** |
| ≤ 500 | ≤ 1,500 | 0 § | – | – | – |
| 501 – 3,000 | 1,501 – 7,000 | 3 § | – | – | – |
| 3,001 – 10,000 | 7,001 – 20,000 | 7 | 14.3 | 28.6 | 64.3 |
| 10,001 – 30,000 | 20,001 – 55,000 | 20 | 50.0 | 75.0 | 90.0 |
| > 30,000 | > 55,000 | 70 | 85.5 | 97.9 | 100.0 |
| **CD4 201 – 350∞ cells/mm³ Plasma Viral Load (copies/mL)†** | | **Percentage of AIDS-defining illness ‡** | | | |
| **bDNA** | **RT-PCR** | **n** | **3 years** | **6 years** | **9 years** |
| ≤ 500 | ≤ 1,500 | 3 § | – | – | – |
| 501 – 3,000 | 1,501 – 7,000 | 27 | 0 | 20.0 | 32.2 |
| 3,001 – 10,000 | 7,001 – 20,000 | 44 | 6.9 | 44.4 | 66.2 |
| 10,001 – 30,000 | 20,001 – 55,000 | 53 | 36.4 | 72.2 | 84.5 |
| > 30,000 | > 55,000 | 104 | 64.4 | 89.3 | 92.9 |
| **CD4 > 350 cells/mm³ Plasma Viral Load (copies/mL)†** | | **Percentage of AIDS-defining illness ‡** | | | |
| **bDNA** | **RT-PCR** | **n** | **3 years** | **6 years** | **9 years** |
| ≤ 500 | ≤ 1,500 | 119 | 1.7 | 5.5 | 12.7 |
| 501 – 3,000 | 1,501 – 7,000 | 227 | 2.2 | 16.4 | 30.0 |
| 3,001 – 10,000 | 7,001 – 20,000 | 342 | 6.8 | 30.1 | 53.5 |
| 10,001 – 30,000 | 20,001 – 55,000 | 323 | 14.8 | 51.2 | 73.5 |
| > 30,000 | > 55,000 | 262 | 39.6 | 71.8 | 85.0 |

* Adapted for this report from data from the Multicenter AIDS Cohort Study (MACS) (Source: Mellors JW, Rinaldo CR Jr, Gupta P, et al. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma, Science 1996;272:1167-70. Erratum: Science 1997;275:14; adapted by Alvaro Muñoz, PhD, John Hopkins University, Baltimore, MD 2001).

† MACS numbers reflect plasma HIV RNA values obtained by version 2.0 bDNA testing. RT-PCR values are consistently 2–2.5-fold higher than first-generation bDNA values, as indicated. The version 3.0 bDNA assay provides similar HIV-1 RNA values as RT-PCR, except at the lower end of the linear range (<1,500 copies/mL). The Organon Teknika NucliSens® HIV-1 QT assay, an in vitro nucleic acid amplification test for HIV RNA, has been approved by the Food and Drug Administration for monitoring the effects of antiretroviral therapy among adults with baseline HIV RNA of >28,000 copies/mL.

‡ In the reference study, AIDS was defined according to the 1987 CDC definition, which did not include asymptomatic persons with CD4+ T cells counts <200 cells/mm³.

§ Too few subjects were in the category to provide a reliable estimate of AIDS risk.

∞ A recent evaluation of data from the MACS cohort of 231 persons with CD4+ T cell counts >200 and <350 cells/mm³ demonstrated that of 40 (17%) persons with plasma HIV RNA <10,000 copies/mL, none progressed to AIDS by 3 years (Source: Phair JP, Mellors JW, Detels R, Margolick JB, Muñoz A. Virologic and immunologic values allowing safe deferral of antiretroviral therapy. *AIDS* 2002; 16(18): 2455-9). Of 28 individuals (29%) with plasma viremia of 10,000 – 20,000 copies/mL, 4% and 11% progressed to AIDS at 2 and 3 years, respectively. Plasma HIV RNA was calculated as RT-PCR values from measured bDNA values.

## Table 6. 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 5, the potential benefits and risks of therapy indicated in Table 4, and the willingness of the patient to accept therapy.

| Clinical Category | $CD4^+$ Cell Count | Plasma HIV RNA | Recommendation |
|---|---|---|---|
| Symptomatic (AIDS or severe symptoms) | Any value | Any value | Treat |
| Asymptomatic, AIDS | $CD4^+$ T cells <200/$mm^3$ | Any value | Treat |
| Asymptomatic | $CD4^+$ T cells >200/$mm^3$ but ≤350/$mm^3$ | Any value | Treatment should be offered, although controversial.* |
| Asymptomatic | $CD4^+$ T cells >350/$mm^3$ | >55,000 (by RT-PCR or bDNA) ϕ | Some experienced clinicians recommend initiating therapy, recognizing that the 3-year risk for untreated patients to develop AIDS is >30%; in the absence of increased levels of plasma HIV RNA, other clinicians recommend deferring therapy and monitoring the $CD4^+$ T cell count and level of plasma HIV RNA more frequently; clinical outcome data after initiating therapy are lacking. |
| Asymptomatic | $CD4^+$ T cells >350/$mm^3$ | <55,000 (by RT–PCR or bDNA) ϕ | Most experienced clinicians recommend deferring therapy and monitoring the $CD4^+$ T cell count, recognizing that the 3-year risk for untreated patients to experience AIDS is <15%. |

* 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 recent evaluation of data from the Multicenter AIDS Cohort Study (MACS) of 231 persons with $CD4^+$ T cell counts >200 and <350 cells/$mm^3$ demonstrated that of 40 (17%) persons with plasma HIV RNA <10,000 copies/mL, none progressed to AIDS by 3 years (Source: Phair JP, Mellors JW, Detels R, Margolick JB, Muñoz A. Virologic and immunologic values allowing safe deferral of antiretroviral therapy. *AIDS* 2002; 16(18): 2455-9). Of 28 persons (29%) with plasma viremia of 10,000–20,000 copies/mL, 4% and 11% progressed to AIDS at 2 and 3 years respectively. Plasma HIV RNA was calculated as RT-PCR values from measured bDNA values (For additional information, see "Considerations for Initiating Therapy for the Patient with Asymptomatic HIV-1 Infection").

ϕ Although a 2–2.5 fold difference existed between RT-PCR and the first bDNA assay (version 2.0), with the 3.0 version bDNA assay, values obtained by bDNA and RT-PCR are similar except at the lower end of the linear range (<1,500 copies/mL).

## Table 7. Strategies to Improve Adherence: Patient and Medication-Related

- Inform patient regarding side effects.
- Anticipate and treat side effects.
- Simplify food requirements.
- Avoid adverse drug interactions.
- If possible, reduce dose frequency and number of pills.
- Negotiate a treatment plan that the patient understands and to which he/she commits.
- Spend time and multiple encounters to educate and explain goals of therapy and need for adherence.
- Establish readiness to take medication *before* writing first prescription.
- Recruit family and friends to support the treatment plan.
- Develop concrete plan for specific regimen by considering meals schedule, daily routines, and side effects.
- Provide written schedule and pictures of medications, daily or weekly pillboxes, alarm clocks, pagers, or other mechanical aids for adherence.
- Develop adherence support groups or add adherence concerns to agenda of other support groups.
- Develop link with local community-based organizations regarding adherence combined with educational sessions and practical strategies.
- Consider practice sessions using candy instead of pills.

## Table 8. Strategies to Improve Adherence: Clinician and Health Team-Related

- Establish trust.
- Serve as educator and information source with ongoing support and monitoring.
- Provide access between visits for questions or problems (e.g., by providing a pager number), including during vacation or conferences.
- Monitor ongoing adherence; intensify management during periods of suboptimal adherence (i.e., more frequent visits, recruitment of family or friends, deployment of other team members, and referral for mental health or chemical dependency services).
- Use health team for all patients, including patients with special needs (e.g., use peer educators for adolescents or for injection drug users).
- Consider impact of new diagnoses on adherence (e.g., depression, liver disease, wasting, or recurrent chemical dependency), and include adherence intervention in management.
- Use nurses, pharmacists, peer educators, volunteers, case managers, drug counselors, clinician's assistants, nurse practitioners, and research nurses to reinforce adherence message.
- Provide training to support team regarding antiretroviral therapy and adherence.
- Add adherence interventions to job descriptions of support team members; add continuity-of-care role to improve patient access.

## Table 9. Interventions To Improve Adherence

- Pharmacist-based adherence encounters and clinics.
- Multidisciplinary adherence encounters at each visit.
- Reminders, alarms, pagers, or timers on pillboxes.
- Patient education aids, including regimen pictures, calendars, or stickers.
- Clinician education aids (e.g., medication guides, pictures, or calendars).

## Table 10. Goals of HIV Therapy and Tools To Achieve Them

| Goals of Therapy |
|---|
| • Maximal and durable suppression of viral load.<br>• Restoration or preservation of immunologic function.<br>• Improvement in quality of life.<br>• Reduction of HIV-related morbidity and mortality. |

| Tools To Achieve Goals of Therapy |
|---|
| • Maximize adherence to the antiretroviral regimen.<br>• Rational sequencing of drugs.<br>• Preservation of future treatment options.<br>• Use of drug-resistance testing in selected clinical settings. |

## Table 11. Advantages and Disadvantages of Class-Sparing Regimens Used in HIV-1 Therapy

| Regimen | Possible Advantages | Possible Disadvantages | Drug-Interaction Complications | Impact on Future Options |
|---|---|---|---|---|
| PI-based HAART regimen (NNRTI-sparing) | • Clinical, virologic, and immunologic efficacy well-documented<br>• Resistance requires multiple mutations<br>• Avoid NNRTI-associated side effects<br>• Targets HIV at two steps of viral replication (RT and PI) | • Some regimens are difficult to use and adhere to<br>• Long-term side effects often include lipodystrophy*, hyperlipidemia, and insulin resistance | • Mild to severe inhibition of cytochrome P450 pathway; ritonavir is most potent inhibitor, (but this effect can be exploited to boost levels of other PIs) | • Preserves NNRTIs for use in treatment failure<br>• Resistance primes for cross-resistance with other PIs |
| NNRTI-based HAART regimen (PI-sparing**)** | • Virologic, and immunologic efficacy well-documented<br>• Spares PI-related side effects<br>• Easier to use and adhere to, compared with PIs | • Resistance conferred by a single or limited number of mutations | • Fewer drug interactions compared with PIs | • Preserves PIs for use in treatment failure<br>• Resistance usually leads to cross-resistance across entire NNRTI class |
| Triple NRTI regimen (NNRTI- and PI-sparing) | • Generally easier to use and adhere to compared with PIs<br>• Sparing PI and NNRTI side effects<br>• Cross-resistance to all drugs in the NRTI class is unlikely with initial regimen failure | • Virological efficacy inferior to EFV-based regimen | • No cytochrome P450 interaction | • Preserves both PI and NNRTI classes for use in treatment failure |

* Some side effects being attributed to PI therapy, such as lipodystrophy, have not been proven to the strictly associated with the use of PI-containing regimens. Lipodystrophy has also been described among patients on NRTIs alone (especially stavudine) and in patients on no antiretroviral therapy.

## Table 12a. Antiretroviral Regimens Recommended for Treatment of HIV-1 Infection in Antiretroviral Naïve Patients

This table is a guide to treatment regimens for patients who have no previous experience with HIV therapy. Regimens should be individualized based on the advantages and disadvantages of each combination such as pill burden, dosing frequency, toxicities, and drug-drug interactions, and patient variables, such as pregnancy, co-morbid conditions, and level of plasma HIV-RNA. Clinicians should refer to Table 12b to review the pros and cons of different components of a regimen and to Tables 14–17 for adverse effects and dosages of individual antiretroviral agents. Preferred regimens are in bold type; these regimens have been selected by experts based on the totality of virologic, immunologic, and toxicity data. 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*", which can be found at http://www.aidsinfo.nih.gov/guidelines/.

| NNRTI-Based Regimens | | # of pills per day |
|---|---|---|
| **Preferred Regimens** | **efavirenz + lamivudine + (zidovudine or tenofovir DF or stavudine[*]) – except for pregnant women or women with pregnancy potential** | **3–5 pills/day** |
| Alternative Regimens | efavirenz + lamivudine + didanosine **-** except for pregnant women or women with pregnancy potential | 3–5 pills/day |
| | nevirapine + lamivudine + (zidovudine or stavudine or didanosine) | 4–6 pills/day |
| **PI-Based Regimens** | | **# of pills per day** |
| **Preferred Regimens** | **Kaletra® (lopinavir+ ritonavir) + lamivudine + (zidovudine or stavudine)** | **8–10 pills/day** |
| Alternative Regimens | amprenavir + ritonavir[†] + lamivudine + (zidovudine or stavudine) | 12–14 pills/day |
| | indinavir + lamivudine + (zidovudine or stavudine) | 8–10 pills/day |
| | indinavir + ritonavir[†] + lamivudine + (zidovudine or stavudine) | 8–12 pills/day |
| | nelfinavir[§] + lamivudine + (zidovudine or stavudine) | 6–14 pills/day |
| | saquinavir (sgc or hcg)[ϕ] + ritonavir[†] + lamivudine + (zidovudine or stavudine) | 14–16 pills/day |
| **Triple NRTI Regimen – As Alternative to PI- or NNRTI-based regimens** | | **# of pills per day** |
| Alternative Regimens | abacavir + lamivudine + zidovudine | 2 pills/day |
| | abacavir + lamivudine + stavudine | 4–6 pills/day |

* Preliminary 96-week data comparing stavudine + lamivudine vs tenofovir + lamivudine revealed higher incidence of lipodystrophy and lipid abnormalities in the stavudine group

† Low-dose (100–400 mg) ritonavir

§ Nelfinavir 625 mg tablet – soon to be available

ϕ sgc = soft gel capsule; hgc = hard gel capsule

**Table 12b: Two Pages**

## Table 12b. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy

| ARV Class | Antiretroviral Agent(s) | Advantages | Disadvantages |
|---|---|---|---|
| NNRTIs | | **NNRTI Class Advantages:**<br>• Less fat maldistribution and dyslipidemia than PI-based regimens<br>• Save PI options for future use | **NNRTI Class Disadvantages:**<br>• Resistance confered by a single mutation<br>• Cross-resistance among NNRTIs<br>• Skin rash<br>• Potential for CYP450 drug interactions |
| | Efavirenz | • Potent antiretroviral activity<br>• Low pill burden and frequency (1 tablet per day) | • Neuropsychiatric side effects<br>• Teratogenic in nonhuman primates, contraindicated in pregnancy and avoid use in women with pregnant potential |
| | Nevirapine | • More safety experience in pregnant women | • Higher incidence of rash than with other NNRTIs, including rare serious hypersensitivity reaction<br>• Higher incidence of hepatotoxicity than with other NNRTIs; including serious cases of hepatic necrosis |
| PIs | | **PI Class Advantage:**<br>• NNRTI options saved for future use<br>• Longest prospective study data including data on survival benefit | **PI Class Disadvantages:**<br>• Metabolic complications - fat maldistribution, dyslipidemia, insulin resistance<br>• CYP3A4 inhibitors & substrates – potential for drug interactions (esp. with ritonavir-based regimens) |
| | Lopinavir/ ritonavir | • Potent antiretroviral activity<br>• Co-formulated as Kaletra® | • Gastrointestinal intolerance<br>• Hyperlipidemia<br>• Little experience in pregnant women<br>• Food requirement |
| | Amprenavir/ ritonavir | • No food effect<br>• FDA-approved once-daily regimen | • Less extensive experience<br>• Frequent skin rash<br>• High pill burden and capsule size |
| | Indinavir | • Long-term virologic and immunologic efficacy experience | • 3-times-daily dosing and food restriction reduced adherence<br>• High fluid intake required (1.5–2 liters of fluid per day)<br>• Nephrolithiasis |
| | Indinavir/ ritonavir | • Low-dose ritonavir ↑ indinavir $T_{1/2}$ & Cmin allows for twice-daily instead of 3-times-daily dosing<br>• Eliminates food restriction of indinavir | • Possibly higher incidence of nephrolithiasis than with IDV alone<br>• High fluid intake required (1.5–2 liters of fluid per day) |
| | Nelfinavir | • More extensive experience in pregnant women than with other PIs | • Diarrhea<br>• Higher rate of virologic failure than with other PIs in comparative trials<br>• Food requirement |
| | Saquinavir (hgc or sgc) + ritonavir | • Low-dose ritonavir reduces saquinavir daily dose and frequency<br>- ↑ Cmax, Cmin, & $T_{1/2}$ | • Gastrointestinal intolerance (sgc worse than hgc) |

**Table 12b: Two Pages**

## Table 12b. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy

| ARV Class | Antiretroviral Agent(s) | Advantages | Disadvantages |
|---|---|---|---|
| **NRTIs** | | • Established backbone of combination antiretroviral therapy | • Rare but serious cases of lactic acidosis with hepatic steatosis reported with most NRTIs |
| **Triple NRTI regimen** | | • Abacavir + zidovudine + lamivudine - Co-formulated as Trizivir®<br>• Minimal drug-drug interactions<br>• Saves PI & NNRTI for future option | • Inferior virologic response when compared to efavirenz-based regimens<br>• Inferior virologic response when compared to indinavir in patients with baseline HIV-RNA > 100,000 copies/mL<br>• Potential for abacavir hypersensitivity reaction<br>• Potential for higher incidence of mitochondrial toxicity with stavudine than with other NRTIs |
| **Dual NRTIs backbone of three or more drug combination therapy** | Zidovudine + lamivudine | • Most extensive and favorable virological experience<br>• Co-formulated as Combivir® – ease of dosing<br>• No food effect<br>• Lamivudine – minimal side effects | Bone marrow suppression with zidovudine<br>Gastrointestinal intolerance |
| | Stavudine + lamivudine | • No food effect<br>• Once-daily dosing (when extended release stavudine formulation becomes available) | **Adverse effects associated with stavudine:**<br>• Peripheral neuropathy, lipoatrophy, hyperlactatemia and lactic acidosis, reports of progressive ascending motor weakness, potential for hyperlipidemia |
| | Tenofovir + lamivudine | • Good virologic response when used with efavirenz<br>• Well tolerated<br>• Once-daily dosing | • Data lacking for tenofovir use in patients with renal insufficiency<br>• Tenofovir – reports of renal impairment<br>• Tenofovir – food requirement |
| | Didanosine + lamivudine | • Once-daily dosing | • Peripheral neuropathy, pancreatitis – associated with didanosine<br>• Food effect – needs to be taken on an empty stomach |

## Table 13. Antiretroviral Regimens or Components That Should Not Be Offered At Any Time

| | Rationale | Exception |
|---|---|---|
| **Antiretroviral Regimens Not Recommended** | | |
| Monotherapy | • Rapid development of resistance<br>• Inferior antiretroviral activity when compared to combination with three or more antiretrovirals | • Pregnant women with HIV-RNA <1,000 copies/mL using zidovudine monotherapy for prevention of perinatal HIV transmission* |
| Two-agents drug combinations | • Rapid development of resistance<br>• Inferior antiretroviral activity when compared to combination with three or more antiretrovirals | • For patients currently on this treatment, it is reasonable to continue if virologic goals are achieved |
| **Antiretroviral Components Not Recommended As Part of Antiretroviral Regimen** | | |
| Saquinavir hard gel capsule (Invirase®) as single protease inhibitor | • Poor oral bioavailability (4%)<br>• Inferior antiretroviral activity when compared to other protease inhibitors | • No exception |
| d4T + ddI in pregnancy | • 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* |
| Efavirenz in pregnancy | • Teratogenic in nonhuman primate | • When no other antiretroviral options are available and potential benefits outweigh the risks* |
| Amprenavir oral solution in:<br>• pregnant women;<br>• children <4 yr old;<br>• patients with renal or hepatic failure; and<br>• patients treated with metronidazole or disulfiram | • Oral liquid contains large amount of the excipient propylene glycol, which may be toxic in the patients at risk | • No exception |
| d4T + ZDV | • Antagonistic | • No exception |
| ddC + d4T | • Additive peripheral neuropathy | • No exception |
| ddC + ddI | • Additive peripheral neuropathy | • No exception |
| Hydroxyurea | • ↓ CD4 count<br>• ↑ ddI-associated side effects – such as pancreatitis & peripheral neuropathy<br>• Inconsistent evidence of improved viral suppression<br>• Contraindicated in pregnancy (Pregnancy Category D) | • 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 14: Two Pages**

## Table 14. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

| Generic Name/Trade Name | Form | Dosing Recommendations | Food Effect | Oral Bio-availability | Serum half-life | Intracellular half-life | Elimination | Adverse Events |
|---|---|---|---|---|---|---|---|---|
| **Abacavir (ABC) Ziagen®** | 300 mg tablets or 10 mg/mL oral solution | 300 mg two times/day or with ZDV and 3TC as Trizivir‡, 1 dose two times/day | Take without regard to meals; Alcohol increases abacavir levels 41%; has no effect on alcohol | 83% | 1.5 hours | 3.3 hours | Metabolized by alcohol dehydrogenase and glucuronyl transferase. Renal excretion of metabolites 82% | 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®, Videx EC®** | 25, 50, 100, 150, 200 mg* chewable/ dispersible buffered tablets; 100, 167, 250 mg buffered powder for oral solution; 125, 200, 250, or 400 mg enteric coated capsules | Body weight >60kg: 200 mg two times/day (buffered tablets), 250 mg two times/day (buffered tablets), or 400 mg daily§ (buffered tablets), or enteric coated capsules. | Levels decrease 55%; Take 1/2 hour before or 2 hours after meal | 30–40% | 1.6 hours | 25–40 hours | Renal excretion 50% | Pancreatitis¶; peripheral neuropathy; nausea; diarrhea Lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity associated with using of NRTIs.# |
| **Lamivudine (3TC) Epivir®** | 150 mg and 300mg tablets or 10 mg/mL oral solution | 150 mg two times/day; or 300 mg daily With ZDV as Combivir†, or with ZDV and abacavir as Trizivir‡, 1 dose two times/day | Take without regard to meals | 86% | 3–6 hours | 12 hours | Renal excretion | Minimal toxicity; lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with using of NRTIs. |
| **Stavudine (d4T) Zerit** | 15, 20, 30, 40 mg capsules or 1mg/mL for oral solution (100mg extended release capsule - FDA approved, not yet in market) | Body weight >60kg: 40 mg two times/day; Body weight <60kg: 30 mg two times/day | Take without regard to meals | 86% | 1.0 hour | 3.5 hours | Renal excretion 50% | • Peripheral neuropathy; • Lipodystrophy • Rapidly progressive ascending neuromuscular weakness (rare) • Pancreatitis¶ • Lactic acidosis with hepatic steatosis# has been reported with stavudine |

† Each Combivir tablet contains 300 mg zidovudine and 150 mg lamivudine.
‡ Each Trizivir tablet contains 300 mg zidovudine, 150 mg lamivudine, and 300 mg abacavir.
* 200 mg tablet for once-daily dosing only. Twice-daily dosing is preferred; however, once-daily dosing might be appropriate for patients who require a simplified dosing schedule.
§ Twice-daily dosing is preferred; however, once daily dosing might be appropriate for patients who require a simplified dosing schedule.
¶ Cases of fatal and nonfatal pancreatitis have occurred among treatment-naïve and treatment-experienced patients during therapy with didanosine alone or in combination with other drugs, such as stavudine, or stavudine plus hydroxyurea, or ribavirin.
# Pregnant women might be at increased risk for lactic acidosis and liver damage when treated with the combination of stavudine and didanosine. This combination should be used for pregnant women only when the potential benefit outweighs the potential risk.
** Patients who experience signs or symptoms of hypersensitivity, which may include fever, rash, fatigue, nausea, vomiting, diarrhea, and abdominal pain, should discontinue abacavir as soon as a hypersensitivity reaction is suspected. Abacavir should not be restarted because more severe symptoms may recur within hours and may include life-threatening hypotension and death. Cases of abacavir hypersensitivity syndrome should be reported to the Abacavir Hypersensitivity Registry at 1-800-270-0425.

**Table 14: Two Pages**

## Table 14. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

| Generic Name/Trade Name | Form | Dosing Recommendations | Food Effect | Oral Bio-availability | Serum half-life | Intracellular half-life | Elimination | Adverse Events |
|---|---|---|---|---|---|---|---|---|
| **Tenofovir Disoproxil Fumarate**<br>**Viread®** | 300 mg tablet | 300 mg daily for patients with creatinine clearance ≥ 60 mL/min;<br>Not recommended for patients with creatinine clearance <60 mL/min | Increased bio-availability when taken with food | 25% in fasting state; 39% with high-fat meal | 17 hours | 10–50 hours | Primarily renally excreted by glomerular filtration and active tubular secretion | Asthenia, headache, diarrhea, nausea, vomiting, and flatulence; lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with using of NRTIs); rare reports of renal insufficiency. |
| **Zalcitabine**<br>**(ddC)**<br>**Hivid®** | 0.375, 0.75 mg tablets | 0.75 mg three times/day | Take without regard to meals | 85% | 1.2 hours | 3 hours | Renal excretion 70% | • Peripheral neuropathy;<br>• Stomatitis;<br>• Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity with using of NRTIs); pancreatitis |
| **Zidovudine**<br>**(AZT, ZDV)**<br>**Retrovir®** | 100 mg capsules, 300 mg tablets, 10 mg/mL intravenous solution, 10 mg/mL oral solution | 300 mg two times/day or 200 mg three times/ day with<br>lamivudine as Combivir†, 1 dose two times/day<br>or, with abacavir and lamivudine as Trizivir‡, 1 dose two times/day | Take without regard to meals | 60% | 1.1 hours | 3 hours | Metabolized to AZT glucuronide (GAZT).<br>Renal excretion of GAZT | • Bone marrow suppression: anemia or neutropenia;<br>• Subjective complaints: gastrointestinal intolerance, headache, insomnia, asthenia;<br>• Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity associated with using NRTIs. |

† Each Combivir tablet contains 300 mg zidovudine and 150 mg lamivudine.

‡ Each Trizivir tablet contains 300 mg zidovudine, 150 mg lamivudine, and 300 mg abacavir.

* For once-daily dosing only. Twice-daily dosing is preferred; however, once-daily dosing might be appropriate for patients who require a simplified dosing schedule.

§ Twice-daily dosing is preferred; however, once-daily dosing might be appropriate for patients who require a simplified dosing schedule.

¶ Cases of fatal and nonfatal pancreatitis have occurred among treatment-naïve and treatment-experienced patients during therapy with didanosine alone or in combination with other drugs, including stavudine, or stavudine plus hydroxyurea, or ribavirin.

# Pregnant women might be at increased risk for lactic acidosis and liver damage when treated with the combination of stavudine and didanosine. This combination should be used for pregnant women only when the potential benefit outweighs the potential risk.

** Patients who experience signs or symptoms of hypersensitivity, which may include fever, rash, fatigue, nausea, vomiting, diarrhea, and abdominal pain, should discontinue abacavir as soon as a hypersensitivity reaction is suspected. Abacavir should not be restarted because more severe symptoms will recur within hours and may include life-threatening hypotension and death. Cases of abacavir hypersensitivity syndrome should be reported to the Abacavir Hypersensitivity Registry at 1-800-270-0425.

## Table 15. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

| Generic Name/ Trade Name | Form | Dosing Recommendations | Food Effect | Oral Bio-availability | Serum half-life | Elimination | Adverse Events |
|---|---|---|---|---|---|---|---|
| **Delavirdine/ Rescriptor®** | 100 mg tablets or<br><br>200 mg tablets | 400 mg by mouth 3 times/day; 4 100 mg tablets can be dispersed in ≥3 oz. of water to produce slurry; 200 mg tablets should be taken as intact tablets; separate buffered preparations dosing with didanosine or 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*;<br>• Increased transaminase levels;<br>• Headaches |
| **Efavirenz/ Sustiva®** | 50, 100, 200 mg capsules or 600 mg tablets | 600 mg by mouth daily on an empty stomach, preferably at 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); 14%–34% excreted in urine (glucuronidated metabolites, <1% unchanged); 16%–61% in feces. | • Rash*;<br>• Central nervous system symptoms;†<br>• Increased transaminase levels;<br>• False-positive cannabinoid test;<br>• Teratogenic in monkeys‡ |
| **Nevirapine/ Viramune®** | 200 mg tablets or<br><br>50 mg/5 mL oral suspension | 200 mg by mouth daily for 14 days; thereafter, 200 mg 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*<br>• Hepatitis, including hepatic necrosis, have been reported |

**NOTE:** For information regarding drug interactions, see Tables 19-22.

* 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.

‡ Data are unavailable regarding teratogenicity of other NNRTIs among nonhuman primates.

**Table 16: Two Pages**

# Table 16. Characteristics of Protease Inhibitors (PIs)

| Generic Name/ Trade Name | Form | Dosing Recommendations | Food Effect | Oral Bio-availability | Serum half-life | Route of Metabolism | Storage | Adverse Events |
|---|---|---|---|---|---|---|---|---|
| **Amprenavir /Agenerase®** | 50 mg, 150 mg capsules<br>15 mg/mL oral solution (capsules and solution NOT inter-changeable on mg per mg basis) | Body weight >50 kg: 1200 mg two times/day (capsules)<br>or, 1400 mg two times/day (oral solution)<br>Body weight < 50 kg: 20mg/kg two times/day (capsules) maximum 2400 mg daily total; 1.5mL/kg two times/day (oral solution) maximum 2800 mg daily total; with ritonavir: amprenavir 600 mg plus ritonavir 100 mg, two times/day or amprenavir 1,200 mg plus ritonavir 200 mg one time/day | High-fat meal decreases blood concentration curve 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 (less than ritonavir; similar to indinavir, nelfinavir) | Room temperature | • GI intolerance, nausea, vomiting, diarrhea<br>• Rash<br>• Oral paresthesias<br>• Transaminase elevation<br>• Hyperglycemia†<br>• Fat redistribution and lipid abnormalities ‡<br>• Possible increased bleeding episodes in patients with hemophilia<br>• Oral solution contains propylene glycol; contraindicated in pregnant women and children <4 years old, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole |
| **Indinavir/ Crixivan®** | 200, 333, 400 mg capsules | 800 mg every 8 hours;<br>(see Table 21 for dosing recommendation with ritonavir) | Levels decrease 77%<br>Take 1 hour before or 2 hours after meals; may take with skim milk or low-fat meal | 65% | 1.5–2 hours | P450 cytochrome 3A4 inhibitor (less than ritonavir) | Room temperature | • Nephrolithiasis<br>• GI intolerance, nausea<br>• Lab: Increased indirect bilirubinemia (inconsequential)<br>• Misc.: Headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, alopecia, and hemolytic anemia<br>• Hyperglycemia†<br>• Fat redistribution and lipid abnormalities‡<br>• Possible increased bleeding episodes in patients with hemophilia |
| **Lopinavir + Ritonavir/ Kaletra®** | Each capsule contains lopinavir 133.3mg+ ritonavir 33.3 mg<br>Oral solution: Each mL contains lopinavir 80 mg+ ritonavir 20 mg | 400 mg lopinavir +<br>100 mg ritonavir (3 capsules) two times/day | Moderate fat meal increases AUC of capsules and solution by 48% and 80%, respectively. Take with food. | Not determined in humans | 5–6 hours | Cytochrome P450 ( 3A4 inhibitor) | Refrigerated capsules are stable until date on label expires; if stored at room teampearture stable for 2 months | • GI intolerance, nausea, vomiting, diarrhea<br>• Asthenia<br>• Elevated transaminase enzymes<br>• Hyperglycemia†<br>• Fat redistribution and lipid abnormalities‡<br>• Possible increased bleeding episodes in patients with hemophilia<br>• Oral solution continues 42% alcohol |
| **Nelfinavir/ Viracept®** | 250 mg tablets<br>625 mg tablets - FDA approved, not yet in market<br>50 mg/g oral powder | 750 mg three times/day<br>or 1,250 mg two times/day | Levels increase 2-3 fold<br>Take with meal or snack | 20–80% | 3.5–5 hours | Cytochrome P450 (3A4 inhibitor; less than ritonavir) | Room temperature | • Diarrhea<br>• Hyperglycemia†<br>• Fat redistribution and lipid abnormalities‡<br>• Possible increased bleeding episodes among patients with hemophilia<br>• Transaminase elevation |

Table 16: Two Pages

## Table 16. Characteristics of Protease Inhibitors (PIs)

| Generic Name/ Trade Name | Form | Dosing Recommendations | Food Effect | Oral Bio-availability | Serum half-life | Route of Metabolism | Storage | Adverse Events |
|---|---|---|---|---|---|---|---|---|
| **Ritonavir/ Norvir®** | 100 mg capsules<br>600 mg/7.5 mL solution | 600 mg every 12 hours* (when ritonavir is used as sole PI)<br>See Table 21 for alternative dosing suggestions when ritonavir is used as a pharmacokinetic enhancer for other PIs<br>Separate dosing with didanosine by 2 hours | Levels increase 15%<br>Take with food if possible; this may improve tolerability | Not determined | 3–5 hours | Cytochrome P450 (3A4 > 2D6;<br>Potent 3A4 inhibitor) | Refrigerate capsules<br>Capsules can be left at room temperature for ≤30 days; Oral solution should NOT be refrigerated | •GI intolerance, nausea, vomiting, diarrhea<br>•Paresthesias – circumoral and extremities<br>•Hepatitis<br>•Pancreatitis<br>•Asthenia<br>•Taste perversion<br>•Lab.: Triglycerides increase > 200%, transaminase elevation, elevated CPK and uric acid<br>•Hyperglycemia†<br>•Fat redistribution and lipid abnormalities‡<br>•Possible increased bleeding episodes in patients with hemophilia |
| **Saquinavir hard gel capsule/ Invirase®** | 200 mg capsules | Invirase is not recommended to be used as sole PI<br>With Ritonavir: ritonavir 400 mg + Invirase 400 mg two times/day<br>(see Table 21 for alternative dosing suggestions when used with low dose ritonavir) | No food effect when taken with ritonavir | 4% erratic | 1–2 hours | Cytochrome P450 (3A4 inhibitor (less than ritonavir) | Room temperature | • GI intolerance, nausea and diarrhea<br>• Headache<br>• Elevated transaminase enzymes<br>• Hyperglycemia †<br>• Fat redistribution and lipid abnormalities ‡<br>• Possible increased bleeding episodes in patients with hemophilia |
| **Saquinavir soft gel capsule/ Fortovase®** | 200 mg capsules | 1,200 mg three times/day§<br>(see Table 21 for alternative dosing suggestions when used with low dose ritonavir) | Levels increase 6-fold. Take with large meal | (not determined) | 1–2 hours | Cytochrome P450 (3A4 inhibitor (less than ritonavir) | Refrigerate or store at room temperature (up to 3 months) | •GI intolerance, nausea, diarrhea, abdominal pain and dyspepsia<br>•Headache<br>•Elevated transaminase enzymes<br>•Hyperglycemia †<br>•Fat redistribution and lipid abnormalities ‡<br>•Possible increased bleeding episodes in patients with hemophilia |

**NOTE:** For information regarding drug interactions, see Tables 19-22.

† Cases of worsening glycemic control among patients with preexisting diabetes, and cases of new-onset diabetes, including diabetic ketoacidosis, have been reported with the use of all protease inhibitors.

‡ Fat redistribution and lipid abnormalities have been recognized increasingly with the use of protease inhibitors. Patients with hypertriglyceridemia or hypercholesterolemia should be evaluated for risk for cardiovascular events and pancreatitis. Interventions can include dietary modification, lipid-lowering agents, or discontinuation of PIs.

* Dose escalation for Ritonavir: Days 1 and 2: 300 mg two times; day 3-5: 400 mg two times; day 6-13: 500 mg two times; day 14: 600 mg two times/day.

# Table 17. Characteristics of Fusion Inhibitor

| Generic Name/ Trade Name | Form | Dosing Recommendations | Oral Bio-availability | Serum half-life | Route of Metabolism | Storage | Adverse Events |
|---|---|---|---|---|---|---|---|
| **Enfuvirtide/** Fuzeon | • Injectable – in lyophilized powder<br>• 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 90 mg/1 mL | 90 mg (1mL) subcutaneously two times/day | 84.3% (compared to 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<br>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 (pain, erythema, induration, nodules and cysts, pruritus, ecchymosis)<br>• Increased rate of bacterial pneumonia<br>• Hypersensitivity reaction (<1%) - symptoms may include rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases; may recur on rechallenge |

**Table 18: Two Pages**

## Table 18: 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 (see Tables 14-22 for more extensive lists of adverse effects associated with antiretroviral drugs or for drug interactions).

| Antiretroviral Drug | Pertinent Black Box Warning Information |
|---|---|
| Abacavir (Ziagen® or as combination product with zidovudine and lamivudine as Trizivir®) | • Fatal hypersensitivity reactions reported:<br>– Signs or symptoms include fever, skin rash, fatigue, gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea, or abdominal pain), and respiratory symptoms (e.g., pharyngitis, dyspnea, or cough).<br>– Abacavir should be discontinued as soon as hypersensitivity reaction is suspected.<br>– Abacavir **SHOULD NOT** be restarted.<br>– If restarted, more severe symptoms will recur within hours and might include life-threatening hypotension and death.<br>• 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:<br>– children age <4 years<br>– pregnant women<br>– patients with renal or hepatic failure<br>– patients treated with disulfiram or metronidazole<br>• Oral solution should be used only when Agenerase capsules or other protease inhibitors cannot be used. |
| Delavirdine (Rescriptor®) | No box warning. |
| Didanosine (Videx® or Videx-EC®) | • Fatal and nonfatal pancreatitis have occurred with didanosine alone or in combination with other antiretroviral agents.<br>– Didanosine should be withheld if pancreatitis is suspected.<br>– Didanosine should be discontinued if pancreatitis is confirmed.<br>• Fatal lactic acidosis has been reported among pregnant women who received a combination of didanosine and stavudine with other antiretroviral combinations.<br>– Didanosine and stavudine combination should only be used during pregnancy if the potential benefit clearly outweighs the potential risks.<br>• 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®) | No box warning. |
| Enfuvirtide (Fuzeon) | No box warning. |
| Indinavir (Crixivan®) | No box warning. |
| Lamivudine (Epivir®), or as combination product in Combivir® 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.<br>• 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.** |
| Lopinavir/ritonavir (Kaletra®) | No box warning. |

**Table 18: Two Pages**

| Anti-Retroviral Drug | Pertinent Black Box Warning Information |
|---|---|
| Nelfinavir (Viracept®) | No box warning. |
| Nevirapine (Viramune®) | • Severe, life-threatening hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure; patients should be advised to seek medical evaluation immediately if signs and symptoms of hepatitis occur.<br>• 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.<br>• Patients should be monitored intensively during the first 12–16 weeks of nevirapine therapy to detect potentially life-threatening hepatotoxicity or skin reactions.<br>• A 14-day lead-in period with nevirapine 200 mg daily must be followed strictly.<br>• Nevirapine should not be restarted after severe hepatic, skin, or hypersensitivity reactions. |
| Ritonavir (Norvir®) | • Co-administration of ritonavir with certain nonsedating antihistamines, sedative hypnotics, antiarrhythmics, or ergot alkaloids may result in potentially serious or life-threatening adverse events due to possible effects of ritonavir on hepatic metabolism of certain drugs. |
| Saquinavir (Fortovase®, Invirase®) | No box warning. |
| 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.<br>• Fatal lactic acidosis has been reported among pregnant women who received combination of stavudine and didanosine with other antiretroviral combinations.<br>– Stavudine and didanosine combination should only be used during pregnancy if the potential benefit clearly outweighs the potential risks.<br>• Fatal and non-fatal pancreatitis have occurred when stavudine was part of a combination regimen with didanosine with or without hydroxyurea. |
| Tenofovir (Viread®) | • 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. |
| Zalcitabine (Hivid®) | • Zalcitabine can cause severe peripheral neuropathy, use with caution among patients with pre-existing neuropathy.<br>• It rare cases, zalcitabine can cause pancreatitis, therapy should be withheld until pancreatitis is excluded.<br>• Rare cases of hepatic failure and death have been reported among patients with underlying hepatitis B infection.<br>• 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 as combination products in Combivir® and Trizivir® | • Zidovudine can be associated with hematologic toxicities, including granulocytopenia and severe anemia, including among advanced HIV patients.<br>• Prolonged zidovudine use has been associated with symptomatic myopathy.<br>• 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 19. 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[∂] | Neuroleptic | Psychotropic | Ergot Alkaloids (vasoconstrictor) | Herbs |
|---|---|---|---|---|---|---|---|---|---|---|
| **Protease Inhibitors** | | | | | | | | | | |
| **Indinavir** | (none) | (none) | simvastatin lovastatin | rifampin rifapentine | astemizole terfenadine | cisapride | pimozide | midazolam[Σ] triazolam | dihydroergotamine (D.H.E. 45) ergotamine[†] (various forms) | 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) | St. John's wort |
| **Saquinavir** | (none) | (none) | simvastatin lovastatin | rifampin[Δ] rifabutin[Δ] rifapentine | astemizole terfenadine | cisapride | pimozide | midazolam [Σ] triazolam | dihydroergotamine (D.H.E. 45) ergotamine[†] (various forms) | St. John's wort |
| **Nelfinavir** | (none) | (none) | simvastatin lovastatin | rifampin rifapentine | astemizole terfenadine | cisapride | pimozide | midazolam[Σ] triazolam | dihydroergotamine (D.H.E. 45) ergotamine[†] (various forms) | St. John's wort |
| **Amprenavir[*]** | bepridil | (none) | simvastatin lovastatin | rifampin rifapentine | astemizole terfenadine | cisapride | pimozide | midazolam[Σ] triazolam | dihydroergotamine (D.H.E. 45) ergotamine[†] (various forms) | St. John's wort |
| **Lopinavir + Ritonavir** | (none) | flecainide propafenone | simvastatin lovastatin | rifampin[∫] rifapentine | astemizole terfenadine | cisapride | pimozide | midazolam[Σ] triazolam | dihydroergotamine (D.H.E. 45) ergotamine[†] (various forms) | St. John's wort |
| **Nonnucleoside reverse transcriptase inhibitors** | | | | | | | | | | |
| **Nevirapine** | (none) | (none) | (none) | rifapentine[‡] | (none) | (none) | (none) | (none) | (none) | – |
| **Delavirdine** | (none) | (none) | simvastatin lovastatin | rifampin rifapentine[‡] rifabutin | astemizole terfenadine | cisapride H-2 blockers Proton pump inhibitors | (none) | alprazolam midazolam[Σ] triazolam | dihydroergotamine (D.H.E. 45) ergotamine[†] (various forms) | – |
| **Efavirenz** | (none) | (none) | (none) | rifapentine[‡] | astemizole terfenadine | cisapride | (none) | midazolam[Σ] triazolam | dihydroergotamine (D.H.E. 45) ergotamine[†] (various forms) | – |

\# 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 being treated with rifapentine have a higher rate of TB relapse than those treated with other rifamycin-based regimens; an alternative agent is recommended for this population.

Δ Rifampin and rifabutin are contraindicated unless saquinavir is combined with ritonavir.

∫ In one small study, higher boosting doses of RTV offset rifampin-inducing activity of LPV. Further studies are needed.

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

† This is likely a class effect.

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

* Each 150 mg amprenavir Agenerase® capsule has 109 IU (International Units) of Vitamin E and 1 milliliter of Amprenavir oral solution has 46 IU of vitamin E. At FDA approved doses, the daily amount of vitamin E in Agenerase is 58-fold increase over the federal government reference daily intake for adults. Patients should be cautioned to avoid supplemental doses of vitamin E. Multivitamin products containing minimal amounts of vitamin E are likely acceptable.

***Suggested Alternatives***

***Simvastatin, lovastatin:*** pravastatin and fluvastatin have the least potential for drug-drug interactions; atorvastatin should be used with caution.

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

***Astemizole, terfenadine:*** desloratadine, loratadine, fexofenadine, cetirizine

***Midazolam, triazolam:*** temazepam, lorazepam

**Table 20: Four Pages**

# Table 20. Drug Interactions Between Antiretrovirals and Other Drugs: PIs, NNRTIs, and NRTIs

| Drug Interactions Requiring Dose Modifications or Cautious Use | | | |
|---|---|---|---|
| **Drugs Affected** | **Indinavir (IDV)** | **Ritonavir (RTV)** | **Saquinavir† (SQV)** |
| **ANTIFUNGALS** | | | |
| **Ketoconazole** | Levels: IDV ↑ 68%.<br>Dose: IDV 600 mg tid. | Levels: ketoconazole ↑ 3X.<br>Dose: Use with caution; do not exceed 200 mg ketoconazole daily. | Levels: SQV ↑ 3X.<br>Dose: If ketoconazole dose is >200 mg/day, monitor for excessive diarrhea, nausea, abdominal discomfort and adjust doses accordingly. |
| **Voriconazole** | Levels: No significant changes in AUC of azole or IDV (healthy subjects). Dose: Standard | No data, but potential for bi-directional inhibition between voriconazole and PIs, monitor for toxicities | No data, but potential for bi-directional inhibition between voriconazole and PIs, monitor for toxicities |
| **ANTI-MYCOBACTERIALS** | | | |
| **Rifampin**Σ | Levels: IDV ↓ 89%.<br>Contraindicated. | Levels: RTV ↓ 35%.<br>Dose: No Data.<br>Increased liver toxicity possible. | Levels: SQV ↓ 84%.<br>Contraindicated, unless using RTV+SQV, then use rifampin 600 mg qd or 3x/week. |
| **Rifabutin** | Levels: IDV ↓ 32%. Rifabutin ↑ 2X.<br>Dose: ↓ rifabutin to 150 mg qd or 300 mg 3x/week. IDV 1000 mg tid. | Levels: Rifabutin ↑ 4X.<br>Dose: ↓ rifabutin to 150 mg qod. or dose 3x per week.<br>RTV: Standard. | Levels: SQV ↓ 40%.<br>No rifampin dose adjustment unless using RTV+SQV, then use rifabutin 150 mg 3x/week. |
| **Clarithromycin** | Levels: Clarithromycin ↑ 53%.<br>No dose adjustment. | Levels: Clarithromycin ↑ 77%.<br>Dose: Adjust for moderate and severe renal impairment. | Levels: Clarithromycin ↑ 45%.<br>SQV ↑ 177%.<br>No dose adjustment. |
| **ORAL CONTRACEPTIVES** | Levels: Norethindrone ↑ 26%.<br>Ethinylestradiol ↑ 24%.<br>No dose adjustment. | Levels: Ethinyl estradiol ↓ 40%.<br>Use alternative or additional method. | No data. |
| **LIPID–LOWERING AGENTS** | | | |
| **Simvastatin**<br>**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. |
| **Atorvastatin** | Levels: potential for increase in AUC<br>Use with caution. | Levels: 450% ↑ when administered with SQV/RTV combination. Use with extreme caution. | Levels: 450% ↑ when administered with SQV/RTV combination. Use with extreme caution. |
| **Pravastatin** | No Data | Levels: 50% ↓ when administered with SQV/RTV combination. No dose adjustment needed. | Levels: 50% ↓ when administered with SQV/RTV combination. No dose adjustment needed. |
| **ANTICONVULSANTS** | | | |
| **Carbamazepine**<br>**Phenobarbitol**<br>**Phenytoin** | Carbamazepine markedly ↓ IDV AUC. Consider alternative agent. | Carbamazepine: ↑ serum levels when co-administered with RTV.<br>Use with caution.<br>Monitor anticonvulsant levels. | Unknown, but may markedly ↓ SQV levels.<br>Monitor anticonvulsant levels. |
| **METHADONE** | No change in methadone levels. | Methadone ↓ 37%. Monitor and titrate dose if needed.<br>May require ↑ methadone dose. | No data. |
| **MISCELLANEOUS** | Grapefruit juice ↓ IDV levels by 26%. Sildenafil AUC ↑ 3 fold. Use cautiously. Start with reduced dose of 25 mg every 48 hours and monitor for adverse effects. | Many possible interactions<br>Desipramine ↑ 145%, reduce dose.<br>Theophylline ↓ 47%, monitor theophylline levels. Sildenafil AUC ↑ 11 fold. Use cautiously. Start with reduced dose of 25 mg every 48 hours and monitor for adverse effects. | Grapefruit juice ↑ SQV levels.<br>Dexamethasone ↓ SQV levels.<br>Sildenafil AUC ↑ 2 fold. Use a 25 mg starting dose of sildenafil. |

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

† Some drug interaction studies were conducted with Invirase®. May not necessarily apply to use with Fortovase.

Σ There are limited data on RTV-SQV and RTV-LPV demonstrating that RTV compensates for rifampin induction. In one small study, higher boosting doses or ritonavir (up to 400 mg per dose) were needed to fully offset rifampin-inducing activity of LPV. Whether RTV can be used to offset rifampin induction of all other protease inhibitors, or whether this therapeutic maneuver is more broadly applicable, requires further study.

**Table 20: Four Pages**

## Table 20. Drug Interactions Between Antiretrovirals and Other Drugs: PIs, NNRTIs, and NRTIs

| Drug Interactions Requiring Dose Modifications or Cautious Use | | | |
|---|---|---|---|
| **Drugs Affected** | **Nelfinavir (NFV)** | **Amprenavir (APV)** | **Lopinavir(LPV)** |
| **ANTIFUNGALS** | | | |
| **Ketoconazole** | No dose adjustment necessary. | Levels: APV ↑ 31%<br>Keto ↑ 44%.<br>Dose: Standard | Levels: LPV AUC ↓ 13%.<br>Keto ↑ 3-fold.<br>Dose: Use with caution; do not exceed 200 mg ketoconazole daily |
| **Voriconazole** | No data, but potential for bi-directional inhibition between voriconazole and PIs, monitor for toxicities | No data, but potential for bi-directional inhibition between voriconazole and PIs, monitor for toxicities | No data, but potential for bi-directional inhibition between voriconazole and PIs, monitor for toxicities |
| **ANTI-MYCOBACTERIALS** | | | |
| **Rifampin**[Σ] | Levels: NFV ↓ 82%.<br>Should not be coadministered. | Levels: APV AUC ↓ 82%<br>No change in rifampin AUC.<br>Should not be coadministered. | Levels: LPV AUC ↓ 75%.<br>Dose[Σ]: May consider adding 300 mg RTV bid to regimen or ↑ LPV/r to 800/200 mg bid; Rifampin dose standard<br>Increased liver toxicity possible |
| **Rifabutin** | Levels: NFV ↓32%.<br>Rifabutin ↑ 2X.<br>Dose: ↓ rifabutin to 150 mg qd or 300 mg 3x/week.<br>↑ NFV dose to 1000 mg tid. | Levels: APV AUC ↓ 15%.<br>Rifabutin ↑ 193%.<br>Dose: No change in APV dose;<br>Decrease rifabutin to 150 mg qd or 300 mg 3x/week. | Levels: Rifabutin AUC ↑ 3-fold.<br>25-O-desacetyl metabolite ↑ 47.5-fold.<br>Dose: Decrease rifabutin dose to 150 mg qod; LPV/r: Standard. |
| **Clarithromycin** | No data. | Levels: APV AUC ↑ 18%. No change in clarithromycin AUC. No dose adjustment. | Levels: ↑ Clarithromycin AUC 77%.<br>Dose: Adjust for moderate and severe renal impairment. |
| **ORAL CONTRACEPTIVES** | Levels: Norethindrone ↓ 18%.<br>Ethinyl estradiol ↓ 47%.<br>Use alternative or additional method. | Levels: Potential for metabolic interactions; use alternative or additional method. | Levels: ethinyl estradiol ↓ 42%.<br>Use alternative or additional method. |
| **LIPID–LOWERING AGENTS** | | | |
| **Simvastatin**<br>**Lovastatin** | Avoid concomitant use. Simvistatin AUC ↑ 505%—not recommended. Potential for large increase in Lovastatin AUC—not recommended. | Levels: Potential for large increase in statin levels. Avoid concomitant use. | Levels: Potential for large increase in statin levels.<br>Avoid concomitant use. |
| **Atorvastatin** | Atorvastatin AUC ↑ 74%–use with caution and monitor. | Atorvastatin levels have potential for large increase. Use with caution and monitor. | Atorvastatin AUC ↑ 5.88-fold. Use with caution and monitoring. |
| **Pravastatin** | No data. | No data. | Pravastatin AUC ↑ 33%; no dosage adjustment necessary |
| **ANTICONVULSANTS** | | | |
| **Carbamazepine**<br>**Phenobarbitol**<br>**Phenytoin** | Unknown, but may decrease NFV levels substantially. Monitor anticonvulsant levels. | Unknown, but may decrease APV levels substantially. Monitor anticonvulsant levels. | Many possible interactions:<br>carbamazepine: ↑ levels when co-administered with RTV. Use with caution. Monitor anticonvulsant levels.<br>Phenytoin: ↓ levels of LPV, RTV, and ↓ levels of phenytoin when administered together. Avoid concomitant use. |
| **METHADONE** | NFV may decrease methadone levels, but minimal effect on maintenance dose. Monitor and titrate dose if needed. May require ↑ methadone dose. | No data. | Methadone AUC ↓ 53%.<br>Monitor and titrate dose if needed.<br>May require ↑ methadone dose. |
| **SILDENAFIL** | Sildenafil AUC ↑ 2-11 fold. Use cautiously. Start with reduced dose of 25 mg every 48 hours and monitor for adverse effects. | Sildenafil AUC ↑ 2-11 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. Use cautiously. Start with reduced dose of 25 mg every 48 hours and monitor for adverse effects. |

[Σ] There are limited data on RTV-SQV and RTV-LPV demonstrating that RTV compensates for rifampin induction. In one small study, higher boosting doses or ritonavir (up to 400 mg per dose) were needed to fully offset rifampin-inducing activity of LPV. Whether RTV can be used to offset rifampin induction of all other protease inhibitors, or whether this therapeutic maneuver is more broadly applicable, requires further study.

**Table 20: Four Pages**

## Table 20. Drug Interactions Between Antiretrovirals and Other Drugs: PIs, NNRTIs, and NRTIs

| Drug Interactions Requiring Dose Modifications or Cautious Use | | | |
|---|---|---|---|
| **Drugs Affected** | **Nevirapine (NVP)** | **Delavirdine (DLV)** | **Efavirenz (EFV)** |
| **ANTIFUNGALS** | | | |
| **Ketoconazole** | Levels: Keto. ↓ 63%. NVP ↑ 15-30%. Dose: Not recommended. | No data. | No data. |
| **Voriconazole** | No data. | No data. | No data. |
| **ANTI-MYCOBACTERIALS** | | | |
| **Rifampin** | Levels: NVP ↓ 37%. Not recommended. | Levels: DLV ↓ 96%. Contraindicated. | Levels: EFV ↓ 25%. Dose: Consider ↑ EFV to 800 mg qd. |
| **Rifabutin** | Levels: NVP ↓ 16%. No dose adjustment.* | Levels: DLV ↓ 80%. Rifabutin ↑ 100%. Not recommended. | Levels: EFV unchanged; Rifabutin ↓ 35% Dose: ↑ rifabutin dose to 450-600 mg qd or 600 mg 3x/week.* EFV: Standard |
| **Clarithromycin** | Levels: NVP ↑26%. Clarithromycin ↓ 30%. Monitor for efficacy or use alternative agent. | Levels: Clarithromycin ↑100%, DLV ↑ 44%. Dose adjust for renal failure. | Levels: Clarithromycin ↓ 39%. Monitor for efficacy or use alternative agent. |
| **ORAL CONTRACEPTIVES** | Levels: ethinyl estradiol ↓ approx 20%. Use alternative or additional methods. | No data. | Levels: Ethinyl estradiol ↑ 37%. No data on other component. Use alternative or additional methods. |
| **LIPID–LOWERING AGENTS** | | | |
| **Simvastatin Lovastatin** | No data. | Levels: Potential for large increase in statin levels. Avoid concomitant use. | No data. |
| **Pravastatin** | No data. | No data. | No data. |
| **ANTICONVULSANTS** | | | |
| **Carbamazepine Phenobarbitol Phenytoin** | Unknown. Use with caution. Monitor anticonvulsant levels. | Unknown, but may decrease DLV levels substantially. Monitor anticonvulsant levels. | Use with caution. Monitor anticonvulsant levels. |
| **METHADONE** | Levels: NVP unchanged. Methadone ↓ significantly. Titrate methadone dose to effect. | No data. | Levels: methadone ↓ significantly. Titrate methadone dose to effect. |
| **MISCELLANEOUS** | No data. | 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. | Monitor warfarin when used concomitantly. |

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

**Table 20: Four Pages**

## Table 20. Drug Interactions Between Antiretrovirals and Other Drugs: PIs, NNRTIs, and NRTIs

| Drug Interactions Requiring Dose Modifications or Cautious Use | | | | |
|---|---|---|---|---|
| **Drugs Affected** | **Zidovudine (ZDV)** | **Stavudine (d4T)** | **Didanosine (ddI)** | **Tenofovir** |
| **METHADONE** | No data. | Levels: d4T ↓ 27%, methadone unchanged. No dose adjustment. | Levels: ddI ↓ 41%, methadone unchanged. Consider ddI dose increase. | No data. |
| **MISCELLANEOUS** | | | | |
| **Ribavirin** | Ribavirin inhibits phosphorylation of ZDV; this combination should be avoided if possible. | No data. | No data. | No data. |
| **Didanosine buffered tablets** | No data. | Peripheral neuropathy, lactic acidosis, and pancreatitis seen with this combination; use with caution and only if potential benefit outweighs potential risks. | No data. | • Levels: ddI AUC ↑ by 44%, Cmax ↑by 28%<br>• Monitor for ddI-associated toxicities<br>• Consider ddI dose reduction. |
| **Cidofovir, Ganciclovir, Valganciclovir** | No data. | No data. | No data. | • Possibly competes for active tubular secretion with tenofovir, may increase serum concentration of these drugs and/or tenofovir.<br>• Monitor for dose-related toxicities. |

**Table 21: Two Pages**

## Table 21. Drug Effects on Blood Concentration Curves per Dose: PIs and NNRTIs

| Drug Affected | Ritonavir | Saquinavir* | Nelfinavir | Amprenavir | Lopinavir/ Ritonavir |
|---|---|---|---|---|---|
| **Protease Inhibitors** | | | | | |
| **Indinavir (IDV)** | Levels: IDV increase 2-5 times.<br>Dose: 400/400 mg or 800/100 mg or 800/200 mg IDV/RTV bid | Levels: IDV no effect<br>SQV increase 4-7 times†.<br>Dose: Insufficient data. | Levels: IDV increase 50%; NFV increase 80%.<br>Dose: Limited data for IDV 1200 mg bid + NFV 1250 mg bid. | Levels: APV AUC increase 33%.<br>Dose: no change. | Levels: IDV AUC and Cmin increased.<br>Dose: IDV 600 mg bid. |
| **Ritonavir (RTV)** | • | Levels: RTV no effect<br>SQV increase 20 times†‡.<br>Dose: 1000/100 mg SQV sgc or hgc/RTV bid or 400/400 mg bid | Levels: RTV no effect; NFV increase 1.5 times.<br>Dose: RTV 400 mg bid + NFV 500-750 mg bid. | Levels: APV AUC increase 2.5–3.5-fold.<br>Dose: 600/100 mg APV/RTV bid<br>Or 1200/200 mg APV/RTV qd | Lopinavir is co-formulated with ritonavir as Kaletra. |
| **Saquinavir (SQV)** | • | • | Levels: SQV increase 3-5 times; NFV increase 20%†.<br>Dose: Standard NFV;<br>Fortovase 800 mg tid or 1200 mg bid. | Levels: APV AUC decrease 32%.<br>Dose: insufficient data. | Levels: SQV† AUC and Cmin increased.<br>Dose: SQV 1000 mg bid, LPV/r standard. |
| **Nelfinavir (NFV)** | • | • | • | Levels: APV AUC increase 1.5-fold.<br>Dose: insufficient data. | Levels: LPV decrease 27%; NFV increase 25%<br>Dose: Insufficient data. |
| **Amprenavir (APV)** | • | • | • | • | Levels: APV increase AUC and Cmin<br>Dose: APV 600-750 mg bid, LPV/r standard or consider does increase to 533/133 mg bid. Consider monitoring concentrations in PI. |

* 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 21: Two Pages**

## Table 21. Drug Effects on Blood Concentration Curves per Dose: PIs and NNRTIs

| Drug Affected | Nevirapine | Delavirdine | Efavirenz |
|---|---|---|---|
| **PIs and NNRTIs** | | | |
| **Indinavir (IDV)** | Levels: IDV decrease 28%; NVP no effect.<br>Dose: IDV 1000 mg q8h or consider IDV/RTV, NVP standard. | Levels: IDV increase >40%; DLV no effect.<br>Dose: IDV 600 mg q8h.<br>DLV: standard. | Levels: IDV decrease 31%.<br>Dose: IDV 1000 mg q8h or consider IDV/RTV, EFV standard. |
| **Ritonavir (RTV)** | Levels: RTV decrease 11%.<br>NVP no effect.<br>Dose: Standard. | Levels: RTV increase 70%.<br>DLV: no effect.<br>Dose: DLV: standard.<br>RTV: no data. | Levels: RTV increase 18%.<br>EFV increase 21%.<br>Dose: Standard. |
| **Saquinavir (SQV)** | Levels: SQV decrease 25%.<br>NVP no effect.<br>Dose: Consider SQV/RTV. | Levels: SQV‡ increase 5 times ; DLV no effect.<br>Dose: Fortovase 800 mg tid, DLV standard (monitor transaminase levels). | Levels: SQV‡ decrease 62%.<br>EFV decrease 12%.<br>SQV is not recommended to be used as sole PI when EFV is used.<br>Dose: Consider SQV/RTV. |
| **Nelfinavir (NFV)** | Levels: NFV increase 10%.<br>NVP no effect.<br>Dose: Standard. | Levels: NFV increase 2 times; DLV decrease 50%.<br>Dose: No data (monitor for neutropenic complications). | Levels: NFV increase 20%.<br>Dose: Standard. |
| **Amprenavir (APV)** | No data. | Levels: APV AUC increase 130%.<br>DLV AUC decrease 61%.<br>Dose: no data. | Levels: APV AUC decrease 36%.<br>Dose: Administer APV/RTV with EFV, EFV standard. |
| **Lopinavir/ Ritonavir (LPV/RTV)** | Levels: LPV Cmin decrease 55%.<br>Dose: Consider LPV/r 533/133 mg bid in PI-experienced patients; NVP standard. | Levels: LPV levels expected to increase.<br>Dose: Insufficient data. | Levels: LPV AUC decrease 40%. EFV no change.<br>Dose: Consider LPV/r 533/133 mg bid in PI-experienced patients.<br>EFV standard. |
| **Nevirapine (NVP)** | • | No data | Levels: NVP: no effect.<br>EFV: AUC decrease 22%. |
| **Delavirdine (DLV)** | No data. | • | No data. |

* 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 22. 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 | Atovequone | Didanosine |
| Cidofovir | Isoniazid | Didanosine | Adefovir | Clarithromycin | Amprenavir | Didanosine | Ethambutol |
| Cotrimoxazole | Linezolid | Lamivudine (children) | Aminoglycosides | Delavirdine | Atovaquone | Clindamycin | Rifabutin |
| Cytotoxic Chemotherapy | Stavudine | Pentamidine | Amphotericin B | Efavirenz | Cotrimoxazole | Nelfinavir | Cidofovir |
| Dapsone | Zalcitabine | Ritonavir | Cidofovir | Fluconazole | Dapsone | Ritonavir | |
| Flucytosine | | Stavudine | Foscarnet | Isoniazid | Delavirdine | Lopinavir/ ritonavir | |
| Ganciclovir | | Zalcitabine | Indinavir | Itraconazole | Efavirenz | Tenofovir | |
| Hydroxyurea | | | Pentamidine | Ketoconazole | Nevirapine | | |
| Interferon-α | | | | Nevirapine | Sulfadiazine | | |
| Linezolid | | | | Nucleoside reverse transcriptase inhibitors (NRTIs) | | | |
| Pegylated Interferon-α | | | | Protease inhibitors | | | |
| Primaquine | | | | Rifabutin | | | |
| Pyrimethamine | | | | Rifampin | | | |
| Ribavirin | | | | Voriconazole | | | |
| Rifabutin | | | | | | | |
| Sulfadiazine | | | | | | | |
| Trimetrexate | | | | | | | |
| Valganciclovir | | | | | | | |
| Zidovudine | | | | | | | |

## Table 23: Summary of Guidelines For Changing An Antiretroviral Regimen For Suspected Treatment Regimen Failure

**Patient Assessment (AIII)**

- Review antiretroviral treatment history.
- Perform physical exam to assess for signs of clinical progression.
- Assess adherence, tolerability, and pharmacokinetic issues.
- Distinguish between first or second, and multiple treatment regimen failures.
- Perform resistance testing while patient is taking therapy.
- Identify susceptible drugs and drug classes.

**Patient Management: Specific Clinical Scenarios**

- ***Limited 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 viral replication. Consider intensifying with one drug (e.g., tenofovir) (BII) or pharmacokinetic enhancement (use of ritonavir boosting of a protease inhibitor) (BII), or most aggressively, change to a completely new regimen (CIII). If continuing the same treatment regimen, need to follow HIV RNA levels more closely, because ongoing viremia will lead to the accumulation of resistance mutations.
- ***Limited prior treatment with single drug resistance:*** Consider changing one drug (CIII), pharmacokinetic enhancement (few data available) (BII), or, most aggressively, change to a completely new regimen (BII).
- ***Limited prior treatment with more than 1 drug resistance:*** The goal of treatment is to suppress viremia to prevent further selection of resistance mutations. Consider optimizing 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 obtaining 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 see if a resistant strain has been selected (CIII).
- ***Extensive prior treatment:*** 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 development of resistance to that drug. In advanced disease with a high likelihood of clinical progression, adding a single drug may reduce the risk of immediate clinical progression (CIII). In this complicated scenario, expert advice should be sought.

## Table 24: Novel Strategies To Consider For Treatment-Experienced Patients With Few Available Active Treatment Options

- Pharmacokinetic enhancement with ritonavir may increase drug concentrations and may overcome some degree of drug resistance (CII).
- Therapeutic Drug Monitoring may be considered (see Statement on 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). Continued drug pressure and drug substitutions may compromise viral replicative capacity and viral fitness, but it is not known if this has clinical applicability.
- The use of empiric multidrug regimens (including up to 3 PIs and/or 2 NNRTIs) has been advocated by some [1-2], but may be limited ultimately by complexity, tolerability, and drug-drug interactions (CII).
- Structured treatment interruptions in the setting of virologic failure have been investigated prospectively, but results are conflicting [3-4]. 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).
- 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 or through clinical trials may be used. Enfuvirtide (T-20) recently was approved for use in the treatment-experienced patient with ongoing viremia on the basis of antiretroviral activity in this population [5-6]. Given the necessity for parenteral (subcutaneous) administration twice daily, this drug should be reserved for heavily treatment-experienced patients (BII).

**Sources:**


1. Montaner JS, Harrigan PR, Jahnke N, et al. Multiple drug rescue therapy for HIV-infected individuals with prior virologic failure to multiple regimens. *AIDS* 2001;15(1):61-9.
2. Youle M, Tyrer M, Fisher M, et al. Brief report: two-year outcome of a multidrug regimen in patients who did not respond to a protease inhibitor regimen. *J Acquir Immun Defic Syndr* 2002;29(1):58-61.
3. Lawrence J, Mayers D, Huppler Hullsiek K, et al. CPCRA 064: a randomized trial examining structured treatment interruption for patients failing therapy with multi-drug resistant HIV. IN: Abstracts of the 10th Conference on Retroviruses and Opportunistic Infections, Boston, MA, February 10-14, 2003. (Abstract #67).
4. Katlama C, Dominguez S, Duvivier C, et al. Long-term benefit of treatment interruption in salvage therapy (GIGHAART ANRS 097). IN: Abstracts of the 10th Conference on Retroviruses and Opportunistic Infections, Boston, MA, February 10-14, 2003. (Abstract #68).
5. Lalezari JP, Henry K, O'Hearn M, et al. Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. *N Engl J Med* 2003;348(22):2175-85.
6. Lazzarin A, Clotet B, Cooper D, et al. Efficacy of enfuvirtide in patients infected with drug-resistant HIV-1 in Europe and Australia. *N Engl J Med* 2003;348(22):2186-95.

## Table 25: Treatment Options Following Virologic Failure on Initial Recommended Therapy Regimens

| Regimen Class | Initial Regimen | Recommended Change |
|---|---|---|
| NNRTI | 2 nucleosides + NNRTI | • 2 nucleosides (based on resistance testing) + PI (with or without low-dose ritonavir) (AII) |
| PI | 2 nucleosides + PI (with or without low-dose ritonavir) | • 2 nucleosides (based on resistance testing) + NNRTI (AII) |
| Triple nucleosides | 3 nucleosides | • 2 nucleosides (based on resistance testing) + NNRTI or PI (with or without low-dose ritonavir) (AIII)<br>• NNRTI + PI (with or without low-dose ritonavir) (CIII)<br>• Nucleoside(s) (based on resistance testing) + NNRTI + PI (with or without low-dose ritonavir) (CII) |

## Table 26: Suggested Minimum Target Trough Concentrations for Persons with Wild-Type HIV-1

| Drug | Concentration (ng/mL) |
|---|---|
| Amprenavir (Agenerase) | 400 |
| Indinavir (Crixivan) | 100 |
| Lopinavir/ritonavir (Kaletra) | 1000 |
| Nelfinavir (Viracept) [a] | 800 |
| Ritonavir (Norvir) [b] | 2100 |
| Saquinavir (Fortovase, Invirase) | 100-250 |
| Efavirenz (Sustiva) | 1000 |
| Nevirapine (Viramune) | 3400 |

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

**Sources:**


- Acosta EP, and Gerber JG. Position paper on therapeutic drug monitoring of antiretroviral agents. *AIDS Research Human Retroviruses* 2002; 18(12):825-34.
- Back D, Gatti G, Fletcher CV, et al. Therapeutic drug monitoring in HIV infection: current status and future directions. *AIDS* 2002; 16 (suppl 1) S5-S37.
- Burger DM, Aarnoutse RE, Hugen PWH. Pros and cons of therapeutic drug monitoring of antiretroviral agents. *Curr Opin Infect Dis* 2002;15(1):17-22.
- Optimizing TDM in HIV clinical care. (May 20, 2003. http://www.hivpharmacology.com)

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

- ♦ 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

**Source:** Niu MT, Stein DS, Schnittman SM. Primary human immunodeficiency virus type 1 infection: review of pathogenesis and early treatment intervention in humans and animal retrovirus infections. *J Infect Dis* 1993; 168(6):1490-501.

## Table 28. Zidovudine Perinatal Transmission Prophylaxis Regimen

| | |
|---|---|
| **ANTEPARTUM** | Initiation at 14–34 weeks gestation and continued throughout pregnancy of either Regimen A or B, as follows:<br><br>**Regimen A.** Pediatric AIDS Clinical Trials Group protocol 076 regimen:<br><br>ZDV 100 mg 5 times daily<br><br>**Regimen B.** Acceptable alternative regimen:<br><br>ZDV 200 mg 3 times daily<br>or<br>ZDV 300 mg 2 times daily |
| **INTRAPARTUM** | During labor, ZDV 2 mg/kg of mother's body weight, intravenously for 1 hour, followed by a continuous infusion of 1 mg/kg of mother's body weight intravenously until delivery. |
| **POSTPARTUM** | Oral administration of ZDV to the newborn infant (ZDV syrup, 2 mg/kg of infant's body weight every 6 hours) for the first 6 weeks of life, beginning at 8–12 hours after birth. |

## Table 29. Preclinical and Clinical Data Concerning the Use of Antiretrovirals During Pregnancy

(see Safety and Toxicity of Individual Antiretroviral Drugs in Pregnancy for more detail on drugs)

| 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) | Not completed | Positive (rodent anasarca and skeletal malformations at 1000 mg/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 |
| Lamivudine (Epivir, 3TC) | C | Yes (human) [~1.0] | Negative (no tumors, lifetime rodent study) | Negative |
| Stavudine (Zerit, d4T) | C | Yes (rhesus monkey) [0.76] | Not completed | Negative (but sternal bone calcium decreases in rodents) |
| Tenofovir DF (Viread) | B | Yes (rat and monkey) | Not completed | 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** | | | | |
| Efavirenz (Sustiva) | C | Yes (cynomologus monkey, rat, rabbit) [~1.0] | Not completed | Positive (cynomologus monkey- anencephaly, anophthalmia, microophthalmia) |
| Delavirdine (Rescriptor) | C | Unknown | Not completed | Positive (rodent-ventricular septal defect) |
| Nevirapine (Viramune) | C | Yes (human) [~1.0] | Not completed | Negative |
| **Protease inhibitors** | | | | |
| Amprenavir (Agenerase) | C | Unknown | Not Completed | Negative (but deficient ossification and thymic elongation in rats and rabbits) |
| Indinavir (Crixivan) | C | Minimal (humans) | Not completed | Negative (but extra ribs in rodents) |
| Lopinavir/Ritonavir (Kaletra) | C | Unknown | Not Completed | Negative (but delayed skeletal ossification and increase in skeletal variations in rats at maternally toxic doses) |
| Nelfinavir (Viracept) | B | Minimal (humans) | Not completed | Negative |
| Ritonavir (Norvir) | B | Minimal (humans) | Positive (rodent, liver tumors) | Negative (but cryptorchidism in rodents)‡ |
| Saquinavir (Fortovase) | B | Minimal (humans) | Not completed | Negative |
| **Fusion inhibitors** | | | | |
| Enfuvirtide (Fuzeon) | B | Unknown | Incomplete | Negative |

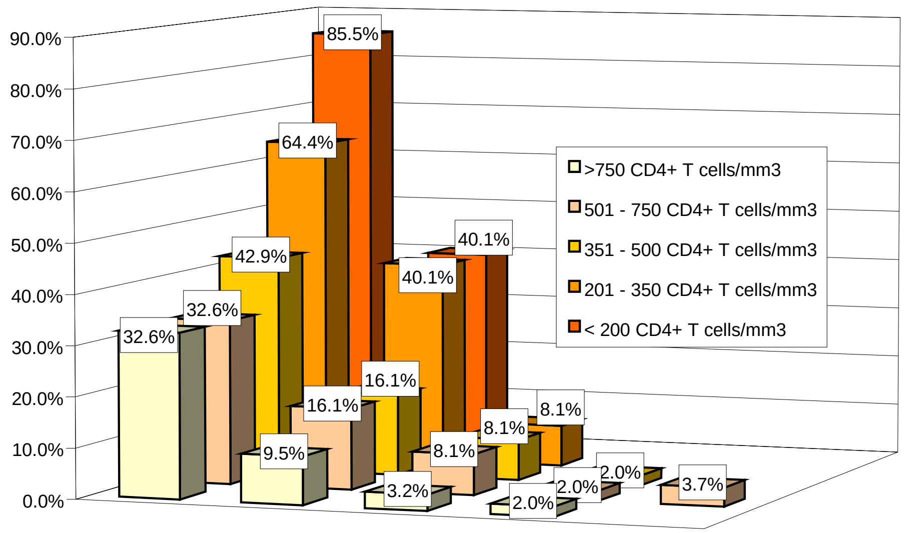
* Food and Drug Administration Pregnancy Categories:

- 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.

† Despite certain animal data indicating potential teratogenicity of zidovudine when near-lethal doses are given to pregnant rodents, substantial human data are available indicating that the risk to the fetus, if any, is limited when administered to the pregnant mother beyond 14 weeks gestation. Follow-up for ≤6 years for 734 infants who had been born to HIV-infected women and had in utero exposure to zidovudine has not demonstrated any tumor development (**Source:** Hart CE, Lennox JL, Pratt-Palmore M, et al. Correlation of HIV type 1 RNA levels in blood and the female genital tract. *J Infect Dis* 1999; 179:871-82). However, no data are available regarding longer follow-up for late effects.

‡ These effects occurred only at maternally toxic doses.

## Figure 1. Likelihood of Developing Acquired Immunodeficiency Syndrome by 3 Years After Becoming Infected with Human Immunodeficiency Virus Type 1




| | | | | | |
|---|---|---|---|---|---|
| BDNA* | >30K | 10K-30K | 3K-10K | 501-3K | <500 |
| RT-PCR** | >55K | 20K-55K | 7K-20K | 1.5K-7K | <1500 |

**Plasma viral load (copies/mL, thousands)**

* b-Deoxyribonucleic acid.
** Reverse transcriptase-polymerase chain reaction.

**Source:** Mellors JW, Muñoz A, Gigorgi JV, et al. Plasma viral load and CD+ lymphocytes as prognostic markers of HIV-1 infection, *Ann Intern Med* 1997; 126(12):946-54.

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# Considerations for Antiretroviral Therapy in Women

Several studies have suggested that plasma HIV RNA levels are significantly lower in adult women compared to men. Several analyses have been reported from the ALIVE cohort of intravenous drug users in Baltimore. In a cross-sectional study from this cohort, there was a consistent trend toward lower viral load (quantitative microculture as well as HIV RNA measured by branched chain DNA and RT-PCR) in women compared to men after adjustment for $CD4^+$ lymphocyte count, race and drug use within the prior 6 months; the difference in RNA levels was approximately 0.25 log *[1]*. When women and men were matched for $CD4^+$ T cell count there was no difference in the risk for progression to AIDS. However, when matched for RNA copy number, the risk of AIDS was 1.6-fold higher for women. In a further longitudinal case-control evaluation of seroconverters from this cohort, the sex-specific difference in viral load was present at seroconversion, but viral load tended to increase more rapidly in women and median viral loads in women and men became similar within 5-6 years of seroconversion *[2]*. The relationship between initial HIV RNA level at seroconversion and progression to AIDS was examined in a longitudinal study of 202 seroconverters (156 men and 46 women) from this cohort *[3]*. HIV RNA levels following seroconversion were significantly lower in women than men (by approximately 0.5 log), but these differences became attenuated over time. There was no significant sex-specific difference in rates of progression to AIDS. In another longitudinal study of 14 women and 28 men in the armed forces, median RNA levels were lower in women, but these differences were less than 0.5 log and diminished over time; no differences in HIV DNA load were observed *[4]*. In a virology substudy of ACTG 175, cross-sectional HIV RNA levels were 0.28 log lower in 71 women at baseline compared with men after adjustment for $CD4^+$ T cell count *[5]*.

Other large cohort studies have had less convincing results. In 647 women from the Swiss HIV Cohort Study, there was a slightly lower viral load among female injection drug users (0.13 log) but not among heterosexually infected women *[6]*. Additionally, there was no difference in disease progression between women and men matched for HIV RNA level and $CD4^+$ T cell count. In 712 women in the ICONA study, viral load was only 0.13 log lower in women after adjustment for $CD4^+$ T cell count; however, in contrast to the Swiss HIV Cohort Study, the sex-specific difference was larger in women with heterosexually acquired HIV infection compared with injection drug use-acquired HIV infection *[7]*. Data reported from Johns Hopkins showed little evidence of lower viral load after stratification by $CD4^+$ T cell count *[8]*, and in a comparison of 1262 women from the Women's Interagency HIV Study and men from the Multicenter AIDS Cohort Study, a small viral load difference of ~0.10-0.14 log was present only at higher CD4 count levels *[9]*. Finally, in an analysis of adults with advanced transfusion-acquired HIV infection, no significant differences in HIV RNA levels between women and men were observed *[10]* and no difference in viral load by sex was observed for age and $CD4^+$ T cell-matched antiretroviral naïve men and women either before or after antiretroviral therapy *[11]*.

Limited studies in HIV-infected adults have indicated that women may have higher $CD4^+$ T cell count than men. In a French study, this difference was observed only for CD4 percentage and was of borderline significance for CD4 absolute number once women and men were matched for age *[12]*. In a second European study, while absolute $CD4^+$ T cell count was higher in women than men, these differences were only statistically significant at AIDS onset and not at seroconversion or death *[13]*. Neither study evaluated the relationship of sex and $CD4^+$ T count to disease progression. However, other studies have shown similar rates of disease progression between men and women matched for $CD4^+$ T cell count and/or HIV RNA level *[6, 14, 15]*.

Taken together, these data suggest that gender-based differences in viral load occur predominantly during a window of time when the $CD4^+$ T cell count is relatively preserved and treatment is recommended only in the setting of high levels of plasma HIV RNA. Clinicians may wish to consider lower plasma HIV RNA thresholds for initiating therapy in women with $CD4^+$ T cell counts >350 cells/mm$^3$, although there are insufficient data to determine an appropriate threshold. In patients with $CD4^+$ T cell counts <350 cells/mm$^3$, very small sex-based differences in viral load are apparent; therefore, no changes in treatment guidelines for women are recommended for this group.

Further study is warranted regarding sex differences in viral and immunologic parameters. It is likely that any such differences would be hormonally related; estrogen-related effects have been described on immune function *[16]*. Consistent with this hypothesis are some preliminary studies of variation in viral load according to menstrual cycle. One study has suggested that the ovulatory cycle influences circulating HIV-1 RNA levels *[17]*. Additionally, another study suggests that pharmacokinetic parameters may vary over the ovulatory cycle; considerable variations in indinavir pharmacokinetics were found during the menstrual cycle, with a trend to more drug exposure during the follicular phase *[18]*.

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# Hydroxyurea

Hydroxyurea is indicated for the treatment of certain malignancies and sickle cell anemia, and has been used investigationally for the treatment of HIV. Its potential safety and effectiveness for treatment of HIV have not been established, and clinicians should be aware of important safety precautions regarding its use. Hydroxyurea does not have direct antiretroviral activity; rather, it inhibits the cellular enzyme ribonucleotide reductase, resulting in reduced intracellular levels of deoxynucleoside triphosphates (dNTPs) that are necessary for DNA synthesis *[1]*. Hydroxyurea preferentially depletes intracellular dATP; therefore, antiretroviral activity and/or toxicity of adenosine analogues, such as ddI, may potentially be enhanced in combination with hydroxyurea. Hydroxyurea also induces the activity of cellular kinases that phosphorylate nucleoside analogue reverse transcriptase inhibitors, potentially further enhancing their antiretroviral activity and/or toxicity.

There have been no data from controlled clinical trials that convincingly support the benefit of hydroxyurea as an adjunct in the treatment of HIV infection. In limited studies, the addition of hydroxyurea to a regimen of ddI +d4T or ddI alone appeared to result in moderately enhanced antiretroviral activity *[2-4]*, although the optimal dosage and dosing schedule were not determined. In contrast, in ACTG 5025, a randomized, controlled clinical trial conducted in subjects on potent antiretroviral therapy with levels of plasma viremia <200 copies/mL *[5]*, no statistically significant differences in viral load suppression were observed in patients receiving hydroxyurea 600 mg twice daily in combination with ddI+d4T+indinavir compared to those receiving the combination regimen without hydroxyurea. Additionally, a substantial decrease in median $CD4^+$ T cell count was observed in the hydroxyurea treatment group. Observations of blunted or reduced CD4 responses were also reported by other investigators *[6-8]*. Importantly, the ACTG 5025 trial was prematurely terminated due to higher rates of drug toxicity in patients randomized to the hydroxyurea-containing arm. Among 68 patients randomized to hydroxyurea, three deaths related to complications of pancreatitis were reported. The increased frequency of fatal pancreatitis in the hydroxyurea-containing arm was not statistically significant and had not been reported previously. These cases of fatal pancreatitis do, however, raise the question of whether hydroxyurea in combination with ddI+d4T may increase the risk of ddI-associated pancreatitis.

Additional concerns regarding the use of hydroxyurea in HIV infection have been raised in this trial and other studies, and include an increased risk of persistent cytopenias *[9]* and hepatotoxicity *[10]*, the drug's teratogenic properties (FDA Pregnancy Category D), and an increased risk of neuropathy *[11, 12]*.

In summary, the current clinical trial data have not demonstrated virological and immunological benefit of hydroxyurea as adjunctive therapy to antiretroviral regimens when compared to antiretroviral therapy alone, and hydroxyurea should generally not be offered. (DII) Clinicians considering the use of hydroxyurea in a treatment regimen for HIV should be aware of the limited and conflicting nature of data in support of its efficacy, and the importance of monitoring patients closely for potentially serious toxicity.

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# Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy

## NUCLEOSIDE & NUCLEOTIDE ANALOGUE REVERSE TRANSCRIPTASE INHIBITORS

There are currently six approved nucleoside analogue reverse transcriptase inhibitors. Data are available from clinical trials in human pregnancy for zidovudine, lamivudine, didanosine**,** and stavudine. Zalcitabine and abacavir have not been studied in pregnant women. Tenofovir disoproxil fumarate is the first nucleotide analogue reverse transcriptase inhibitor. The nucleoside analogue drugs require three intracellular phosphorylation steps to form the triphosphate nucleoside, which is the active drug moiety; tenofovir, an acyclic nucleotide analogue drug, contains a monophosphate component attached to the adenine base, and hence only requires two phosphorylation steps to form the active moiety.

**Abacavir (Ziagen®, ABC)** is classified as FDA pregnancy category C.

- Animal carcinogenicity studies
  Long-term animal carcinogenicity studies of abacavir in rodents are not completed; however, some *in vitro* mutagenesis and clastogenesis screening tests are positive.

- Reproduction/fertility
  No effect of abacavir on reproduction or fertility in male and female rodents has been seen at doses of up to 500 mg/kg/day (about 8 times that of human therapeutic exposure).

- Teratogenicity/developmental toxicity
  Abacavir is associated with developmental toxicity (decreased fetal body weight and reduced crown-rump length) and increased incidence of fetal anasarca and skeletal malformations in rats treated with abacavir during organogenesis at doses of 1000 mg/kg (about 35 times that of human therapeutic exposure based on area under the curve (AUC)). Toxicity to the developing embryo and fetus (increased resorptions and decreased fetal body weight) occurred with abacavir administration to pregnant rodents at 500 mg/kg/day. The offspring of female rats treated with 500 mg/kg of abacavir beginning at embryo implantation and ending at weaning had an increased incidence of stillbirth and lower body weight throughout life. However, in the rabbit, no evidence of drug-related developmental toxicity was observed and no increase in fetal malformations was observed at doses up to 700 mg/kg (about 8.5 times that of human therapeutic exposure).

- Placental and breast milk passage
  Abacavir crosses the placenta and is excreted into the breast milk of lactating rats.

- Human studies in pregnancy
  No studies have been conducted with abacavir in pregnant women or neonates. Serious hypersensitivity reactions have been associated with abacavir therapy in non-pregnant adults and have rarely been fatal; symptoms include fever, skin rash, fatigue, and gastrointestinal symptoms such as nausea, vomiting, diarrhea, or abdominal pain. Abacavir should not be restarted following a hypersensitivity reaction because more severe symptoms will recur within hours and may include life-threatening hypotension and death.

**Didanosine (Videx®, ddI)** is classified as FDA pregnancy category B.

- Animal carcinogenicity studies
  Long-term animal carcinogenicity screening studies in rodents given didanosine have been negative.

- Reproduction/fertility
  There has been no effect of didanosine on reproduction or fertility in rodents or on preimplantation mouse embryos *[1]*.

- Teratogenicity/developmental toxicity
  No evidence of teratogenicity or toxicity was observed with administration of high doses of didanosine to pregnant rats, mice, or rabbits.

- Placental and breast milk passage
  Placental transfer of didanosine was limited in a phase I/II safety and pharmacokinetic study (cord-to-maternal blood ratio, 0.35–0.11) *[2]*. Didanosine is excreted in the milk of lactating rats; it is not known if didanosine is excreted in human breast milk.

- Human studies in pregnancy
  A phase I study (PACTG 249) of didanosine was conducted in 14 HIV-infected pregnant women enrolled at gestational age 26 to 36 weeks and treated through 6 weeks postpartum *[2]*. The drug was well-tolerated during pregnancy by the women and the fetuses. Pharmacokinetic parameters after oral administration were not significantly affected by pregnancy, and dose modification from the usual adult dosage is not needed.

  Cases of lactic acidosis, in some cases fatal, have been described in pregnant women receiving the combination of didanosine and stavudine along with other antiretroviral agents *[3-5]*; the FDA and Bristol Myers Squibb have issued a warning to health care professionals that pregnant women may be at increased risk of fatal lactic acidosis when prescribed the combination of didanosine and stavudine (see "Pregnancy and mitochondrial toxicity" on page 6). The combination of these two drugs should be prescribed for pregnant women only when the potential benefit clearly outweighs the potential risk; clinicians should prescribe this antiretroviral combination during pregnancy with caution and generally only when other nucleoside analog drug combinations have failed or have caused unacceptable toxicity or side effects.

**Lamivudine (Epivir®, 3TC)** is classified as FDA pregnancy category C.

- Animal carcinogenicity studies
  Long-term animal carcinogenicity screening studies in rodents administered lamivudine have been negative.

- Reproduction/fertility
  There appears to be no effect of lamivudine on reproduction or fertility in rodents.

- Teratogenicity/developmental toxicity
  There is no evidence of lamivudine-induced teratogenicity. Early embryolethality was seen in rabbits but not in rats at doses similar to human therapeutic exposure.

  In the Antiretroviral Pregnancy Registry, sufficient numbers of first trimester exposures to lamivudine in humans have been monitored to be able detect at least a two-fold increase in risk of overall birth defects and those in the more common classes, cardiovascular and genitourinary systems. No such increase in birth defects has been observed with lamivudine. The prevalence of birth defects with first trimester lamivudine exposure was 3.0% (95% confidence interval, 2.0-4.3%) compared with total prevalence of birth defects in the U.S. population based on CDC surveillance of 3.1% *[6]*.

- Placental and breast milk passage
  Lamivudine readily crosses the placenta in humans, achieving comparable cord blood and maternal concentrations *[7]*. Lamivudine is excreted into human breast milk.

- Human studies in pregnancy
  A small phase I study in South Africa evaluated the safety and pharmacokinetics of lamivudine alone or in combination with zidovudine in 20 HIV-infected pregnant women; therapy was started at 38 weeks gestation, continued through labor, and given for 1 week following birth to the infants *[7]*. The drug was well-tolerated in the women at the recommended adult dose of 150 mg orally twice daily; pharmacokinetics were similar to those observed in nonpregnant adults, and no pharmacokinetic interaction with zidovudine was observed.

  Zidovudine and lamivudine, given in combination orally intrapartum, were well-tolerated. Lamivudine was well-tolerated in the neonates, but clearance was about 50% that of older children, requiring a reduced dosing regimen (4 mg/kg/day in neonates compared to 8 mg/kg/day for infants older than 3 months). There are currently no data on the pharmacokinetics of lamivudine between 2 to 6 weeks of age, and the exact age at which lamivudine clearance begins to approximate that in older children is not known.

**Stavudine (Zerit®, d4T)** is classified as FDA pregnancy category C.

- Animal carcinogenicity studies
  Long-term animal carcinogenicity studies of stavudine in rodents are not completed; some *in vitro* and *in vivo* mutagenesis and clastogenicity tests are positive.

- Reproduction/fertility
  No effect of stavudine on reproduction or fertility in rodents has been seen. A dose-related cytotoxic effect on preimplantation mouse embryos, with inhibition of blastocyst formation at a concentration of stavudine of 100 μM and of postblastocyst development at 10 μM *[1]*.

- Teratogenicity/developmental toxicity
No evidence of teratogenicity of stavudine has been observed in pregnant rats and rabbits. Developmental toxicity, consisting of a small increase in neonatal mortality and minor skeletal ossification delay, occurred at the highest dose in rats.

  In the Antiretroviral Pregnancy Registry, sufficient numbers of first trimester exposures to stavudine have been monitored to be able detect at least a two-fold increase in risk of overall birth defects and those in the more common classes, cardiovascular and genitourinary systems. No such increase in birth defects has been observed with stavudine. The prevalence of birth defects with first trimester stavudine exposure was 2.2% (95% confidence interval, 0.9-4.4%) compared with total prevalence of birth defects in the U.S. population based on CDC surveillance of 3.1% *[6]*.

- Placental and breast milk passage
Stavudine crosses the rat placenta *in vivo* and the human placenta *ex vivo*, resulting in a fetal/maternal concentration of approximately 0.50. In primates (pigtailed macaques), fetal/maternal plasma concentrations were approximately 0.80 *[8]*. Stavudine is excreted into the breast milk of lactating rats.

- Human studies in pregnancy
A phase I/II safety and pharmacokinetic study of combination d4T and 3TC in pregnant HIV-infected women and their infants has been conducted (PACTG 332). Both drugs were well-tolerated, with pharmacokinectics similar to those in non-pregnant adults *[9]*. Data from primate studies also indicated that pregnancy did not affect the pharmacokinetics of d4T *[10]*.

  Cases of lactic acidosis, in some cases fatal, have been described in pregnant women receiving the combination of didanosine and stavudine along with other antiretroviral agents *[3-5]*; the FDA and Bristol Myers Squibb have issued a warning to health care professionals that pregnant women may be at increased risk of fatal lactic acidosis when prescribed the combination of didanosine and stavudine (see "Pregnancy and mitochondrial toxicity" on page 6). The combination of these two drugs should be prescribed for pregnant women only when the potential benefit clearly outweighs the potential risk; clinicians should prescribe this antiretroviral combination during pregnancy with caution and generally only when other nucleoside analog drug combinations have failed or have caused unacceptable toxicity or side effects.

**Tenofovir disoproxil fumerate [DF] (Viread™)** is classified as FDA pregnancy category B.

- Animal carcinogenicity studies
Long-term animal carcinogenicity studies of tenofovir DF in rodents are not completed; however, some *in vitro* mutagenesis and clastogenesis screening tests are positive.

- Reproduction/fertility
Reproductive toxicity has been evaluated in rats and rabbits. Tenofovir had no adverse effects on fertility or general reproductive performance in rats at doses up to 600 mg/kg/day (exposure equivalent to approximately 10 times the human dose based on body surface area comparisons). However, there was an alteration of the estrous cycle in female rats administered 600 mg/kg/day of tenofovir.

- Teratogenicity/developmental toxicity
No adverse effects on embryo/fetal development were seen when tenofovir was given in doses up to 450 mg/kg/day to pregnant rats and 300 mg/kg/day to pregnant rabbits. When tenofovir was administered to pregnant rats in doses of 450–600 mg/kg/day, which are maternally toxic doses, peri- and post-natal development studies of their offspring showed reduced survival and slight delay in sexual maturation. However, there were no adverse effects on growth, development, behavior, or reproductive parameters when tenofovir was administered to pregnant rodents at doses that were not associated with maternal toxicity (150 mg/kg/day). Chronic exposure of fetal monkeys to tenofovir at a high dose of 30 mg/kg (exposure equivalent to 25 times the AUC achieved with therapeutic dosing in humans) from days 20–150 of gestation did not result in gross structural abnormalities *[11]*. However, significantly lower fetal circulating insulin-like growth factor (IGF)-1 (a primary regulator of linear growth) and higher IGF binding protein (IGFBP)-3 levels were shown and were associated with overall body weights approximately 13% lower than untreated controls. A slight reduction in fetal bone porosity was also observed. Effects on these parameters were observed within 2 months of maternal treatment. Significant changes in maternal monkey bone biomarkers were noted but were primarily limited to the treatment period and were reversible.

  Continued administration of tenofovir at 30 mg/kg/day to the infant monkey postnatally resulted in significant growth restriction and severe bone toxicity in 25% of eight infants and effects on bone biomarkers and defective bone mineralization in all animals. Chronic administration of tenofovir to immature animals of multiple species has resulted in reversible bone abnormalities; these effects were dose-, exposure-, age-, and species-specific. Abnormalities ranged from minimal decrease in bone mineral density and content (with oral dosing in rats and dogs that achieved drug exposures 6 to 10 times that achieved with therapeutic dosing in humans) to severe, pathologic osteomalacia (with subcutaneous dosing given to monkeys). Juvenile monkeys given chronic subcutaneous tenofovir at 30 mg/kg/day (exposure equivalent to 25 times the AUC achieved with therapeutic dosing in humans) developed osteomalacia, bone fractures, and marked hypophosphatemia. However, no clinical or radiologic bone toxicity was seen when juvenile monkeys received subcutaneous dosing of 10 mg/kg/day (exposure equivalent to 8 times the AUC achieved with therapeutic dosing in humans). Evidence of nephrotoxicity was observed in newborn and juvenile monkeys given tenofovir in doses resulting in exposures 12 to 50 times higher than the human dose based on body surface area comparisons.

- Placental and breast milk passage
  Studies in rats have demonstrated that tenofovir is secreted in milk. Intravenous administration of tenofovir to pregnant cynomolgus monkeys resulted in a fetal/maternal concentration of 17%, demonstrating that tenofovir does cross the placenta *[12]*. There are no data on whether tenofovir crosses the placenta or is excreted in breast milk in humans.

- Human studies in pregnancy
  No studies of tenofovir have been conducted in pregnant women or neonates.

**Zalcitabine (HIVID®, ddC)** is classified as FDA pregnancy category C.

- Animal carcinogenicity studies
  High doses of zalcitabine (over 1,000 times that of human therapeutic exposure) have been associated with the development of thymic lymphomas in rodents.

- Reproduction/fertility
  No effect of zalcitabine on reproduction or fertility in rodents has been seen. However, there is a dose-related cytotoxic effect on preimplantation mouse embryos, with inhibition at a zalcitabine concentration of 100 μM; no inhibition of postblastocyst development was observed *[1]*.

- Teratogenicity/developmental toxicity
  Teratogenicity (hydrocephalus) occured in rats given very high doses (over 1,000 times the maximally recommended human exposure) of zalcitabine. Developmental toxicity, consisting of decreased fetal weight and skeletal defects, has been seen in rodents at moderate to high zalcitabine doses. Cytotoxic effects were observed on rat fetal thymocytes at zalcitabine concentrations as low as 10 μM (approximately 100 times human therapeutic exposure).

- Placental and breast milk passage
  In primate and placental perfusion studies, zalcitabine crosses the placenta (fetal-to-maternal drug ratio approximately 0.50 to 0.60) *[13]*. In rodents, zalcitabine concentrates in the fetal kidney and a relatively small proportion (approximately 20%) reaches the fetal brain. It is unknown if ddC is excreted in breast milk.

- Human studies in pregnancy
  No studies of zalcitabine have been conducted in pregnant women or neonates.

**Zidovudine (Retrovir®)** is classified as FDA pregnancy category C.

- Animal carcinogenicity studies
  Prolonged, continuous, high-dose zidovudine administration to adult rodents is associated with the development of nonmetastasizing vaginal squamous tumors in 13% of female rodents (at estimated drug concentrations 3 and 24 times that of human therapeutic exposure in mice and rats, respectively) *[14]*. In rodents, unmetabolized zidovudine is concentrated in urine with reflux into the vaginal vault. Therefore, vaginal tumors could be a topical effect of chronic zidovudine exposure on the vaginal mucosa. The observation that vaginal squamous cell carcinomas were observed in rodents exposed to 20 mg/mL zidovudine intravaginally is consistent with this hypothesis *[14]*. In humans, only metabolized zidovudine is excreted in the urine. No increase in tumors in other organ sites has been seen in adult rodent studies.

  Two transplacental carcinogenicity studies of zidovudine were conducted in mice, with differing results. In one study, two very high daily doses of zidovudine were administered during the last third of gestation in mice *[15]*. These doses were near the maximum dose beyond which lethal fetal toxicity would be observed and approximately 25 and 50 times greater than the daily dose given to humans (although the cumulative dose was similar to the cumulative dose received by a pregnant woman taking 6 months of zidovudine). In the offspring of zidovudine-exposed pregnant mice at the highest dose level followed for 12 months, a statistically significant increase in lung, liver, and female reproductive organ tumors was observed; the investigators also documented incorporation of zidovudine into the DNA of a variety of newborn mouse tissues, although this did not clearly correlate with the presence of tumors. In the second study, pregnant mice were given one of several regimens of zidovudine, at doses intended to achieve blood levels approximately threefold higher than human therapeutic exposure *[16]*. The daily doses received by the mice during gestation ranged from one-twelfth to one-fiftieth the daily doses received in the previous study. Some of the offspring also received zidovudine for varying periods of time over their lifespan. No increase in the incidence of tumors was observed in the offspring of these mice, except among those that received additional lifetime zidovudine exposure, in which vaginal tumors were again noted.

Transplacental carcinogenicity studies have not been performed for any of the other available antiretroviral drugs or combinations of drugs. In January 1997, the National Institutes of Health convened an expert panel to review these animal data *[17]*. The panel concluded that the known benefit of zidovudine in reducing vertical transmission of HIV by nearly 70% (7.2 versus 21.9% with placebo) *[18]* far outweighs the theoretical risks of transplacental carcinogenicity. The panel also concluded that infants with *in utero* exposure to zidovudine (or any other antiretroviral) should have long-term follow-up for potential adverse effects. No tumors have been observed in 727 children with *in utero* ZDV exposure followed for over 1,100 person-years *[19]*. While these data are reassuring, follow-up is still limited and needs to be continued into adulthood before it can be concluded that there is no carcinogenic risk.

- Reproduction/fertility

No effect of zidovudine on reproduction or fertility in rodents has been seen. A dose-related cytotoxic effect on preimplantation mouse embryos can occur, with inhibition of blastocyst and postblastocyst development at a zidovudine concentrations similar to levels achieved with human therapeutic doses *[20]*.

- Teratogenicity/developmental toxicity

No evidence of teratogenicity or toxicity was observed with administration of doses up to 500 to 600 mg/kg/day of zidovudine to pregnant rats, mice or rabbits. However, marked maternal toxicity and an increase in fetal malformations were noted in rats given a zidovudine dose of 3000 mg/kg/day (near the lethal dose, and 350 times the peak human plasma concentration).

In humans, in the placebo-controlled perinatal trial PACTG 076, the incidence of minor and major congenital abnormalities was similar between zidovudine and placebo groups and no specific patterns of defects were seen *[18, 21]*. In the Antiretroviral Pregnancy Registry, sufficient numbers of first trimester exposures to zidovudine have been monitored to be able to detect at least a two-fold increase in risk of overall birth defects and those in the more common classes, cardiovascular and genitourinary systems. No such increase in birth defects has been observed with zidovudine. The prevalence of birth defects with first trimester zidovudine exposure was 2.8% (95% confidence interval, 1.8-4.1%) compared with total prevalence of birth defects in the U.S. population based on CDC surveillance of 3.1% *[6]*.

- Placental and breast milk passage

Zidovudine rapidly crosses the human placenta, achieving cord-to-maternal blood ratios of about 0.80. ZDV is excreted into human breast milk.

- Human studies in pregnancy

Zidovudine is well-tolerated in pregnancy at recommended adult doses and in the full-term neonate at 2 mg/per/kg body weight orally every 6 hours *[18, 22]*. Long-term data on the safety of *in utero* drug exposure in humans are not available for any antiretroviral drug; however, short-term data on the safety of zidovudine are reassuring. No difference in disease progression between women in PACTG 076 who received zidovudine and those who received placebo has been seen in follow-up through 4 years postpartum *[23]*. Infants with *in utero* zidovudine exposure followed for nearly 6 years have shown no significant differences from those who received placebo in immunologic, neurologic and growth parameters *[21, 24]*; follow-up of these infants is continuing.

## Issues Related to Use of Nucleoside Analogue Drugs and Mitochondrial Toxicity

Nucleoside analogue drugs are known to induce mitochondrial dysfunction, as the drugs have varying affinity for mitochondrial gamma DNA polymerase. This affinity can result in interference with mitochondrial replication, resulting in mitochondrial DNA depletion and dysfunction *[25]*. The relative potency of the nucleosides in inhibiting mitochondrial gamma DNA polymerase *in vitro* is highest for zalcitabine (ddC), followed by didanosine (ddI), stavudine (d4T), lamivudine (3TC), ZDV, and abacavir (ABC). Toxicity related to mitochondrial dysfunction has been reported in infected patients receiving long-term treatment with nucleoside analogues, and generally has resolved with discontinuation of the drug or drugs; a possible genetic susceptibility to these toxicities has been suggested *[26]*. These toxicities may be of particular concern for pregnant women and for infants with *in utero* exposure to nucleoside analogue drugs.

**Issues in Pregnancy:** Clinical disorders linked to mitochondrial toxicity include neuropathy, myopathy, cardiomyopathy, pancreatitis, hepatic steatosis, and lactic acidosis. Among these disorders, symptomatic lactic acidosis and hepatic steatosis may have a female preponderance *[27]*.

These syndromes have similarities to the rare but life-threatening syndromes of acute fatty liver of pregnancy and hemolysis, elevated liver enzymes and low platelets (the HELLP syndrome) that occur during the third trimester of pregnancy. A number of investigators have correlated these pregnancy-related disorders with a recessively-inherited mitochondrial abnormality in the fetus/infant that results in an inability to oxidize fatty acids *[28-30]*. Since the mother would be a heterozygotic carrier of the abnormal gene, there may be an increased risk of liver toxicity due to an inability to properly oxidize both maternal and accumulating fetal fatty acids *[31]*. Additionally, animal studies show that in late gestation pregnant mice have significant reductions (25%–50%) in mitochondrial fatty acid oxidation, and that exogeneously administered estradiol and progesterone can reproduce these effects *[32, 33]*; whether this can be translated to humans is unknown. However, these data suggest that a disorder of mitochondrial fatty acid oxidation in the mother or her fetus during late pregnancy may play a role in the etiology of acute fatty liver of pregnancy and HELLP syndrome, and possibly contribute to susceptibility to antiretroviral-associated mitochondrial toxicity.

Lactic acidosis with microvacuolar hepatic steatosis is a toxicity related to nucleoside analogue drugs that is thought to be related to mitochondrial toxicity; it has been reported in infected individuals treated with nucleoside analogue drugs for long periods of time (>6 months). Initially, most cases were associated with AZT, but subsequently other nucleoside analogue drugs have been associated with the syndrome, particularly d4T. In a report from the FDA Spontaneous Adverse Event Program of 106 individuals with this syndrome (60 in patients receiving combination and 46 receiving single nucleoside analogue therapy), typical initial symptoms included 1 to 6 weeks of nausea, vomiting, abdominal pain, dyspnea, and weakness *[27]*. Metabolic acidosis with elevated serum lactate and elevated hepatic enzymes was common. Patients in this report were predominantly female gender and high body weight. The incidence of this syndrome may be increasing, possibly due to increased use of combination nucleoside analogue therapy or increased recognition of the syndrome. In a cohort of infected patients receiving nucleoside analogue therapy followed at Johns Hopkins University between 1989 and 1994, the incidence of the hepatic steatosis syndrome was 0.13% per year *[34]*. However, in a report from a cohort of 964 HIV-infected individuals followed in France between 1997 and 1999, the incidence of symptomatic hyperlactatemia was 0.8% per year for all patients and 1.2% for patients receiving a regimen including d4T *[35]*.

The frequency of this syndrome in pregnant HIV-infected women receiving nucleoside analogue treatment is unknown. In 1999, Italian researchers reported a case of severe lactic acidosis in an infected pregnant woman who was receiving d4T/3TC at the time of conception and throughout pregnancy who presented with symptoms and fetal demise at 38 weeks gestation *[36]*. Bristol-Myers Squibb has reported three maternal deaths due to lactic acidosis, two with and one without accompanying pancreatitis, in women who were either pregnant or postpartum and whose antepartum therapy during pregnancy included d4T and ddI in combination with other antiretroviral agents (either a protease inhibitor or nevirapine) *[3, 4]*. All cases were in women who were receiving treatment with these agents at the time of conception and continued for the duration of pregnancy; all presented late in gestation with symptomatic disease that progressed to death in the immediate postpartum period. Two cases were also associated with fetal demise.

It is unclear if pregnancy augments the incidence of the lactic acidosis/hepatic steatosis syndrome reported in non-pregnant individuals receiving nucleoside analogue treatment. However, because pregnancy itself can mimic some of the early symptoms of the lactic acidosis/hepatic steatosis syndrome or be associated with other significant disorders of liver metabolism, these cases emphasize the need for physicians caring for HIV-infected pregnant women receiving nucleoside analogue drugs to be alert for early diagnosis of this syndrome. Pregnant women receiving nucleoside analogue drugs should have hepatic enzymes and electrolytes assessed more frequently during the last trimester of pregnancy, and any new symptoms should be evaluated thoroughly. Additionally, because of the reports of several cases of maternal mortality secondary to lactic acidosis with prolonged use of the combination of d4T and ddI by HIV-infected pregnant women, clinicians should prescribe this antiretroviral combination during pregnancy with caution and generally only when other nucleoside analogue drug combinations have failed or caused unacceptable toxicity or side effects.

**Issues with *In Utero* Exposure:** A French group reported eight cases of uninfected infants with *in utero* and/or neonatal exposure to either ZDV/3TC (four infants) or ZDV alone (four infants) who developed indications of mitochondrial dysfunction after the first few months of life *[35]*. Two of these infants developed severe neurologic disease and died (both of whom had been exposed to ZDV/3TC), three had mild to moderate symptoms, and three had no symptoms but had transient laboratory abnormalities. It is important to note that an association between these findings and *in utero* exposure to antiretroviral drugs has not been established.

In infants followed through age 18 months in PACTG 076, the occurrence of neurologic events was rare — seizures occurred in one child exposed to ZDV and two exposed to placebo, and one child in each group had reported spasticity; mortality at 18 months was 1.4% in ZDV-exposed compared to 3.5% in placebo infants *[21]*. The Perinatal Safety Review Working Group performed a retrospective review of deaths occurring among children born to HIV-1-infected women and followed during 1986-1999 in five large prospective U.S. perinatal cohorts. No deaths similar to those reported from France or with clinical findings attributable to mitochondrial dysfunction were identified in a database of >16,000 uninfected children born to HIV-1-infected women with and without antiretroviral drug exposure *[37]*. However, most of the infants with antiretroviral exposure had been exposed to ZDV alone and only a relatively small proportion (approximately 6%) had been exposed to ZDV-3TC. In an African perinatal trial (PETRA) that compared three regimens of ZDV-3TC (during pregnancy starting at 36 weeks' gestation, during labor, and through 1 week postpartum; during labor and postpartum; and during labor only) with placebo for prevention of transmission, data have been reviewed relating to neurologic adverse events among 1,798 children who participated. No increased risk of neurologic events was observed among children treated with ZDV-3TC compared with placebo, regardless of the intensity of treatment *[38]*. Finally, in a study of 382 uninfected infants born to HIV-1-infected women, echocardiograms were prospectively performed every 4 to 6 months during the first 5 years of life; 9% of infants had been exposed to ZDV prenatally *[39]*. No significant differences in ventricular function were observed between infants exposed and not exposed to ZDV.

Even if the association of mitochondrial dysfunction and *in utero* antiretroviral exposures is demonstrated, the development of severe or fatal mitochondrial disease in these infants appears to be extremely rare and should be compared against the clear benefit of ZDV in reducing transmission of a fatal infection by nearly 70% *[40]*. These data emphasize the importance of the existing Public Health Service recommendation for long-term follow-up for any child with in utero exposure to antiretroviral drugs.

# NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

**Delavirdine (Rescriptor®)** is classified as FDA pregnancy category C.

- Animal carcinogenicity studies
  Long-term animal carcinogenicity studies with delavirdine in rodents are not completed; *in vitro* screening tests have been negative.

- Reproduction/fertility
  Delavirdine does not impair fertility in rodents. Teratogenicity/developmental toxicity animal studies: Delavirdine is teratogenic in rats; doses of 50 to 200 mg/kg/day during organogenesis caused ventricular septal defects. Exposure of rats to doses approximately 5 times human therapeutic exposure resulted in marked maternal toxicity, embryotoxicity, fetal developmental delay, and reduced pup survival.

Abortions, embryotoxicity, and maternal toxicity were observed in rabbits at doses approximately 6 times human therapeutic exposure.

- Placental and breast milk passage
  Whether delavirdine crosses the placenta is unknown. Delavirdine is excreted in the milk of lactating rats; however, it is unknown if the drug is excreted in human breast milk.

- Human studies in pregnancy
  Delavirdine has not been evaluated in HIV-infected pregnant women. In premarketing clinical studies, the outcomes of seven unplanned pregnancies were reported: three resulted in ectopic pregnancies, three resulted in healthy live births, and one infant was born prematurely with a small muscular ventricular septal defect to a patient who received approximately 6 weeks of treatment with delavirdine and zidovudine early in the course of pregnancy.

**Efavirenz (Sustiva®)** is FDA pregnancy category C.

- Animal carcinogenicity studies
  Long-term animal carcinogenicity studies with efavirenz in rats and mice are not completed; *in vitro* screening tests have been negative.

- Reproduction/fertility
  No effect of efavirenz on reproduction or fertility in rodents has been seen. An increase in fetal resorptions has been observed in rats at doses comparable to or lower than those used to achieve human therapeutic exposure.

- Teratogenicity/developmental toxicity
  Significant central nervous system malformations were observed in 3 of 20 infants born to pregnant cynomolgus monkeys receiving efavirenz from gestational days 20 to 150 at a dose of 30 mg/kg twice daily (resulting in plasma concentrations comparable to systemic human therapeutic exposure) *[41]*. The malformations included anencephaly and unilateral anophthalmia in one; microphthalmia in another; and cleft palate in the third. Primate teratogenicity studies have not been conducted for delavirdine or nevirapine.

- Placental and breast milk passage
  Efavirenz crosses the placenta in rats, rabbits, and primates, producing cord blood concentrations similar to concentrations in maternal plasma. It is unknown whether efavirenz is excreted in human breast milk.

- Human studies in pregnancy
  No clinical trials with efavirenz in pregnant humans are planned. There has been a case report of myelomeningocele in a human infant born to a woman who was receiving efavirenz at the time of conception and during the first trimester *[42, 43]*. Because of the potential for teratogenicity, pregnancy should be avoided in women receiving efavirenz. It should be noted that non-nucleoside reverse transcriptase inhibitors like nevirapine and efavirenz as well as the protease inhibitors may affect estrogen and/or norethindrone blood concentrations in women receiving oral contraceptives; additional or alternative contraception should be used by women using oral contraceptives who are receiving these antiretroviral agents. There are insufficient data on drug interactions with injectable hormones (DEPO-PROVERA) to make recommendations regarding the need for additional contraception. Theoretically, since hormone levels are much higher with injectable than oral contraceptives, interactions with antiretroviral drugs may be less significant.

**Nevirapine (Viramune®)** is FDA pregnancy category C.

- Animal carcinogenicity studies
  Long-term animal carcinogenicity studies with nevirapine in rats and mice are not completed; *in vitro* screening tests have been negative.

- Reproduction/fertility
  Evidence of impaired fertility was seen in female rats at nevirapine doses providing systemic exposure comparable to human therapeutic exposure.

- Teratogenicity/developmental toxicity
  Teratogenic effects of nevirapine have not been observed in reproductive studies with rats and rabbits. In rats, however, a significant decrease in fetal weight occurred at doses producing systemic concentrations approximately 50% higher than human therapeutic exposure.

  In the Antiretroviral Pregnancy Registry, sufficient numbers of first trimester exposure to nevirapine in humans have been monitored to be able to detect at least a two-fold increase in risk of overall birth defects and those in the more common classes, cardiovascular and genitourinary systems. No such increase in birth defects has been observed with nevirapine. The prevalence of birth defects with first trimester nevirapine exposure was 2.0% (95% confidence interval, 0.7-4.7%) compared with total prevalence of birth defects in the U.S. population based on CDC surveillance of 3.1% *[6]*.

- Placental and breast milk passage
Nevirapine crosses the placenta and achieves neonatal blood concentrations equivalent to that in the mother (cord-to-maternal blood ratio approximately 0.90) *[44]*. Nevirapine is excreted into human breast milk; the median concentration in four breast milk samples obtained from three women during the first week after delivery was approximately 76% (range 54 to 104%) of serum levels *[44]*.

- Human studies in pregnancy
A phase I study (PACTG 250) evaluated the safety and pharmacokinetics of nevirapine, administered to infected pregnant women as a single 200 mg dose at the onset of labor and as a single 2 mg/kg dose to the infant at age 48 to 72 hours *[44]*. No adverse effects were seen in the women or the infants. Pharmacokinetic parameters in pregnant women receiving intrapartum nevirapine were similar though somewhat more variable than in nonpregnant adults, possibly due to incomplete drug absorption associated with impaired gastrointestinal function during labor. Nevirapine elimination was prolonged in the infants. The regimen maintained serum concentrations associated with antiviral activity in the infants for the first week of life.

The safety, toxicity and pharmacokinetics of nevirapine were also studied in HIV-infected pregnant women beginning chronic therapy late in the third trimester and their infants *[45]*. Initial dose pharmacokinetic profiles in pregnant women were similar to those seen in non-pregnant adults. Serum nevirapine concentrations fell below the 100 ng/mL target concentration by day 7 of life in 4 of 8 infants, suggesting that nevirapine elimination was accelerated in infants whose mother received chronic nevirapine administration compared with newborns whose mothers received only a single intrapartum nevirapine dose.

The HIVNET 012 study in Uganda compared nevirapine (200 mg orally to the mother at the onset of labor and 2 mg/kg to the neonate within 72 hours of birth) with zidovudine (600 mg orally to the mother at the onset of delivery and 300 mg every 3 hours until delivery, and 4 mg/kg orally twice daily for the first 7 days of life to the neonate). In this study, nevirapine lowered the risk of HIV transmission by nearly 50% during the first 14–16 weeks of life compared with zidovudine *[46]*. However, the women in this African trial were not receiving any other antiretroviral therapy.

In the U.S., most infected women who know their HIV status during pregnancy receive combination antiretroviral therapy, usually including ZDV, as well as intravenous ZDV during delivery, with 6 weeks of ZDV given to their infant. A phase III perinatal trial (PACTG 316) conducted in the U.S., Europe, the Bahamas and Brazil evaluated whether the HIVNET 012 single-dose nevirapine regimen in combination with standard antiretroviral therapy (at minimum the PACTG 076 ZDV regimen; 77% of women in the trial received combination therapy) would provide additional benefits in reducing transmission. Transmission was not significantly different between those having the addition of single-dose nevirapine (1.4%) and those who did not (1.6%) *[47]*. Nevirapine resistance can be induced by a single mutation. Nevirapine resistance mutations were detected at 6 weeks postpartum in 19% of antiretroviral naïve women in HIVNET 012 and 15% of a subset of women receiving additional antiretroviral drugs during pregnancy in PACTG 316 who received single-dose nevirapine during labor *[40, 48]*. In HIVNET 012, these mutations were no longer detectable in plasma virus in women at 13-18 months postpartum *[38]*. Evaluation at later time points was not done in PACTG 316.

Severe, life-threatening, and in some cases, fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure, has been reported in HIV-infected patients receiving nevirapine in combination with other drugs for treatment of HIV disease and in a small number of individuals receiving nevirapine as part of a combination regimen for post-exposure prophylaxis of nosocomial or sexual HIV exposure *[49]*. These events have generally occurred during the first 12 weeks of therapy, and may present with non-specific prodromal signs or symptoms of hepatitis. This has not been reported in women or infants receiving two-dose nevirapine (the HIVNET 012 regimen) for prevention of perinatal transmission. Severe, life-threatening hypersensitivity skin reactions, including Stevens-Johnson syndrome, have been reported in HIV-infected individuals receiving nevirapine for treatment, usually during the first 12 weeks of therapy. This has not been reported with use of the HIVNET 012 two-dose nevirapine regimen.

# PROTEASE INHIBITORS

## Issues Related to the Use of Protease Inhibitors

### Hyperglycemia and Diabetes Mellitus

Hyperglycemia, new onset diabetes mellitus, exacerbation of existing diabetes mellitus, and diabetic ketoacidosis have been reported with administration of protease inhibitor antiretroviral drugs in HIV-infected patients *[50-53]*. In addition, pregnancy is itself a risk factor for hyperglycemia; it is unknown if the use of protease inhibitors will exacerbate the risk for pregnancy-associated hyperglycemia. Clinicians caring for HIV-infected pregnant women who are receiving protease inhibitor therapy should be aware of the risk of this complication, and closely monitor glucose levels. Symptoms of hyperglycemia should be discussed with pregnant women who are receiving protease inhibitors.

**Combination Therapy and Pregnancy Outcome:** There are limited data concerning combination antiretroviral therapy in pregnancy. A retrospective Swiss report evaluated the pregnancy outcome in 37 HIV-infected pregnant women treated with combination therapy; all received two reverse transcriptase inhibitors and 16 received one or two protease inhibitors *[54]*. Almost 80% of women developed one or more typical adverse effects of the drugs such as anemia, nausea/vomiting, aminotransferase elevation, or hyperglycemia. A possible association of combination antiretroviral therapy with preterm births was noted, as 10 of 30 babies were born prematurely. The preterm birth rate did not differ between women receiving combination therapy with or without protease inhibitors. The contribution of maternal HIV disease stage and other covariates that might be associated with a risk for prematurity were not assessed. Furthermore, some studies have shown elevated preterm birth rates in HIV-infected women who have not received any antiretroviral therapy *[55-57]*.

The European Collaborative Study and the Swiss Mother + Child HIV-1 Cohort Study investigated the effects of combination retroviral therapy in a population of 3,920 mother - child pairs. Adjusting for $CD4^+$ T-lymphocyte count ($CD4^+$ count) and intravenous drug use, they found a 2.6-fold (95% confidence interval [CI] = 1.4 - 4.8) increased odds of preterm delivery for infants exposed to combination therapy with or without protease inhibitors compared with no treatment; women receiving combination therapy that had been initiated before their pregnancy were twice as likely to deliver prematurely as those starting therapy during the third trimester *[58]*. However, combination therapy was received by only 323 (8%) women studied. Exposure to monotherapy was not associated with prematurity.

In contrast, in a French open-label study of 445 HIV-1-infected women receiving ZDV who had lamivudine (3TC) added to their therapy at 32 weeks' gestation, the rate of preterm delivery was 6%, similar to the 9% rate in a historical control group of women receiving only ZDV *[59]*. Additionally, in a large meta-analysis of seven clinical studies that included 2,123 HIV-infected pregnant women who delivered infants during 1990-1998 and had received antenatal antiretroviral therapy and 1,143 women who did not receive antenatal antiretroviral therapy, use of multiple antiretroviral drugs as compared with no treatment or treatment with one drug was not associated with increased rates of preterm labor, low birth weight, low Apgar scores, or stillbirth *[60]*.

Until more information is known, it is recommended that HIV-infected pregnant women who are receiving combination therapy for treatment of their HIV infection should continue their provider-recommended regimen. They should receive careful, regular monitoring for pregnancy complications and for potential toxicities.

## Individual Agents: Protease Inhibitors

Phase I studies of four of the approved protease inhibitors (indinavir, ritonavir, nelfinavir and saquinavir soft gel capsule in combination with ZDV and 3TC) in pregnant HIV-infected women and their infants are ongoing in the United States. However, complete data are not yet available regarding drug dosage, safety, and tolerance of the protease inhibitors in pregnancy or in neonates. Amprenavir and lopinavir/ritonavir (Kaletra™), two more recently approved protease inhibitors, have not yet been studied in pregnant women or neonates.

**Amprenavir (Agenerase®)** is classified as FDA pregnancy category C.

- Animal carcinogenicity studies
  Long-term animal carcinogenicity studies of amprenavir in rats and mice are not completed; *in vitro* screening tests have been negative.

- Reproduction/fertility
  No effect has been seen on reproductive performance, fertility, or embryo survival in rats at exposures about twice those of human therapeutic exposure.

- Teratogenicity/developmental toxicity
  In pregnant rabbits, administration of amprenavir resulting in systemic exposures about one-twentieth of that observed with human therapeutic exposure was associated with abortions and an increased incidence of minor skeletal variations resulting from deficient ossification of the femur, humerus trochlea and humerus. In rat fetuses, thymic elongation and incomplete ossification of bones were also attributed to amprenavir at systemic exposures about one-half that associated with the recommended human dose. Reduced body weights of approximately 10–20% were observed in offspring of rodents administered amprenavir from day 7 of gestation to day 22 of lactation (exposures approximately twice that observed with the human therapeutic dose). However, the subsequent development of the offspring, including fertility and reproductive performance, was not affected by maternal administration of amprenavir.

- Placental and breast milk passage
  Whether amprenavir crosses the placenta is unknown. Amprenavir is excreted in the milk of lactating rats; it is not known if it is excreted in human milk.

- Human studies in pregnancy
  There have been no studies of amprenavir in pregnant women or neonates. Amprenavir oral solution contains high levels of excipient propylene glycol in the oral solution vehicle; this is not true for the capsular formulation. Propylene glycol is metabolized by the alcohol and aldehyde dehydrogenase enzyme pathway. Some patients, including infants and children below the age of four years, pregnant women, patients with hepatic or renal failure, and patients treated with disulfiram or metronidazole, are not able to adequately metabolize and eliminate propylene glycol, thereby leading to its accumulation and potential adverse events. Thus, while the capsule formulation of amprenavir may be used in pregnancy, amprenavir oral solution is contraindicated in pregnant women and infants and in children under the age of four years.

**Indinavir (Crixivan®)** is classified as FDA pregnancy category C.

- Animal carcinogenicity studies
  Long-term animal carcinogenicity studies with indinavir in rats and mice are not completed; *in vitro* screening tests have been negative.

- Reproduction/fertility
  No effect of indinavir has been seen on reproductive performance, fertility, or embryo survival in rats.

- Teratogenicity/developmental toxicity
  There has been no evidence of teratogenicity of indinavir in rats, rabbits or dogs. In rats, developmental toxicity manifested by an increase in supernumerary and cervical ribs was observed at doses comparable to those administered to humans. No treatment-related external, visceral or skeletal changes were seen in rabbits (fetal exposure limited, approximately 2% of maternal levels) or dogs (fetal exposure approximately 50% of maternal levels). Indinavir was administered to Rhesus monkeys during the third trimester of pregnancy (at doses up to 160 mg/kg twice daily) and to neonatal Rhesus monkeys (at doses up to 160 mg/kg twice daily). When administered to neonates, indinavir caused an exacerbation of the transient physiologic hyperbilirubinemia seen in this species after birth; serum bilirubin values were approximately fourfold above controls at 160 mg/kg twice daily. A similar exacerbation did not occur in neonates after *in utero* exposure to indinavir during the third trimester of pregnancy. In Rhesus monkeys, fetal plasma drug levels were approximately 1–2% of maternal plasma drug levels approximately 1 hour after maternal dosing at 40, 80, or 160 mg/kg twice daily.

- Placental and breast milk passage
  Significant placental passage of indinavir occurs in rats and dogs, but only limited placental transfer occurs in rabbits. In a phase I study in pregnant women and their infants (PACTG 358, see below), transplacental passage of indinavir was minimal *[61]*. Additionally, in a study of cord blood samples from 21 women treated with indinavir during pregnancy, the cord blood concentration of indinavir was below the assay limit of detection in samples from all women *[62]*. Indinavir is excreted in the milk of lactating rats at concentrations slightly above maternal levels (milk-to-plasma ratio 1.26 to 1.45); it is not known if indinavir is excreted in human milk.

- Human studies in pregnancy:
  A phase I/II safety and pharmacokinetic study (PACTG 358) of indinavir (800 mg tid) in combination with ZDV and lamivudine in pregnant HIV-infected women and their infants is being conducted (the infants do not receive indinavir in this study). Preliminary data are available from five women and infants *[61]*. One woman discontinued indinavir due to nausea and vomiting; adverse effects in the women included one case of moderately severe hyperbilirubinemia and one case of flank pain without renal stones, both of which resolved spontaneously and did not require drug discontinuation. Pharmacokinetic data from three women indicate that the plasma area under the curve (AUC) indinavir level was lower during pregnancy than postpartum or than observed in non-pregnant HIV-infected individuals. However, HIV RNA levels in the four women who completed the study decreased to undetectable levels (<400 copies/mL) prior to delivery and CD4 cell number and percentage significantly increased. The median gestational age of the five infants was 39 weeks (range 36–39 weeks). In a pharmacokinetic study of two pregnant HIV-infected women receiving combination therapy including indinavir (800 mg tid), a marked difference was noted between the AUC indinavir exposure between the third trimester and postpartum evaluations *[63]*. The AUC during the third trimester was reduced by 63% in one and 86% in the other woman when compared to 9–12 week postpartum evaluations in the same women. Similar reductions in maximum plasma indinavir concentrations were observed.

**Lopinavir + Ritonavir (Kaletra™ )** is classified as FDA pregnancy category C.

- Animal carcinogenicity studies
  Long-term animal carcinogenicity screening studies of lopinavir + ritonavir in animal systems are not completed. *In vitro* mutagenicity and clastogenicity screening tests are negative for both lopinavir and ritonavir.

  Carcinogenicity studies in mice and rats have been carried out for ritonavir. In male mice, at levels of 50, 100 or 200 mg/kg/day, a dose-dependent increase in liver adenomas and combined adenomas and carcinomas was observed; based on AUC, exposure in male mice at the highest dose was approximately fourfold that in male humans at the recommended therapeutic dose (400 mg lopinavir/100 mg ritonavir bid). No carcinogenic effects were observed in female mice with exposures ninefold that of female humans at the recommended therapeutic dose. No carcinogenic effects were observed in rats at exposures up to 0.7-fold that of humans at the recommended therapeutic dose.

- Reproduction/fertility
  Lopinavir in combination with ritonavir at a 2:1 ratio produced no effects on fertility in male and female rats with exposures approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir of the exposures in humans at the recommended therapeutic dose.

- Teratogenicity/developmental toxicity
  There has been no evidence of teratogenicity with administration of lopinavir + ritonavir to pregnant in rats or rabbits. In rats treated with maternally toxic dosage (100 mg lopinavir/50 mg ritonavir/kg/day), embryonic and fetal developmental toxicities (early resorption, decreased fetal viability, decreased fetal body weight, increased incidence of skeletal variations and skeletal ossification delays) were observed; drug exposure in the pregnant rats was 0.7-fold for lopinavir and 1.8-fold for ritonavir of the exposures in humans at the recommended therapeutic dose. In a peri- and postnatal study in rats, a decrease in survival of pups between birth and postnatal day 21 occurred with exposures of 40 mg lopinavir/20 mg ritonavir/kg/day or greater. In rabbits, no embryonic or fetal developmental toxicities were observed with maternally toxic dosage, where drug exposure was 0.6-fold for lopinavir and 1.0-fold for ritonavir of the exposures in humans at recommended therapeutic dose.

- Placental and breast milk passage
  Data on placental passage of lopinavir in animals are not available. For ritonavir, data in humans indicates only minimal transplacental passage (see Ritonavir). Lopinavir and ritonavir are secreted in the breast milk of lactating rats; it is not known if either drug is excreted in human milk.

- Human studies in pregnancy
  No studies of lopinavir in human pregnancies have been conducted. A phase I/II safety and pharmacokinetic study of ritonavir given at therapeutic doses (600 mg bid) in combination with ZDV and lamivudine in pregnant HIV-infected women and their infants (PACTG 354) is being conducted but complete data are not yet available; preliminary data indicate that there is minimal, if any, placental passage of ritonavir in humans.

**Nelfinavir (Viracept®)** is classified as FDA pregnancy category B.

- Animal carcinogenicity studies
  Long-term animal carcinogenicity studies of nelfinavir in rats and mice are not completed; *in vitro* screening tests have been negative.

- Reproduction/fertility
  No effect of nelfinavir has been seen on reproductive performance, fertility, or embryo survival in rats at exposures comparable to human therapeutic exposure.

- Teratogenicity/developmental toxicity
  No evidence of teratogenicity has been observed in pregnant rats and rabbits. Developmental toxicity, consisting of small increase in neonatal mortality and minor skeletal ossification delay, occurred at the highest dose in rats. In the Antiretroviral Pregnancy Registry, sufficient numbers of first trimester exposures to nelfinavir have been monitored to be able to detect at least a two-fold increase in risk of overall birth defects and those in the more common classes, cardiovascular and genitourinary systems. No such increase in birth defects has been observed with nelfinavir. The prevalence of birth defects with first trimester nelfinavir exposure was 2.9% (95% confidence interval, 1.4-5.3%) compared with total prevalence of birth defects in the U.S. population based on CDC surveillance of 3.1% *[6]*.

- Placental and breast milk transfer
  In a phase I study in pregnant women and their infants (PACTG 353, see below), transplacental passage of nelfinavir was minimal *[64]*. Additionally, in a study of cord blood samples from 38 women who were treated with nelfinavir during pregnancy, the cord blood nelfinavir concentration was below the assay limit of detection in 24 (63%), and the cord blood concentration was low (median, 0.35 ug/mL) in the remaining 14 women *[62]*. Nelfinavir is excreted in the milk of lactating rats; it is not known if it is excreted in human milk.

- Human studies in pregnancy
  A phase I/II safety and pharmacokinetic study (PACTG 353) of nelfinavir in combination with ZDV and lamivudine in pregnant HIV-infected women and their infants was conducted *[64]*. Nelfinavir administered at a dose of 750 mg tid produced drug exposures in the first nine pregnant HIV-infected women enrolled in the study that were variable and generally lower than those reported in non-pregnant adults for both tid and bid dosing. Therefore, the study was modified to evaluate an increased dose of nelfinavir given twice daily, 1250 mg bid, which resulted in adequate levels of nelfinavir in pregnancy.

**Ritonavir (Norvir®)** is classified as FDA pregnancy category B.

- Animal carcinogenicity studies
  *In vitro* mutagenicity and clastogenicity screening tests are negative for ritonavir. Carcinogenicity studies in mice and rats have been completed. In male mice, at levels of 50, 100 or 200 mg/kg/day, a dose-dependent increase in liver adenomas and combined adenomas and carcinomas was observed; based on AUC, exposure in male mice at the highest dose was approximately fourfold that in male humans at the recommended therapeutic dose (400 mg lopinavir/100 mg ritonavir bid). No carcinogenic effects were observed in female mice with exposures ninefold that of female humans at the recommended therapeutic dose. No carcinogenic effects were observed in rats at exposures up to 0.7-fold that of humans at the recommended therapeutic dose.

- Reproduction/fertility
  No effect of ritonavir has been seen on reproductive performance or fertility in rats at drug exposures 40% (male) and 60% (female) of that achieved with human therapeutic dosing; higher doses were not feasible due to hepatic toxicity in the rodents.

- Teratogenicity/developmental toxicity
  No ritonavir-related teratogenicity has been observed in rats or rabbits. Developmental toxicity was observed in rats, including early resorptions, decreased body weight, ossification delays, and developmental variations such as wavy ribs and enlarged fontanelles; however, these effects occurred only at maternally toxic dosages (exposure equivalent to 30% of human therapeutic exposure). In addition, a slight increase in cryptorchidism was also noted in rats at exposures equivalent to 22% of the human therapeutic dose. In rabbits, developmental toxicity (resorptions, decreased litter size, and decreased fetal weight) was observed only at maternally toxic doses (1.8 times human therapeutic exposure).

- Placental and breast milk transfer
  Transplacental passage of ritonavir has been observed in rats with fetal tissue to maternal serum ratios >1.0 at 24 hours post-dose in mid- and late-gestation fetuses. In a human placental perfusion model, the clearance index of ritonavir was very low, with little

accumulation in the fetal compartment and no accumulation in placental tissue *[65]*. In a phase I study in pregnant women and their infants (PACTG 354, see below), transplacental passage of ritonavir was minimal *[66]*. Additionally, in a study of cord blood samples from 6 women treated with ritonavir during pregnancy, the cord blood concentration was below the assay limit of detection in 83%, and was only 0.38 *u*g/mL in the remaining woman *[62]*. Ritonavir is excreted in the milk of lactating rats; it is unknown if it is excreted in human milk.

- <u>Human studies in pregnancy</u>
  A phase I/II safety and pharmacokinetic study (PACTG 354) of ritonavir in combination with zidovudine and lamivudine in pregnant HIV-infected women and their infants is being conducted, but complete data are not yet available. Preliminary data indicate minimal, if any, placental passage of ritonavir.

**Saquinavir (Invirase® [Hard Gel Capsule]/Fortavase® [Soft Gel Capsule])** is classified as FDA pregnancy category B.

- <u>Animal carcinogenicity studies</u>
  Long-term animal carcinogenicity studies of saquinavir in rats and mice are not completed; *in vitro* screening tests have been negative.

- <u>Reproduction/fertility</u>
  No effect of saquinavir has been seen on reproductive performance, fertility, or embryo survival in rats. Administration of low doses of saquinavir to newborn rats was associated with gastrointestinal toxicity, including inflammation at the rectoanal junction and red anal fluid; mortality was seen at very high doses (1200 mg/kg/day).

- <u>Teratogenicity/developmental toxicity</u>
  No evidence for embryotoxicity or teratogenicity of saquinavir has been found in animal studies.

- <u>Placental and breast milk transfer</u>
  Placental transfer of saquinavir in the rat and rabbit was minimal. In a phase I study in pregnant women and their infants (PACTG 386, see below), transplacental passage of saquinavir was minimal *[67]*. Additionally, in a study of cord blood samples from 8 women treated with saquinavir during pregnancy, the cord blood concentration of saquinavir was below the assay limit of detection in samples from all women *[62]*. Saquinavir is excreted in the milk of lactating rats; it is not known if it is excreted in human milk.

- <u>Human studies in pregnancy</u>
  A phase I/II safety and pharmacokinetic study (PACTG 386) of saquinavir in combination with ZDV and lamivudine in pregnant HIV-infected women and their infants was conducted. The standard adult dose of saquinavir (1200 mg TID) was not sufficient to produce adequate drug levels in the first four pregnant HIV-infected women enrolled in the study compared to those obtained with standard dosing in non-pregnant adults. Thus, the study was modified to evaluate the combination of saquinavir (800 mg) plus ritonavir (100 mg), both administered BID. This regimen was well-tolerated and achieved adequate saquinavir levels in the women *[67, 68]*.

## FUSION INHIBITORS

Enfuvirtide is the first of the fusion inhibitor class of antiretroviral drugs; these drugs inhibit binding or fusion of HIV to host target cells. This drug requires subcutaneous administration. Binding of the viral envelope glycoprotein gp120 to the $CD4^+$ receptor induces conformational changes that enable gp120 to interact with a chemokine receptor on the host cell; binding of gp120 to the coreceptor causes subsequent conformational changes in the viral transmembrane glycoprotein gp41, exposing the “fusion peptide” of gp41, which inserts into the cell membrane. A helical region of gp41, called HR1, then interacts with a similar helical region, HR2, on gp41, resulting in a “zipping” together of the two helices and mediating the fusion of cellular and viral membranes. Enfuvirtide is a synthetic 36 amino acid peptide derived from a naturally occurring motif within the HR2 domain of viral gp41. As a molecular mimic of the HR2 region, the drug binds to the HR1 region, preventing the HR1-HR2 interaction and correct folding of gp41 into its secondary structure, thereby inhibiting virus-cell fusion. Enfurvirtide (T-20) was approved in March 2003 for HIV-infected adults and children 6 years or older for use in combination with other antiretroviral drugs for the treatment of HIV infection in treatment-experienced patients with evidence of HIV replication despite ongoing antiretroviral therapy.

**Enfuvirtide (Fuzeon, T-20 )** is classified as FDA pregnancy category B.

- <u>Animal carcinogenicity studies</u>
  Long-term animal carcinogenicity studies of enfuvirtide have not been conducted. Enfuvirtide was neither mutagenic or clastogenic in a series of *in vitro* and animal *in vivo* screening tests.

- Reproduction/fertility
  Reproductive toxicity has been evaluated in rats and rabbits. Enfuvirtide produced no adverse effects on fertility of male or female rats at doses up 30 mg/kg/day administered subcutaneously (1.6 times the maximum recommended adult human daily dose on a $mg/m^2$ basis).

- Teratogenicity/developmental toxicity
  Studies in rats and rabbits revealed no evidence of harm to the fetus from enfuvirtide administered in doses up to 27 times and 3.7 times, respectively, the adult human daily dose on a $mg/m^2$ basis.

- Placental and breast milk transfer
  Studies of radio-labeled enfuvirtide administered to lactating rats indicated radioactivity was present in the milk; however, it is not known if this reflected radio-labeled enfuvirtide or from radio-labeled metabolites (e.g., amino acid and peptide fragments) of enfuvirtide. It is not known if enfuvirtide crosses the human placenta or is excreted in human milk.

- Human studies in pregnancy
  No studies of enfuvirtide have been conducted in pregnant women or neonates.

## MISCELLANEOUS AGENTS

**Hydroxyurea** is classified as FDA pregnancy category D.

Hydroxyurea is a cytotoxic and antimitotic agent that inhibits DNA synthesis and has been used for treatment of myeloproliferative disorders and sickle cell anemia. It has recently been studied for treatment of HIV disease in combination with nucleoside analogue antiretroviral agents. By inhibiting ribonucleotide reductase, it depletes the pool of deoxynucleoside triphosphates, particularly dATP, thereby potentiating the incorporation of the nucleoside analogue drugs into viral DNA and increasing their antiretroviral effect. However, the drug has significant toxicities and its role in HIV therapy is not well defined.

- Animal carcinogenicity studies and human data
  Hydroxyurea is genotoxic in a wide range of *in vitro* and *in vivo* animal test systems, causes cellular transformation to a tumorigenic phenotype, and is a transspecies carcinogen, which implies a potential carcinogenic risk to humans. Conventional long-term animal carcinogenicity studies have not been performed. However, intraperitoneal administration of 125 to 250 mg/kg of hydroxyurea (approximately 0.6 to 1.2 times the maximum recommended human oral dose on a $mg/m^2$ basis) three times weekly for 6 months to female rats increased the incidence of mammary tumors in rats surviving to 18 months compared to controls.

  In humans receiving long-term hydroxyurea for myeloproliferative disorders such as polycythemia vera, secondary leukemias have been reported. It is unknown whether this leukemogenic effect is secondary to hydroxyurea or is associated with the patients' underlying disease. Skin cancer has also been reported in patients receiving long-term therapy.

- Reproduction/fertility
  Hydroxyurea administered to male rats at doses of 60 mg/kg/day (about 0.3 times the maximum recommended human daily dose on a $mg/m^2$ basis) produced testicular atrophy, decreased spermatogenesis, and significantly reduced their ability to impregnate females.

- Teratogenicity/developmental toxicity
  Potent teratogenic effects have been observed in all animal species tested, with defects reported in multiple organ systems *[69-75]*. Administration of hydroxyurea to pregnant rats at doses as low as 180 mg/kg/day (about 0.8 times the maximum recommended human daily dose on a $mg/m^2$ basis) and pregnant rabbits at 30 mg/kg/day (about 0.3 times the maximum recommended human daily dose on a $mg/m^2$ basis) was associated with embryotoxicity and fetal malformations. In pregnant rats administered doses ranging from 185 to 1000 mg/kg body weight, fetal defects that have been observed include central nervous system, cardiovascular, ocular, craniofacial, and skeletal anomalies, limb deformities, and diaphragmatic hernia, with the pattern of defects dependent on gestational day of exposure *[69, 72, 73]*. Exposure early in gestation was associated with embryo death in a large percentage of cases. In pregnant rats, single doses of 375 mg/kg body weight or more (about 1.7 times the maximum recommended human daily dose on a $mg/m^2$ basis), were associated with growth retardation and impaired learning ability in their offspring. In hamsters, neural tube defects and cardiovascular abnormalities were produced after a 50 mg dose of hydroxyurea was given intravenously *[70]*. In pregnant rhesus monkeys administered a cumulative dose greater than 500 mg/kg body weight, multiple skeletal, genitourinary, cardiac, and ocular anomalies were found in their offspring *[72]*. Teratogenicity was

also demonstrated in pregnant cats given a single oral dose of 50 or 100 mg/kg body weight *[71]*.

- Placental and breast milk passage
  Hydroxyurea has been shown to cross the placenta in animals.

- Placental and breast milk passage
  Hydroxyurea is excreted in human milk *[76]*.

- Human studies in pregnancy
  Published reports of hydroxyurea during human pregnancy include 16 women, all treated for primary hematologic illnesses (e.g., chronic myeloid leukemia, sickle cell anemia, primary thrombocytopenia) *[77]*. Doses ranged from 0.5 to 3 g/day and 13 women had first trimester exposure. No fetal anomalies were seen and normal pregnancy outcomes were reported, except for one stillbirth with eclampsia at 26 weeks gestation and four elective pregnancy terminations.

Because of concerns raised by the significant anomalies seen in multiple animal species exposed to hydroxyurea and limited human information, as well as the uncertain role of hydroxyurea in HIV therapy, hydroxyurea use as an antiretroviral regimen component should be avoided during pregnancy. Clinicians should counsel women of childbearing potential about potential risks of teratogenicity if they are treated with hydroxyurea and become pregnant, and encouraged to use effective contraception and avoid becoming pregnant while being treated with hydroxyurea.

## ANTIRETROVIRAL PREGNANCY REGISTRY

The Antiretroviral Pregnancy Registry is an epidemiologic project to collect observational, nonexperimental data on antiretroviral exposure during pregnancy for the purpose of assessing the potential teratogenicity of these drugs. Registry data will be used to supplement animal toxicology studies and assist clinicians in weighing the potential risks and benefits of treatment for individual patients. The registry is a collaborative project of the pharmaceutical manufacturers with an advisory committee of obstetric and pediatric practitioners.
It is strongly recommended that health care providers who are treating HIV-1-infected pregnant women and their newborns report cases of prenatal exposure to antiretroviral drugs (either alone or in combination) to the Antiretroviral Pregnancy Registry. The registry does not use patient names, and birth outcome follow-up is obtained by registry staff from the reporting physician.

**Referrals should be directed to**
**Antiretroviral Pregnancy Registry**
**Research Park**
**1011 Ashes Drive**
**Wilmington, NC  28405**
**Telephone: 1–800–258–4263**
**Fax: 1–800–800–1052**
**Internet access** www.APRegistry.com**.**

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