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

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Summary

The availability of an increasing number of antiretroviral agents and the rapid evolution of new information has introduced extraordinary complexity into the treatment of HIV-infected persons. 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 the clinical management of HIV-infected adults and adolescents.

This report recommends that care should be supervised by an expert, and makes recommendations for laboratory monitoring including plasma HIV RNA, CD4 cell counts and HIV drug resistance testing. The report also provides guidelines for antiretroviral therapy, including when to start treatment, what drugs to initiate, when to change therapy, and therapeutic options when changing therapy. Special considerations are provided for adolescents and pregnant women. As with treatment of other chronic conditions, therapeutic decisions require a mutual understanding between the patient and the health care provider regarding the benefits and risks of treatment. Antiretroviral regimens are complex, have major side effects, pose difficulty with adherence, and carry serious potential consequences from the development of viral resistance due to non-adherence to the drug regimen or suboptimal levels of antiretroviral agents. Patient education and involvement in therapeutic decisions is important for all medical conditions, but is considered especially critical for HIV infection and its treatment.

With regard to specific recommendations, treatment should be offered to all patients with the acute HIV syndrome, those within six months of HIV seroconversion, and all patients with symptoms ascribed to HIV infection. Recommendations for offering antiretroviral therapy in asymptomatic patients require analysis of many real and potential risks and benefits. In general, treatment should be offered to individuals with fewer than 350 $CD4^+$ T cells/mm^3 or plasma HIV RNA levels exceeding 30,000 copies/mL (bDNA assay) or 55,000 copies/mL (RT-PCR assay). The strength of the recommendation to treat asymptomatic patients should be based on the willingness and readiness of the individual to begin therapy; the degree of existing immunodeficiency as determined by the $CD4^+$ T cell count; the risk of 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 asymptomatic individuals; and the likelihood, after counseling and education, of adherence to the prescribed treatment regimen. Once the decision has been made to initiate antiretroviral therapy, the goals should be maximal and durable suppression of viral load, restoration and/or preservation of immunologic function, improvement of quality of life, and reduction of HIV-related morbidity and mortality. Results of therapy are evaluated primarily with plasma HIV RNA levels; these are expected to show a one-$\log_{10}$ decrease at eight weeks and no detectable virus (<50 copies/mL) at 4-6 months after initiation of treatment. Failure of therapy at 4-6 months may be ascribed to non-adherence, 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. Optimal changes in therapy may be especially difficult to achieve for patients in whom the preferred regimen has failed, due to limitations in the available alternative antiretroviral regimens that have documented efficacy; these decisions are further confounded by problems with adherence, toxicity, and resistance. In some settings it

may be preferable to participate in a clinical trial with or without access to new drugs or to use a regimen that may not achieve complete suppression of viral replication.

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 **HIV/AIDS Treatment Information Service website** (http://www.hivatis.org).

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

Introduction

This document was developed by the Panel on Clinical Practices for Treatment of HIV Infection convened by the Department of Health and Human Services (DHHS) and the Henry J. Kaiser Family Foundation. The document contains recommendations for the clinical use of antiretroviral agents in the treatment of HIV-infected adults and adolescents (defined here as late puberty or Tanner V). Guidance for the use of antiretroviral treatment in pediatric HIV infection is not contained in this document. While the pathogenesis of HIV infection and the general virologic and immunologic principles underlying the use of antiretroviral therapy are similar for all HIV-infected individuals, there are unique therapeutic and management considerations in HIV-infected children. In recognition of these differences, a separate document addresses pediatric-specific issues related to antiretroviral therapy, and is available at (**http://www.hivatis.org**).

These guidelines are intended for use by clinicians and other health care providers who use antiretroviral therapy to treat HIV-infected adults and adolescents and serve as a companion to the therapeutic principles formulated by the National Institutes of Health (NIH) Panel to Define Principles of Therapy of HIV Infection *(1)*. Together the documents should provide the pathogenesis-based rationale for therapeutic strategies as well as practical guidelines for implementing these strategies. While the guidelines represent the current state of knowledge regarding the use of antiretroviral agents, this is a rapidly evolving field of science, and the availability of new agents or new clinical data regarding the use of existing agents will result in changes in therapeutic options and preferences. Thus, in recognition of the need for frequent updates to this document, a subgroup of the Panel, the Antiretroviral Working Group, meets monthly to review new data; recommendations for changes in this document are then submitted to the Panel and incorporated as appropriate. Copies of this document and all updates are available from the HIV/AIDS Treatment Information Service-ATIS (1–800–448–0440; TTY 1–888–480–3739; Fax 301–519–6616) and on the ATIS Web site (**http://www.hivatis.org**). They are also available from the National Prevention Information Network (NPIN) Web site (**http://www.cdcnpin.org**). These recommendations are not intended to substitute for the judgment of a clinician who is an expert in the care of HIV-infected individuals. It is important to note that the Panel felt that, where possible, the treatment of HIV-infected patients should be directed by a clinician with extensive experience in the care of these patients. When this is not possible, it is important to have access to such expertise 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 on the 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, based on the opinion of the Panel, while the Roman numeral rating reflects the nature of the evidence supporting the recommendation (Table 1). Thus, recommendations based on data from clinical

trials with clinical endpoints are differentiated from those with laboratory endpoints such as $CD4^+$ T lymphocyte count or plasma HIV RNA levels; where no clinical trial data are available, recommendations are based on the opinions of experts familiar with the relevant scientific literature.

This document addresses the following issues: the use of testing for plasma HIV RNA levels (viral load) and $CD4^+$ T cell count; the use of testing for antiretroviral drug resistance; considerations for when to initiate therapy in established HIV infection; adherence to antiretroviral therapy; special considerations for therapy in patients with advanced stage disease; therapy-related adverse events; interruption of therapy; considerations for changing therapy and available therapeutic options; the treatment of acute HIV infection; considerations for antiretroviral therapy in adolescents; and considerations for antiretroviral therapy in the pregnant woman.

Use of Testing for Plasma HIV RNA Levels and $CD4^+$ T Cell Count in Guiding Decisions for 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, as well as the clinical condition of the patient. Results of these two laboratory tests give the physician important information about the virologic and immunologic status of the patient and the risk of disease progression to AIDS *(3, 4)*. It should be noted that HIV viral load testing has been approved by the FDA for determining prognosis and for monitoring the response to therapy only for the RT- PCR assay (Roche). Multiple analyses in over 5000 patients who participated in approximately 18 trials with viral load monitoring showed a statistically significant dose-response type association between decreases in plasma viremia and improved clinical outcome based on standard endpoints of new AIDS-defining diagnoses and survival. This relationship was observed over a range of patient baseline characteristics including: pretreatment plasma RNA level, $CD4^+$ T cell count, and prior drug experience. Thus, it is the consensus of the Panel that viral load testing is an essential parameter in decisions to initiate or change antiretroviral therapies. Measurement of plasma HIV RNA levels (viral load), using quantitative methods, should be performed at the time of diagnosis and every 3–4 months thereafter in the untreated patient (AIII) (Table 2). $CD4^+$ T cell counts should be measured at the time of diagnosis and generally every 3-6 months thereafter (AIII). These intervals between tests are merely recommendations and flexibility should be exercised according to the circumstances of the individual case. Plasma HIV RNA levels should also be measured immediately prior to and again at 2-8 weeks after initiation of antiretroviral therapy (AIII). This second time point allows the clinician to evaluate the initial effectiveness of therapy, since in most patients adherence to a regimen of potent antiretroviral agents should result in a large decrease (~ 1.0 $\log_{10}$) in viral load by 2-8 weeks. The viral load should continue to decline over the following weeks and in most individuals becomes below detectable levels (currently defined as <50 RNA copies/mL) by 16-20 weeks. The rate of viral load decline towards undetectable is affected by the baseline $CD4^+$ T cell count, the initial viral load, potency of the regimen, adherence to the regimen, prior exposure to antiretroviral agents, and the presence of any OIs. These individual differences must be considered when monitoring the effect of therapy. However, the absence of a virologic response of the magnitude discussed above should prompt the physician to reassess patient

adherence, rule out malabsorption, consider repeat RNA testing to document lack of response, and/or consider a change in drug regimen. Once 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 6 months should be undetectable, that is, below 50 copies of HIV RNA per mL of plasma *(5)*. Data from clinical trials strongly suggest that lowering plasma HIV RNA to below 50 copies/mL is associated with a more complete and durable viral suppression, compared with reducing HIV RNA to levels between 50-500 copies/mL *(6)*. If HIV RNA remains detectable in plasma after 16-20 weeks of therapy, the plasma HIV RNA test should be repeated to confirm the result and a change in therapy should be considered, according to the guidelines in the section "Considerations for Changing a Failing Regimen" (see p. 22) (BIII).

When making decisions regarding the initiation of therapy, the $CD4^+$ T lymphocyte count and plasma HIV RNA measurement should ideally be performed on two occasions to ensure accuracy and consistency of measurement (BIII). However, in patients who present with advanced HIV disease, antiretroviral therapy should generally be initiated after the first viral load measurement is obtained in order to prevent a potentially deleterious delay in treatment. It is recognized that the requirement for two measurements of viral load may place a significant financial burden on patients or payers. Nonetheless, the Panel feels that two measurements of viral load will provide the clinician with the best information for subsequent follow-up of the patient. Plasma HIV RNA levels should not be measured during or within four weeks after successful treatment of any intercurrent infection, resolution of symptomatic illness, or immunization. Because there are differences among commercially available tests, confirmatory plasma HIV RNA levels should be measured by the same laboratory using the same technique in order to ensure consistent results.

A minimally significant change in plasma viremia is considered to be a 3-fold or 0.5 $\log_{10}$ increase or decrease. A significant 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 can occur and was found in 20% of patients in one cohort studied *(8)*. Such discordance can complicate decisions regarding antiretroviral therapy and may be due to a number of factors that affect plasma HIV RNA testing. In general, viral load and trends in viral load are felt to be more informative for guiding decisions regarding antiretroviral therapy than are $CD4^+$ T cell counts; exceptions to this rule do occur, however. For further discussion refer to "Considerations for Changing a Failing Regimen", p. 22. In many such cases, expert consultation should be considered.

Testing for Drug Resistance

Background

Testing for HIV resistance to antiretroviral drugs is a rational adjunct to guide antiretroviral therapy. When combined with a detailed drug history and efforts aimed at maximizing drug adherence, these assays may help to maximize the benefits of antiretroviral therapy. Many studies in treatment experienced patients have shown strong associations between the presence of

drug resistance (identified by either genotyping or phenotyping resistance assays) and failure of the antiretroviral treatment regimen to suppress HIV replication. Genotyping assays detect drug resistance mutations that are present in the relevant viral genes (i.e., RT and protease). Some genotyping assays involve sequencing of the entire RT and protease genes, while others utilize probes to detect selected mutations that are known to confer drug resistance. Genotyping assays can be performed relatively rapidly, such that results can be reported within 1-2 weeks of sample collection. Interpretation of test results requires an appreciation of the range of mutations that are selected for by various antiretroviral drugs, as well as the potential for cross-resistance to other drugs conferred by some of these mutations (see the **http://hiv-web.lanl.gov** Web site). Consultation with an expert in HIV drug resistance is encouraged to facilitate interpretation of genotypic test results.

Phenotyping assays measure the ability of viruses to grow in various concentrations of antiretroviral drugs. Automated, recombinant phenotyping assays are commercially available with turn-around times of 2-3 weeks; however, phenotyping assays are generally more costly to perform compared with genotypic assays. Recombinant phenotyping assays involve insertion of the RT and protease gene sequences derived from patient plasma HIV RNA into the backbone of a laboratory clone of HIV either by cloning or *in vitro* recombination. Replication of the recombinant virus at various drug concentrations is monitored by expression of a reporter gene and is compared with replication of a reference strain of HIV. The concentrations of drugs that inhibit 50% and 90% of viral replication (i.e., the IC50 and IC90) are calculated, and the ratio of the IC50s of the test and reference viruses is reported as the fold increase in IC50, or fold resistance. Interpretation of phenotyping assay results is complicated by the paucity of data on the specific level of resistance (fold increase in IC50) that is associated with failure of different drugs; again, consultation with an expert may be helpful for interpretation of test results.

Further limitations of both genotyping and phenotyping assays include the lack of uniform quality assurance for all assays that are currently available, relatively high cost, and insensitivity for minor viral species; if drug-resistant viruses are present but constitute less than 10-20% of the circulating virus population, they will likely not be detected by current assays. This limitation is of particular importance when interpreting data about susceptibility to drugs that the patient has taken in the past but 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 *(9)*. Consequently, resistance assays should be performed while the patient is taking his/her antiretroviral regimen, and data suggesting the absence of resistance should be interpreted carefully in relation to the prior treatment history.

Use of resistance assays in clinical practice

Resistance assays may be useful in the setting of virologic failure on antiretroviral therapy and in acute HIV infection (Table 3). Recent prospective data supporting the use of resistance testing in clinical practice come from trials in which the utility of resistance tests were assessed in the setting of virologic failure. The VIRADAPT *(10)* and GART *(11)* studies compared virologic responses to antiretroviral treatment regimens when genotyping resistance tests were available to help guide therapy with those observed when changes in therapy were guided solely by clinical judgment. The results of both studies indicated that the short-term virologic response to therapy

was significantly greater when results of resistance testing were available. Similarly, a recent prospective, randomized, multicenter trial has shown that therapy selected on the basis of phenotypic resistance testing significantly improves the virological response to antiretroviral therapy, compared with therapy selected without the aid of phenotypic testing *(12)*. Thus, resistance testing appears to be a useful tool in selecting active drugs when changing antiretroviral regimens in the setting of virologic failure (BII). Similar rationale applies to the potential use of resistance testing in the setting of suboptimal viral load reduction, as detailed in "Criteria for Changing Therapy", p.23 (BIII). It should be noted that virologic failure in the setting of HAART (Highly Active Antiretroviral Therapy) is in some instances associated with resistance only to one component of the regimen *(13)*; in this situation, it may be possible to substitute individual drugs in a failing regimen, although this concept requires clinical validation ("Considerations for Changing a Failing Regimen", p. 22). There are currently no prospective data to support the use of one type of resistance assay over the other (i.e., genotyping vs. phenotyping) in different clinical situations. Therefore, one type of assay is generally recommended per sample; however, in the setting of a complex prior treatment history, both assays may provide important and complementary information.

Transmission of drug-resistant strains of HIV has been documented, and may be associated with a suboptimal virologic response to initial antiretroviral therapy *(14-17)*. Treatment of acute HIV infection is associated with improved immunological outcome *(18, 19)*, and optimization of the initial antiretroviral regimen through the use of resistance testing is a reasonable, albeit untested, strategy (CIII). Because of its more rapid turnaround time, the use of a genotypic assay may be preferred in this setting; however, therapy should not be withheld while awaiting the results of resistance testing. The use of resistance testing prior to initiation of antiretroviral therapy in chronic HIV infection is not generally recommended (DIII) because of uncertainty about the prevalence of resistance in treatment-naive individuals and the fact that currently available resistance assays may fail to detect drug resistant species that were transmitted at the time of primary infection but became a minor species in the absence of selective drug pressure. The currently favored approach would be to reserve resistance testing for cases in which viral load suppression was suboptimal after initiation of therapy (see above), although this may change as more information becomes available on the prevalence of resistant virus in antiretroviral-naïve individuals.

In general, recommendations for resistance testing in pregnancy should be the same as for non-pregnant patients: acute HIV infection, virologic failure on an antiretroviral regimen, or suboptimal viral load suppression after initiation of antiretroviral therapy are all appropriate indications for resistance testing. If an HIV^+ pregnant woman is taking an antiretroviral regimen that does not include zidovudine, or if zidovudine was discontinued because of maternal drug resistance, intrapartum and neonatal zidovudine prophylaxis should still be administered to prevent mother-to-infant HIV transmission ("Considerations for Antiretroviral Therapy in the HIV-Infected Pregnant Woman", see p. 28 and Table 24). It is important to note that not all of zidovudine's activity in preventing mother-to-infant transmission of HIV can be accounted for by its effect on maternal viral load *(20)*; furthermore, preliminary data indicate that the rate of perinatal transmission following zidovudine prophylaxis may not differ between those with and without zidovudine resistance mutations *(21, 22)*. Further studies are needed to determine the

best strategy to prevent mother-to-infant HIV transmission in the presence of zidovudine resistance.

Considerations for Patients with Established HIV Infection

Patients with established HIV infection are discussed in two arbitrarily defined clinical categories: 1) asymptomatic infection or 2) symptomatic disease (wasting, thrush or unexplained fever for > 2 weeks) including AIDS, defined according to the 1993 CDC classification system *(23)*. All patients in the second category should be offered antiretroviral therapy. Considerations for initiating antiretroviral therapy in the first category of patients are complex and are discussed separately below. Before initiating therapy in any patient, 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 pertinent to the prevention of OIs, if not already performed (RPR or VDRL, tuberculin skin test, toxoplasma IgG serology, and gynecologic exam with Pap smear), and other tests as clinically indicated (e.g., chest X-ray, hepatitis C virus (HCV) serology, ophthalmologic exam) (AII). Hepatitis B virus (HBV) serology is indicated in a patient who is a candidate for the hepatitis B vaccine or has abnormal liver function tests (AII), and CMV serology may be useful in certain individuals, as discussed in the "USPHS/IDSA Guidelines for the Prevention of Opportunistic Infections in Persons Infected with the Human Immunodeficiency Virus" *(2)* (BIII).

Considerations for Initiating Therapy in the Patient with Asymptomatic HIV Infection

Initial placebo-controlled trials of zidovudine clearly established that antiretroviral treatment was associated with clinical benefit in HIV-infected individuals with advanced HIV disease and immunosuppression *(24)*. Later studies of immediate versus delayed zidovudine therapy in HIV-infected patients without AIDS demonstrated only a modest and transient advantage in favor of immediate therapy when probabilities of AIDS-free survival were compared *(25)*. As more nucleoside analogue reverse transcriptase inhibitors became available, it was shown that combinations of these drugs provided additional, more durable clinical benefit compared with monotherapy *(25)*. When protease inhibitors became available, studies in patients with advanced HIV disease demonstrated substantial additional clinical benefit when protease inhibitor plus dual nucleoside regimens were compared with dual nucleoside therapy alone *(26-28)*. These clinical trials data as well as observational data indicating that the risk of opportunistic diseases increases markedly when the $CD4^+$ T cell count declines to <200 cells/mm^3 strongly support the recommendation that all patients with a $CD4^+$ T cell count <200 cells/mm^3 or clinically-defined AIDS should be offered antiretroviral therapy.

Although there is theoretical benefit to antiretroviral therapy for patients with $CD4^+$ T cell counts greater than 200 cells/mm^3, no studies have been conducted comparing immediate versus delayed potent combination antiretroviral therapy in these patients. A major dilemma confronting patients and practitioners is that the antiretroviral regimens currently available that have the greatest potency in terms of viral suppression and $CD4^+$ T cell preservation are medically complex, are associated with a number of specific side effects and drug interactions, and pose a substantial challenge for adherence. Furthermore, the development of mutations associated with drug resistance can render therapy less effective or ineffective. Thus, decisions regarding treatment of asymptomatic, chronically infected individuals with $CD4^+$ T cell counts >200 cells/mm^3 must balance a number of competing factors that influence risk and benefit.

The optimal time to initiate antiretroviral therapy is not known. Table 4 summarizes the potential benefits and risks of early and of delayed initiation of therapy in the asymptomatic patient that the clinician and the patient must consider in deciding when to initiate therapy. Potential benefits of early therapy include earlier suppression of viral replication; preservation of immune function; prolongation of disease-free survival; and decrease in the risk of viral transmission. Risks include i) the adverse effects of the drugs on quality of life; ii) the inconvenience of most of the suppressive regimens currently available leading to reduced adherence; iii) development of drug resistance over time because of early initiation of therapy; iv) limitation of future treatment options due to premature cycling of the patient through the available drugs; v) the risk of transmission of virus resistant to antiretroviral drugs; vi) serious and unknown toxicities associated with some antiretroviral drugs (e.g., elevations in serum levels of cholesterol and triglycerides, alterations in the distribution of body fat, insulin resistance and even frank diabetes mellitus); and vii) the unknown durability of effect of the currently available therapies. The benefits of delayed therapy include minimization of treatment-related negative effects on quality of life and drug-related toxicities; preservation of treatment options; and delay in the development of drug resistance. Risks of delayed therapy include the theoretical possibility that some damage to the immune system that might otherwise be salvaged by earlier therapy is irreversible; the possibility that suppression of viral replication may be more difficult at a later stage of disease; and the increased risk of HIV transmission to others during a longer untreated period.

The strength of the recommendation for therapy must balance the readiness of the patient for treatment; consideration of the prognosis for disease-free survival in the absence of treatment as determined by baseline $CD4^+$ T cell count, viral load, (Table 5 and Figure 1), and the slope of the $CD4^+$ T cell count decline; and assessment of the risks and potential benefits associated with initiating antiretroviral therapy. [Note that the HIV RNA values shown in Table 5 and Figure 1 (first line or column) were obtained with the bDNA assay from the Multicenter AIDS Cohort Study (MACS). Expected values of HIV RNA obtained with the RT-PCR assay are also shown in Table 5 and Figure 1; comparison of the results obtained from the RT-PCR and bDNA assays using the manufacturer's controls consistently indicate that the HIV-1 RNA values obtained by RT-PCR are approximately two times higher than those obtained by the bDNA assay *(4)*. Thus, the MACS HIV RNA values have been multiplied by approximately 2 to be consistent with current RT-PCR values. A third test for HIV RNA, the Nucleic-Acid Sequence Based Amplification (NASBA), is currently used in some clinical settings. However, formulas for converting values obtained from either bDNA or RT-PCR assays to NASBA-equivalent values

cannot be derived from the limited data available at this time. This information will be added to the guidelines when it becomes available.]

Increasing recognition of the risks associated with initiation of antiretroviral therapy has shifted expert opinion to a more conservative position concerning the initiation of therapy compared with earlier editions of these guidelines. In general, it is now felt that patients with fewer than 350 $CD4^+$ T cells/mm^3 should be offered therapy (Table 6) (AII). This recommendation is based in part on the substantial short-term risk of disease progression for untreated patients with fewer than 350 $CD4^+$ T cells/mm^3 at all levels of plasma HIV RNA (Table 5 and Figure 1). In addition, data from observational cohorts suggest that i) initiation of therapy at a $CD4^+$ T cell count <200 cells/mm^3 is associated with shorter survival compared with initiation of therapy at higher $CD4^+$ T cell counts *(29)*, and ii) initiation of therapy at $CD4^+$ T cell counts >350 cells/mm^3 was associated with a higher rate of AIDS-free survival at 2 years compared with deferral of therapy *(30)*. 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 most patients who initiate therapy with $CD4^+$ T cell counts in the 200-350 cells/mm^3 range, and that toxicities and adherence challenges may outweigh benefits at $CD4^+$ T cell counts >350 cells/mm^3. In the conservative approach, high levels of plasma HIV RNA (i.e., >30,000 by bDNA or 55,000 RT-PCR) are an indication for more frequent monitoring of $CD4^+$ T cell counts and plasma HIV RNA levels, 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 >30,000 (bDNA) or 55,000 (RT-PCR) would be treated because of the risk of immunologic deterioration and disease progression. The aggressive approach is supported by the observation in many 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, 31-34)*. Long-term clinical outcomes data, however, are not available to fully endorse this approach.

Data are conflicting regarding sex-specific differences in viral load and $CD4^+$ T cell counts (see "Considerations for Antiretroviral Therapy in Women", p. 79). Several studies *(35-41)*, though not others *(42-45)*, have concluded that after adjustment for $CD4^+$ T cell count, levels of HIV RNA are lower in women compared with men. In those studies that have indicated a possible gender difference in HIV RNA levels, women have had RNA levels that ranged between 0.13 to 0.28 $\log_{10}$ lower than observed in men. In two studies of HIV seroconverters, HIV RNA copy numbers were significantly lower in women than men at seroconversion, but these differences decreased over time, and median viral load in women and men became similar within 5-6 years after seroconversion *(36, 37, 41)*. Some data suggest that $CD4^+$ T cell counts may be higher in women than men *(46)*. However, importantly, rates of disease progression do not differ in a sex-dependent manner *(39, 41, 47, 48)*. Taken together, these data suggest 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 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.

Thus, the decision to begin therapy in 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. The factors that must be considered in this decision are: 1) the willingness and readiness of the individual 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 (Table 5 and Figure 1; see also reference *(1)*); 4) the potential benefits and risks of initiating therapy in asymptomatic individuals, as discussed above; and 5) the likelihood, after counseling and education, of adherence to the prescribed treatment regimen. In this regard, no individual patient should automatically be excluded from consideration for antiretroviral therapy simply because he or she exhibits a behavior or other characteristics judged by some to lend itself to nonadherence. Rather, the likelihood of patient adherence to a complex drug regimen should be discussed and determined by the individual patient and clinician before therapy is initiated. To achieve the level of adherence necessary for effective therapy, providers are encouraged to utilize strategies for assessing and assisting adherence; in this regard, intensive patient education 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 take place to assess adherence to treatment and to continue patient counseling for the prevention of sexual and drug injection-related transmission (see below "Adherence to Potent Antiretroviral Therapy").

Considerations for Discontinuing Therapy

As recommendations evolve, patients who have begun highly active antiretroviral therapy at CD4 T cell counts >350/mm^3 may wish to discontinue treatment. There are no clinical data addressing whether or not this should be done or can be accomplished safely. Potential benefits include reduction of toxicities, drug-drug interactions, selection of resistant variants, and improvement in the quality of life. Potential risks include rebound in viral replication and renewed immunologic deterioration. If the patient and physician agree to discontinue therapy the patient should be closely monitored.

Adherence to Potent Antiretroviral Therapy

Introduction

These Guidelines call for many people living with HIV, many of whom are asymptomatic, to be treated with highly active antiretroviral therapy (HAART) for the rest of their lives. The ability of the patient to adhere to the regimen is essential for successful treatment. Excellent adherence has been shown to increase the likelihood of sustained virologic control, which is important for reducing HIV-related morbidity and mortality. Conversely, poor adherence has been shown to increase the likelihood of virologic failure and has been associated with increased morbidity and mortality *(49, 50)*. Poor adherence leads to the development of drug resistance, limiting the effectiveness of therapy *(51)*. The determinants, measurements, and interventions to improve adherence to HAART are poorly characterized and understood, and more research on this critical topic is needed.

Adherence in HIV Disease

Adherence is an important determinant of both the degree and duration of virologic suppression. In addition, numerous studies have found an association between poor adherence and virologic failure. In several studies, non-adherence in patients on HAART was the strongest predictor of failure to achieve viral suppression below the level of detection *(52, 53)*. A high degree of adherence is necessary for optimal virologic suppression with HAART; several studies have shown that 90-95% of doses must be taken for optimal suppression, and lesser degrees of adherence are more often associated with virologic failure *(49, 54)*. To date, there is no conclusive evidence that the degree of adherence required varies with different classes of agents or different specific medications in the HAART regimen.

Imperfect adherence is common. Surveys have shown that one-third of patients missed doses within 3 days of the survey *(55)*. The 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 *(56)*. One fifth of HIV infected patients in one urban center never filled their prescriptions. The instability of homelessness may lead to poor adherence, but not without exception; one recent program achieved a 70% adherence rate among the homeless utilizing flexible clinic hours, accessible clinical staff, and incentives *(57)*.

Many predictors of poor adherence to HIV medications have been identified. These include poor clinician-patient relationship, active drug and alcohol use, active mental illness, in particular depression, lack of patient education and inability of patients to identify their medications (reviewed in reference *(56)*), and lack of reliable access to primary medical care or medication *(58)*. Other sources of instability that may influence adherence include domestic violence and discrimination *(58)*. Medication side effects may also cause poor adherence *(59)*. More recently, fear of or the experience of metabolic and morphologic side effects of HAART has been associated with poor adherence *(59)*.

Predictors of good adherence to HIV medications have also been identified. These include: 1) availability of emotional and practical life supports; 2) the ability of patients to fit the medications into their daily routine; 3) the understanding that poor adherence leads to resistance; 4) the recognition that taking all medication doses is important; and 5) feeling comfortable taking medications in front of people *(60)*. Importantly, optimal viral suppression is associated with keeping clinic appointments *(32)*.

The measurement of adherence is imperfect and lacking a gold standard. Patient self-report is weakly predictive of the likelihood of adherence; however, an estimate of poor adherence by a patient has a strong predictive value and should be regarded seriously *(61, 62)*. Physician estimation of a patient's likelihood of adherence is a poor predictor *(63)*. Each of several aids to measure adherence, such as pill counts, pharmacy records, smart pill bottles with computer chips recording each opening (i.e. Medication Event Monitoring Systems or "MEMSCaps”), and other devices may be of use, though each requires comparison to patient self-reports *(61, 64)*. In some studies, clinician and patient estimates of the degree of adherence have been found to exceed measures based on MEMSCaps. Due to its complexity and cost, MEMSCaps technology is best used as an adjunct to adherence research, but is not useful in most clinical settings.

Self-report should include a short term assessment of each dose that was taken over the recent past (e.g., the past 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. It may also be helpful for patients to bring their medications and medication diary to clinic visits.

Adherence to HAART: Approach to the Patient

Patient-related strategies

Suggestions for strategies to improve adherence are noted in Tables 7-9. The first principle is to negotiate a treatment plan that the patient understands and to which he/she commits *(65, 66)*. Before the first prescription is written, patient "readiness" to take medication should be clearly established. Such negotiation takes time, commonly two or three office visits, and patience. Specific education should include the goals of therapy, including a review of expected outcomes based on baseline viral load and $CD4^+$ T cell counts (i.e., the Multicenter AIDS Cohort Study (MACS) data from the Guidelines), the reason for the need for adherence, and the plan for and mechanics of adherence. Patients must understand that the first HAART regimen has the best chance of long-term success *(1)*. The clinician and health team should develop a concrete plan for the specific regimen in question, including the timing of doses of medications around meals and other daily activities. Some centers offer "dry runs" with jellybeans in order to familiarize the patient with the rigors of HAART; however, there are no data to indicate whether or not this exercise improves adherence. Daily or weekly pillboxes, timers with alarms, pagers and other devices may be useful. The development of side effects can affect the ability to adhere to treatment. Clinicians should inform patients in advance about possible side effects and when they are likely to occur; treatment for likely side effects should be included with the first prescription along with instructions on the appropriate response and the possible need to contact the clinician. In some studies, low literacy has been associated with poor adherence; clinicians should take care to assess a patient's literacy level before relying on written information, and to tailor the adherence intervention to the individual patient. Visual aids and audio or video sources of information may be useful in these patients *(67)*.

Education of family and friends regarding the importance of adherence, as well as recruitment of family and friends to become participants in the plan for medication adherence can be invaluable. Community interventions can be of assistance, including adherence support groups, or the addition of adherence issues to regular support group interactions. Community-based case managers and peer educators can greatly assist adherence education and adherence strategies in individual patients.

Temporary postponement of HAART initiation has been proposed for patients with identified risks for poor adherence *(68, 69)*. For example, a patient with active substance abuse or mental illness may benefit from immediate psychiatric treatment or treatment for chemical dependency. Appropriate therapy during the 1-2 months needed for treatment of these conditions may be limited to opportunistic infection prophylaxis, if indicated, and therapy directed towards the symptoms of drug withdrawal and detoxification or the underlying mental illness. In addition, readiness for HAART can be assessed and adherence education can be instituted during this

time. Other sources of patient instability, such as homelessness, may also be addressed during this interval. Patients should be informed and in agreement with such a plan for future treatment and time-limited treatment deferral.

Clinicians are reminded that such factors as gender, race, socio-economic status, educational level, and a past history of drug use do not reliably predict poor adherence. Conversely, a higher socio-economic status and educational levels and a lack of a history of drug abuse do not predict adequate adherence *(69)*. No individual patient should automatically be excluded from consideration from antiretroviral therapy simply because he or she exhibits a behavior or other characteristics judged by some to lend itself to nonadherence.

Clinician and health team-related strategies

Clinician and health team-related strategies to enhance adherence are noted in Table 8. A trusting relationship is essential. The clinician should commit to a feasible mechanism for communication between clinic visits, to ongoing monitoring of adherence, and to timely and appropriate responses to adverse events or interim illness. Interim management during physician vacations or other absences must be clarified.

Adherence requires full deployment of the available health care team. Regular reinforcement by two or more team members will assist the goals of adherence. Provider attitudes and behaviors that are supportive and non-judgmental will encourage patients to be honest about their adherence and about problems they have experienced with adherence. Interventions that have been associated with improved adherence include a pharmacist-based adherence clinic *(70)*, a street-level drop-in center with medication storage and flexible hours for the homeless *(71)*, an adolescent-specific adherence training program *(72)*, and medication counseling and behavioral intervention *(73)*; these and others are noted in Table 9. For all health care team members, specific training on HAART and adherence should be offered and updated regularly.

Monitoring may identify periods of poor adherence. There is evidence that adherence wanes over time, even in highly adherent patients, a phenomenon described as “pill fatigue” or “treatment fatigue” *(68, 74)*. Thus monitoring adherence at every clinical 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 nature of the problem *(69)*. Intermittent drug use or emotional crisis might lead to referral for mental health or chemical dependency assessment or further recruitment and intervention with family or friends. Some patients may require ongoing assistance from support team members from the outset, including chemically dependent patients, mentally retarded patients in the care of another, children and adolescents, or patients in crisis.

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

The response to the problem of adherence in special populations has not been well studied. There is evidence that programs designed specifically for adolescents, for women and families, for

injection drug users, and for homeless persons increase the likelihood of medication adherence *(70, 72, 75, 76)*. In particular, the incorporation of adherence interventions into convenient primary care settings, the training and deployment of peer educators, pharmacists, nurses, and other health care personnel in adherence interventions, and the monitoring of clinician and patient performance regarding adherence are beneficial *(71, 77, 78)*. In the absence of data, a reasonable response is to address and monitor adherence in all HIV primary care encounters and incorporate adherence goals in all patient treatment plans and interventions. This may 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 into the work of chemical dependency counselors and programs.

Regimen-related strategies

To the extent possible, regimens should be simplified by reducing the number of pills and the frequency of therapy, and by minimizing drug interactions and side effects. This is particularly true for patients with strong biases against many pills and frequent dosing; for some patients, these issues are of lesser importance. There is evidence that simplified regimens with reduced pill numbers and dose frequencies improve adherence *(79, 80)*. With the numerous effective options for initial therapy noted in these Guidelines and the observed benefit of less frequent dosing on adherence, twice daily dosing of HAART regimens is feasible in most circumstances. Regimens should be chosen with review and discussion of specific food requirements in mind and patient understanding and agreement to such restrictions. Regimens requiring an empty stomach numerous times daily may be difficult for patients with wasting, just as regimens requiring high fat intake may be difficult for patients with lactose intolerance or fat aversion. Fortunately, an increasing number of effective regimens have no specific food requirements.

Directly Observed Therapy

Directly observed therapy (DOT), in which a health care provider observes the ingestion of medication, has been shown to be successful in the management of tuberculosis, specifically in patients who are poorly adherent to medications. However, it is labor-intensive, expensive, intrusive, and programmatically complex to initiate and complete and, unlike tuberculosis, HIV requires lifelong therapy.

Several pilot programs have studied DOT in HIV patients with some preliminary success *(81-84)*. Programs have studied once daily regimens in prisons, in methadone programs, and in other cohorts of patients with a record of repeated poor adherence. Modified DOT programs have also been studied, in which the morning dose is observed and evening and weekend doses are self-administered. The goal of these programs is to improve patient education and medication self-administration over a time-limited (i.e., 3-6 months) period. It is too early to judge the outcomes of these programs, particularly with regard to long term adherence following completion of DOT.

Goals of Therapy

Eradication of HIV infection cannot be achieved with currently available antiretroviral regimens; in large measure, this is due to the establishment of a pool of latently infected $CD4^+$ T cells during the very earliest stages of acute HIV infection *(85)* that persists with an extremely long half-life, even with prolonged suppression of plasma viremia to <50 copies/mL *(86-89)*. The primary goals of antiretroviral therapy are maximal and durable suppression of viral load, restoration and/or 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 articulated in these guidelines has resulted in substantial reductions in HIV-related morbidity and mortality *(90-92)*.

Plasma viremia is a strong prognostic indicator in HIV infection *(3)*. Furthermore, reductions in plasma viremia achieved with antiretroviral therapy account for much of the clinical benefit associated with therapy *(93)*. Therefore, suppression of plasma viremia as much as possible for as long as possible is an important goal of antiretroviral therapy. However, this goal must be balanced against the need to preserve effective treatment options. Switching antiretroviral regimens for any detectable level of plasma viremia may rapidly exhaust treatment options; reasonable parameters that may prompt a change in therapy are discussed below (see "Criteria for Changing Therapy", p. 23).

HAART often leads to increases in the $CD4^+$ T cell count of 100-200 cells/μl or more, although individual responses are quite variable. $CD4^+$ T cell responses are generally related to the degree of viral load suppression *(94)*. In turn, continued viral load suppression is more likely among those who achieve higher $CD4^+$ T cell counts during therapy *(95)*. A favorable $CD4^+$ T cell response can occur with incomplete viral load suppression and may not necessarily indicate a poor prognosis *(96)*. The durability of these immunologic responses that occur with suboptimal suppression of viremia is unknown. Therefore, while viral load is the strongest single predictor of long-term clinical outcomes, strong consideration should also be given to sustained rises in $CD4^+$ T cell counts and partial immune restoration. The urgency of the need to change therapy in the presence of low level viremia is clearly tempered by this observation. The expectation that continuing the existing therapy in this situation will inevitably lead to rapid accumulation of drug resistant virus may not always be realized. One reasonable strategy is maintenance of the regimen, but with redoubled efforts at optimizing adherence, and more frequent monitoring.

Partial reconstitution of immune function induced by HAART may allow for elimination of unnecessary therapies, such as some of those used for prevention and maintenance therapy against opportunistic infections. The appearance of naïve T cells *(97, 98)*, partial normalization of perturbed T cell receptor Vβ repertoires *(99)*, and evidence of residual thymic function in patients receiving HAART *(100, 101)* suggest that partial immune reconstitution frequently occurs in these patients. Further evidence of functional immune restoration can be found in the return during HAART of *in vitro* responses to microbial antigens associated with opportunistic infections *(102)*, and the lack of cases of *Pneumocystis carinii* pneumonia (PCP) among patients who discontinued primary PCP prophylaxis when their $CD4^+$ T cell counts rose to >200 cells/mm^3 during HAART *(103-105)*. Current guidelines include some recommendations

regarding the discontinuation of prophylaxis and maintenance therapy for certain opportunistic infections in the setting of HAART-induced increases in $CD4^+$ T cell counts *(2)*.

Tools to Achieve the Goals of Therapy

Although as many as 70-90% of antiretroviral drug-naïve patients achieve maximal viral load suppression 6-12 months after initiation of therapy, only about 50% of patients in a city clinic setting achieve similar results *(31, 32)*. Predictors of virologic success include low baseline viremia and high baseline $CD4^+$ T cell count *(31-33)*, rapid decline of viremia *(6)*, decline of viremia to <50 HIV RNA copies/mL *(6)*, adequate serum levels of antiretroviral drugs *(6, 106)*, and adherence to the drug regimen *(32, 49, 53)*. While optimal strategies for achieving the goals of antiretroviral therapy have not yet been fully delineated, efforts to improve patient adherence to therapy are likely important (see "Adherence to Potent Antiretroviral Therapy", p. 9).

Another tool to maximize the benefits of antiretroviral therapy is the rational sequencing of drugs and the preservation of future treatment options for as long as possible. Table 11 shows the possible advantages and disadvantages of three alternative regimens, including a PI with 2 NRTIs, an NNRTI with 2 NRTIs, or a 3 NRTI regimen. The goal of a class-sparing regimen is to preserve or "spare" one or more than one class of drugs for later use. By sequencing drugs in this fashion, it may be possible to extend the overall long-term effectiveness of the available therapy options. Moreover, this strategy makes it possible to selectively delay the risk of certain side effects uniquely associated with a single class of drugs. The efficacy of PI-containing HAART regimens has been demonstrated to include durable viral load suppression, partial immunologic restoration, and decreased incidence of AIDS and death *(26-28)*. Viral load suppression and $CD4^+$ T cell responses that are similar to those observed with PI-containing regimens have been achieved with selected PI-sparing regimens, such as efavirenz + 2 NRTIs *(107)* or abacavir + 2 NRTIs *(108)*; however, it is not yet known whether such PI-sparing regimens will provide comparable efficacy with regard to clinical endpoints.

The presence of drug resistant HIV in treatment-experienced patients is a strong predictor of virologic failure and disease progression *(109-111)*. The results of several prospective studies indicate that the virologic response to a new antiretroviral regimen after virologic failure on a previous regimen can be significantly improved when results of resistance testing were available to guide the choice of drugs in the new regimen *(10, 11)*. Thus, resistance testing appears to be a useful tool in selecting active drugs when changing antiretroviral regimens in the setting of virologic failure (see "Testing for Drug Resistance", p. 3).

Initiating Therapy in the Patient with Asymptomatic HIV Infection

When initiating therapy in the patient naïve to antiretroviral therapy, one should begin with a regimen that is expected to achieve sustained suppression of plasma HIV RNA, a sustained increase in $CD4^+$ T cell count, and a favorable clinical outcome (i.e., delayed progression to AIDS and death). Additional consideration should be given to the regimen's pill burden, dosing frequency, food requirements, convenience, toxicity, and drug interaction profile compared with other regimens. Strongly recommended regimens include either indinavir, nelfinavir, ritonavir + saquinavir, ritonavir + indinavir, ritonavir + lopinavir or efavirenz in combination with one of

several 2 NRTI combinations (Table 12). Clinical outcome data support the use of a PI in combination with 2 NRTIs *(26-28)* (BI). It should be noted that ritonavir as the sole PI is considered as an alternative agent because of the difficulty many patients have tolerating standard doses of ritonavir *(32)*, and because of the drug's many interactions. A similar rationale applies to saquinavir-SGC, because of the difficulty many patients have tolerating standard doses and because of the large pill burden associated with its use; however, then there is no reason to switch a patient off of a ritonavir or saquinavir-based regimen if they are tolerating it and if the regimen is effective.

The use of ritonavir to increase plasma concentrations of other protease inhibitors (PIs) has rapidly evolved from an investigational concept to widespread practice. Standard doses of individual PIs result in trough drug levels that are often only slightly higher than the effective antiviral concentration; this may afford an opportunity for viral replication. In contrast, protease "boosting" or "enhancement" by ritonavir increases the trough levels of other protease inhibitors well above the IC_{50} or IC_{95}, minimizing opportunities for viral replication, and potentially allowing for drug activity even against moderately resistant strains of virus. In addition, these dual PI combinations often lead to more convenient regimens in terms of pill burden, scheduling, and elimination of food restrictions. They also may prevent efavirenz or nevirapine-induced drug interactions.

Ritonavir increases plasma concentrations of other PIs by at least two mechanisms, including inhibition of gastrointestinal CYP450 during absorption, and metabolic inhibition of hepatic CYP450. The 20-fold increase in saquinavir plasma concentrations with ritonavir co-administration is likely caused by inhibition of CYP450 at both sites and leads to a marked increase primarily in the saquinavir Cmax *(112)*. For lopinavir, the addition of ritonavir increases both the peak concentration and the half-life (which subsequently results in a higher trough concentration). The result is a lopinavir AUC that is 100-fold higher compared to lopinavir alone *(113)*. For other PIs, metabolism in the gastrointestinal tract plays a relatively minor role and the enhancement is primarily due to CYP450 inhibition in the liver. The addition of ritonavir to amprenavir, nelfinavir, or indinavir results in marked increases in half-life and trough levels, with a more moderate or minimal increase in the peak concentration *(114, 115)*.

The dose of ritonavir that is used for PI "boosting" also appears to be important for some protease inhibitors but not others. With saquinavir and amprenavir, increases in the ritonavir dose above 100 mg BID do not significantly increase the PI levels further *(114, 116)*. However, increasing ritonavir doses above 100 mg BID do appear to provide additional enhancement for indinavir and nelfinavir *(115, 117)*. While a considerable body of pharmacokinetic data support the use of most of these ritonavir + PI combinations, few efficacy data are available yet for combinations other than ritonavir + saquinavir *(118)* or ritonavir + lopinavir *(119)*. In addition, the long term risks and toxicities of dual PI combinations remain unknown.

Disappointing results with antiretroviral regimens prescribed in the setting of virologic failure with a previous regimen suggest that the first regimen affords the best opportunity for long-term control of viral replication. Because the genetic barrier to resistance is greatest with PIs, many would consider a PI + 2 NRTIs to be the preferred initial regimen. However, efavirenz + 2NRTIs appears to be at least as effective as a PI + 2 NRTIs in suppressing plasma viremia and

increasing $CD4^+$ T cell counts *(107)*, and many would argue that such a regimen is the preferred initial regimen because it may spare the toxicities of PIs for a considerable time (BII). Although no direct comparative trials exist that would allow a ranking of the relative efficacy of the NNRTIs, the demonstrated ability of efavirenz in combination with 2 NRTIs to suppress viral replication and increase $CD4^+$ T cell counts to a similar degree as a PI with 2 NRTIs support a preference for efavirenz over the other available NNRTIs at this time. Abacavir + 2 NRTIs, a triple NRTI regimen, has been used with some success as well *(108)* (CII). Such a regimen, however, may have short-lived efficacy when the baseline viral load is >100,000 copies/mL. Using 2 NRTIs alone does not achieve the goal of suppressing viremia to below detectable levels as consistently as does a regimen in the "strongly recommended" or "alternative" categories and should be used only if more potent treatment is not possible (DI). Use of antiretroviral agents as monotherapy is contraindicated (DI), except when there are no other options, or in pregnancy to reduce perinatal transmission as noted below. When initiating antiretroviral therapy, all drugs should be started simultaneously at full dose with the following three exceptions: dose escalation regimens are recommended for ritonavir, nevirapine, and, in some cases, ritonavir plus saquinavir.

Hydroxyurea has been used investigationally in combination with antiretroviral agents for treatment of HIV infection, however its utility in this setting has not been established. Clinicians considering 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 (See "Hydroxyurea", p. 83).

Detailed information comparing the different nucleoside RT inhibitors, non-nucleoside RT inhibitors, the protease inhibitors, and drug interactions between the protease inhibitors and other agents can be found in Tables 13-19. In addition, because certain investigational new drugs are available to physicians for use in selected patients, Table 20 has been provided for the physician treating patients under investigational protocols. Particular attention should be paid to Tables 16-18 regarding drug interactions between the protease inhibitors and other agents, as these are extensive and often require dose modification or substitution of various drugs. Toxicity assessment is an ongoing process; assessment at least twice during the first month of therapy and every 3 months thereafter is a reasonable management approach.

Initiating Therapy in Advanced HIV Disease

All patients diagnosed with advanced HIV disease, which is defined as any condition meeting the 1993 CDC definition of AIDS *(23)* should be treated with antiretroviral agents regardless of plasma viral levels (AI). All patients with symptomatic HIV infection without AIDS, defined as the presence of thrush or unexplained fever, should also be treated. When the patient is acutely ill with an OI or other complication of HIV infection, the clinician should consider clinical issues such as drug toxicity, ability to adhere to treatment regimens, drug interactions, and laboratory abnormalities when determining the timing of initiation of antiretroviral therapy. Once therapy is initiated, a maximally suppressive regimen should be used, as indicated in Table 12. Advanced stage patients being maintained on an antiretroviral regimen should not have the therapy discontinued during an acute opportunistic infection or malignancy, unless there are concerns regarding drug toxicity, intolerance, or drug interactions.

Patients who have progressed to AIDS are often treated with complicated combinations of drugs and the potential for multiple drug interactions must be appreciated by clinician and patient. Thus, the choice of which antiretroviral agents to use must be made with consideration given to potential drug interactions and overlapping drug toxicities, as outlined in Tables 13-19. For instance, the use of rifampin to treat active tuberculosis is problematic in a patient receiving a protease inhibitor, which adversely affects the metabolism of rifampin but is frequently needed to effectively suppress viral replication in these advanced patients. Conversely, rifampin lowers the blood level of protease inhibitors, which may result in suboptimal antiretroviral therapy. While rifampin is contraindicated or not recommended for use with all of the protease inhibitors, one might consider using rifabutin at a reduced dose, as indicated in Table 17; this topic is discussed in greater detail elsewhere *(120)*. Other factors complicating advanced disease are wasting and anorexia, which may prevent patients from adhering to the dietary requirements for efficient absorption of certain protease inhibitors. Bone marrow suppression associated with ZDV and the neuropathic effects of ddC, d4T and ddI may combine with the direct effects of HIV to render the drugs intolerable. Hepatotoxicity associated with certain protease inhibitors may limit the use of these drugs, especially in patients with underlying liver dysfunction. The absorption and half-life of certain drugs may be altered by antiretroviral agents, particularly the protease inhibitors and NNRTIs whose metabolism involves the hepatic cytochrome p450 (CYP450) enzymatic pathway. PIs inhibit the CYP450 pathway, whereas NNRTIs have variable effects; nevirapine is an inducer, delavirdine is an inhibitor, and efavirenz is a mixed inducer/inhibitor. CYP450 inhibitors have the potential to increase blood levels of drugs metabolized by this pathway. At times, adding a CYP450 inhibitor can improve the pharmacokinetic profile of selected agents (such as adding ritonavir therapy to saquinavir) as well as contribute an additive antiviral effect; however, these interactions can also result in life threatening drug toxicity, as indicated in Tables 16-19. Thus, health care providers should inform their patients of the need to discuss any new drugs, including over the counter agents and alternative medications, that they may consider taking, and careful attention should be given to the relative risks versus benefits of specific combinations of agents.

Initiation of potent antiretroviral therapy is often associated with some degree of recovery of immune function. In this setting, patients with advanced HIV disease and subclinical opportunistic infections such as MAI or CMV may develop a new immunologic response to the pathogen and thus new symptoms may develop in association with the heightened immunologic and/or inflammatory response. This should not be interpreted as a failure of antiretroviral therapy and these newly presenting opportunistic infections should be treated appropriately while maintaining the patient on the antiretroviral regimen. Viral load measurement is helpful in clarifying this situation.

HAART-Associated Adverse Clinical Events

Lactic Acidosis/ Hepatic Steatosis

While the occurrence of severe lactic acidosis and hepatomegaly with steatosis during use of nucleoside analogue reverse transcriptase inhibitors (NRTIs) is rare, it is associated with a high fatality rate *(121-124)*. Risk factors for the development of this toxicity include female gender, obesity, and prolonged use of NRTIs, although some cases have been reported to occur without known risk factors *(123)*. Mitochondrial toxicity is one possible mechanism of cellular injury as NRTIs also inhibit DNA polymerase gamma, which is the enzyme responsible for mitochondrial DNA synthesis. The ensuing mitochondrial dysfunction may result in lactic acidosis and hepatic steatosis and may be related to other adverse events including myopathy, cardiomyopathy, pancreatitis, and peripheral neuropathy *(125)*.

The initial clinical presentations of patients with the lactic acidosis syndrome are variable and may include nonspecific gastrointestinal symptoms without dramatic elevation of hepatic enzymes, and in some cases dyspnea *(126)*. The clinical "prodrome" may include otherwise unexplained onset and persistence of abdominal distention, nausea, abdominal pain, vomiting, diarrhea, anorexia, generalized weakness, weight loss, and hepatomegaly. In addition to hyperlactatemia, laboratory evaluation may reveal an increased anion gap (Na - [Cl + CO2]> 16), elevated aminotransferases, CPK, LDH, lipase, and amylase *(122, 126, 127)*. Echotomography and CT scan may demonstrate an enlarged fatty liver; histological examination of the liver reveals microvesicular steatosis *(126)*.

In some cases the adverse event has resolved after discontinuation of NRTIs *(126, 128)*, and some patients have tolerated rechallenge with a new NRTI-containing regimen *(126, 129)*; however, at present there are insufficient data to recommend this strategy vs. treatment with an NRTI-sparing regimen. If NRTI treatment is not discontinued, in some patients progressive mitochondrial toxicity may produce severe lactic acidosis manifested clinically by tachypnea and dyspnea; respiratory failure may follow, requiring mechanical ventilation. In addition to discontinuation of antiretroviral treatment and intensive therapeutic strategies that include bicarbonate infusions and hemodialysis *(130)* (AI), some clinicians have administered thiamine *(131)*, riboflavin *(132)*, coenzyme Q, and carnitine based upon the pathophysiological hypothesis that sustained cellular dysfunctions of the mitochondrial respiratory chain cause this clinical syndrome; the efficacy of these latter interventions requires clinical validation.

In conclusion, antiretroviral treatment should be suspended if clinical and laboratory manifestations of the lactic acidosis syndrome occur (BIII). Since there are significant technical problems associated with lactate testing *(133)*, one must rely on laboratory abnormalities PLUS symptoms. Some experts suggest monitoring of serum bicarbonate and electrolytes for the early identification of an increased anion gap every three months.

Hyperglycemia/Diabetes Mellitus

Hyperglycemia, new onset diabetes mellitus, diabetic ketoacidosis, and exacerbation of pre-existing diabetes mellitus have been reported in patients receiving HAART *(134-136)*. These

metabolic derangements are strongly associated with PI use *(137)*, though they may occur independent of PI use as well *(138)*. The pathogenesis of these abnormalities is unknown; however, beta cell dysfunction and peripheral insulin resistance appear to be the proximate causes of hyperglycemia *(137-139)*. Hyperglycemia with or without diabetes has been reported in 3 to 17 percent of patients in various retrospective studies. Among these reports, symptom onset occurred a median of approximately 60 days, ranging from 2-390 days following initiation of PI therapy. Hyperglycemia resolved in some patients who discontinued PI therapy; however, the reversibility of these events is currently unknown due to limited data. Some patients continued PI therapy and initiated treatment with oral hypoglycemic agents or insulin. Clinicians are advised to monitor HIV-infected patients with pre-existing diabetes closely when PIs are prescribed, and to be aware of the risk for drug-related new-onset diabetes in patients without a history of diabetes (BIII). Patients should be advised about the warning signs of hyperglycemia (i.e., polydipsia, polyphagia, and polyuria) when these medications are prescribed. Some experts recommend routine fasting blood glucose measurements at 3-4 month intervals during the first year of PI treatment in patients with no prior history of diabetes (CIII). Routine use of glucose tolerance tests to detect this complication is not recommended (DIII). There are no data to aid in the decision to continue or discontinue drug therapy in cases of new-onset or worsening diabetes; however, most experts would recommend continuation of HAART in the absence of severe diabetes (BIII). Several studies have attempted to examine the potential of reversing insulin resistance after switching from PI-containing HAART regimens to NNRTI-based regimens; the results have been inconclusive.

Fat Maldistribution

Changes in body fat distribution, sometimes referred to as "lipodystrophy syndrome" or "pseudo-Cushing's syndrome" have been observed in 6 to 80 percent of patients receiving HAART; the wide range of estimates of the incidence of this syndrome reflects the lack of a uniform case definition and other variables that are poorly understood. The morphologic changes occur gradually, and are generally not apparent until months after the initiation of HAART. Clinical findings include central obesity, peripheral fat wasting, and lipomas; pathologic changes may include visceral fat accumulation, dorsocervical fat accumulation ("buffalo hump"), extremity wasting with venous prominence, facial thinning, and breast enlargement *(140-143)*. Some patients may have a cushingoid appearance despite the absence of confounding medications (i.e., corticosteroids) or adrenal function laboratory abnormalities *(141)*. Hyperlipidemia and insulin resistance are frequently but not always associated with lipodystrophy *(144)*; it is unclear whether these various clinical manifestations represent distinct entities with different etiologies, or whether they occur as a result of a single pathologic process. Lipodystrophy has been associated with the use of PIs *(140, 144)*, but may occur with NRTI therapy *(141, 145, 146)* or in the absence of therapy *(147)*. Compared with PI-associated lipodystrophy, the NRTI-associated syndrome(s) may be associated with recent onset fatigue and nausea; weight loss; higher levels of lactate and alanine aminotransferase; and lower levels of albumin, cholesterol, triglycerides, glucose, and insulin *(146)*. Therapeutic strategies aimed at reversing or halting the progression of lipodystrophy include switching classes of antiretroviral agents *(148, 149)* and exercise training *(150)*; however, insufficient data are currently available to guide the management of lipodystrophy.

Hyperlipidemia

Changes in triglycerides and/or cholesterol have occurred with or without the clinical findings of fat maldistribution, and may occur during the first month of HAART *(137, 138, 140, 144)*. In clinical studies all PIs have been implicated; however, increases in cholesterol and triglyceride levels may be more dramatic during treatment with ritonavir *(151)*. The mechanism of these effects has not yet been defined, but may be due in part to interference by protease inhibitors with normal cellular proteins involved in lipid metabolism *(152)*. Although the long-term consequences of dysregulated lipid metabolism are unknown, substantial increases in triglycerides or cholesterol are of concern because of the possible association with cardiovascular events and pancreatitis. In this regard, case reports have appeared describing premature coronary artery disease, cerebrovascular disease, pancreatitis and cholelithiasis in patients receiving PI therapy. Controlled studies have not yet demonstrated an increased risk of cardiovascular events associated with PI therapy; however, longer follow-up time will be needed to accurately assess this issue *(153, 154)*. Some experts recommend monitoring serum levels of cholesterol and triglycerides (preferably fasting) at 3-4 month intervals during PI therapy (CIII). For individuals with elevated triglyceride levels at baseline and who may be at increased risk of pancreatitis, it is preferable to repeat a lipid profile sooner (e.g., within 1-2 months of initiating HAART). Assessment should include evaluation for independent risks for cardiovascular disease (i.e., family history, medical history, smoking, diet, weight, etc.) and the magnitude of lipid changes. Intervention is often recommended for triglyceride levels > 750-1000 mg/dL and/or LDL cholesterol levels > 130 mg/dL (in individuals without known coronary disease and with 2 or more coronary risk factors) or >160 mg/dL (in individuals without known coronary disease and with fewer than 2 coronary risk factors) *(155)*. The effectiveness of lifestyle modifications (i.e., dietary changes, exercise, and smoking cessation) and lipid lowering drugs such as gemfibrozil, niacin, and the HMG coenzyme A reductase inhibitors (i.e., “statins”) is not clear. Concurrent use of PIs and statins should be undertaken with caution due to the potential for enhanced statin-related toxicity in this setting (Tables 13 and 14). Some patients have had resolution of serum lipid abnormalities following discontinuation of PIs and substitution of PI-sparing antiretroviral regimens; however, this decision requires a risk-benefit analysis.

Increased Bleeding Episodes in Patients with Hemophilia

Increased spontaneous bleeding episodes in patients with hemophilia A and B have been observed with the use of protease inhibitors *(156)*. Most of the reported episodes involved joints and soft tissues; however, more serious bleeding episodes including intracranial and gastrointestinal bleeding have been reported. The bleeding episodes occurred a median of 22 days after initiation of protease inhibitor therapy. Some patients received additional coagulation factor while continuing protease inhibitor therapy.

Osteopenia and Osteoporosis

Anecdotal reports of avascular necrosis of the hip and compression fractures of the spine in HIV-infected patients receiving HAART have prompted concern about an adverse effect of HAART on bone metabolism. In this regard, the risk of osteopenia and osteoporosis is significantly higher in patients taking PIs compared with patients taking non-PI containing regimens *(157)*.

Furthermore, these effects are independent of PI-related lipodystrophy.

Rash

Rash is a relatively common toxicity encountered during use of NNRTIs. A significant minority (occurring in up to approximately 5% of patients receiving NNRTIs) of these rashes are severe, and potentially fatal cases of Stevens-Johnson syndrome have been reported.

Interruption of Antiretroviral Therapy

There are multiple reasons for temporary discontinuation of antiretroviral therapy, including intolerable side effects, drug interactions, first trimester of pregnancy when the patient so elects, and unavailability of drug. There are no studies and no reliable estimate of the number of days, weeks, or months that constitute a clinically important interruption of one or more components of a therapeutic regimen that would increase the likelihood of drug resistance. If there is a need to discontinue any antiretroviral medication for an extended time, clinicians and patients should be advised 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.

Considerations for Changing a Failing Regimen

As with the initiation of antiretroviral therapy, the decision to change regimens should be approached with careful consideration of several complex factors. These factors include: recent clinical history and physical examination; plasma HIV RNA levels measured on two separate occasions; absolute $CD4^+$ T lymphocyte count and changes in these counts; assessment of adherence to medications; remaining treatment options; potential resistance patterns from prior antiretroviral therapies; and preparation of the patient for the implications of the new regimen which include side effects, drug interactions, dietary requirements and possible need to alter concomitant medications. Failure of a regimen may occur for many reasons, including initial viral resistance to one or more agents, altered absorption or metabolism of the drug, multi-drug pharmacokinetics that adversely affect therapeutic drug levels, and poor patient adherence to a regimen. In this regard, it is important to carefully assess patient adherence prior to changing antiretroviral therapy; health care workers involved in the care of the patient, such as the case manager or social worker, may be of assistance in this evaluation. Clinicians should be aware of the prevalence of mental health disorders and psychoactive substance use disorders in certain HIV-infected persons; inadequate mental health treatment services may jeopardize the ability of such individuals to adhere to their medical treatment. Proper identification of and intervention in these mental health disorders can greatly enhance adherence to medical HIV treatment.

It is important to distinguish between the need to change therapy due to drug failure versus drug toxicity. In the latter case, it is appropriate to substitute one or more alternative drugs of the same potency and from the same class of agents as the agent suspected to be causing the toxicity. In the case of drug failure where more than one drug had been used, a detailed history of current and past antiretroviral medications, as well as other HIV-related medications, should be obtained. Testing for antiretroviral drug resistance may also be very helpful in maximizing the number of active drugs in a regimen (see “Testing for Drug Resistance”, p. 3). Viral resistance to

antiretroviral drugs is an important, but not the only, reason for treatment failure. Genetically distinct viral variants emerge in each HIV-infected individual over time after initial infection. Viruses with single drug resistant mutations exist even prior to therapy, but are selected for replication by antiviral regimens that are only partially suppressive. The more potent a regimen is in durably suppressing HIV replication, the less likely the emergence of resistant variants. Thus the goal of therapy should be to reduce plasma HIV RNA to below detectable limits using the most sensitive assay available (<50 copies/mL), thereby providing the strongest genetic barrier possible to the emergence of resistance.

Three different populations of patients should be considered with regard to a change in therapy: 1) individuals who are receiving incompletely suppressive antiretroviral therapy, such as single or double nucleoside therapy, with detectable or undetectable plasma viral load (discussed further below); 2) individuals who have been on potent combination therapy and whose viremia was initially suppressed to undetectable levels but has again become detectable; and 3) individuals who have been on potent combination therapy and whose viremia was never suppressed to below detectable limits.

Criteria for Changing Therapy

The goal of antiretroviral therapy, to improve the length and quality of the patient's life, is likely best accomplished by maximal suppression of viral replication to below detectable levels (currently defined as <50 copies/mL) sufficiently early to preserve immune function. However, this is not always achievable with a given therapeutic regimen and frequently regimens must be modified. In general, the plasma HIV RNA level is the most important parameter to evaluate response to therapy, and increases in levels of viremia that are significant, confirmed and not attributable to intercurrent infection or vaccination indicate failure of the drug regimen regardless of changes in the $CD4^+$ T cell counts. Clinical complications and sequential changes in $CD4^+$ T cell count may complement the viral load test in evaluating a response to treatment. Specific criteria that should prompt consideration for changing therapy include:

- *Less than a 0.5–0.75 log_{10} reduction in plasma HIV RNA by 4 weeks following initiation of therapy, or less than a 1 log_{10} reduction by 8 weeks (CIII);*
- *Failure to suppress plasma HIV RNA to undetectable levels within 4–6 months of initiating therapy (BIII).* In this regard, the degree of initial decrease in plasma HIV RNA and the overall trend in decreasing viremia should be considered. For instance, a patient with 10^6 viral copies/mL prior to therapy who stabilizes after 6 months of therapy at an HIV RNA level that is detectable but <10,000 copies/mL may not warrant an immediate change in therapy.
- *Repeated detection of virus in plasma after initial suppression to undetectable levels, suggesting the development of resistance (BIII).* However, the degree of plasma HIV RNA increase should be considered; the physician may consider short-term further observation in a patient whose plasma HIV RNA increases from undetectable to low-level detectability (e.g., 50–5000 copies/mL) at 4 months. In this situation the patient should be followed very closely. It should be noted, however, that most patients who

fall into this category will subsequently show progressive increases in plasma viremia that will likely require a change in the antiretroviral regimen.

- *Any reproducible significant increase, defined as 3-fold or greater, from the nadir of plasma HIV RNA not attributable to intercurrent infection, vaccination, or test methodology except as noted above (BIII);*
- *Undetectable viremia in the patient receiving double nucleoside therapy (BIII).* Patients currently receiving 2 NRTIs who have achieved the goal of no detectable virus have the option of continuing this regimen or may have modification to conform to regimens in the strongly recommended category (Table 12). Prior experience indicates that most of these patients on double nucleoside therapy will eventually have virologic failure with a frequency that is substantially greater compared to patients treated with the strongly recommended regimens.
- *Persistently declining $CD4^+$ T cell numbers, as measured on at least two separate occasions (CIII); and*
- *Clinical deterioration (DIII).* In this regard, a new AIDS-defining diagnosis that was acquired after the time treatment was initiated suggests clinical deterioration but may or may not suggest failure of antiretroviral therapy. If the antiretroviral effect of therapy was poor (e.g., <10-fold reduction in viral RNA), then a judgment of therapeutic failure could be made. However, if the antiretroviral effect was good but the patient was already severely immunocompromised, the appearance of a new opportunistic disease may not necessarily reflect a failure of antiretroviral therapy, but rather a persistence of severe immunocompromise that did not improve despite adequate suppression of virus replication. Similarly, an accelerated decline in $CD4^+$ T cell counts suggests progressive immune deficiency providing there are sufficient measurements to assure quality control of $CD4^+$ T cell measurements.

A final consideration in the decision to change therapy is the recognition of the still limited choice of available agents and the knowledge that a decision to change may reduce future treatment options for the patient. This may influence the physician to be somewhat more conservative when deciding to change therapy. Consideration of alternative options should include potency of the substituted regimen and probability of tolerance of or adherence to the alternative regimen. Clinical trials have shown that partial suppression of virus is superior to no suppression of virus. On the other hand, some physicians and patients may prefer to suspend treatment in order to preserve future options or because a sustained antiviral effect cannot be achieved. Referral to or consultation with an experienced HIV clinician is appropriate when one is considering a change in therapy. When possible, patients requiring a change in an antiretroviral regimen but without treatment options using currently approved drugs should be referred for consideration for inclusion in an appropriate clinical trial.

Therapeutic Options When Changing Antiretroviral Therapy

Recommendations for changes in treatment differ according to the indication for the change. If the desired virologic objectives have been achieved in patients who have intolerance or toxicity, there should be substitution for the offending drug, preferably using an agent in the same class

with a different toxicity or tolerance profile. If virologic objectives have been achieved, but the patient is receiving a regimen not in the preferred category (such as two NRTIs or monotherapy), there is the option to continue treatment with careful monitoring of viral load or to add drugs to the current regimen to comply with strongly recommended treatment regimens. As discussed above, most authorities feel that treatment with regimens not in the strongly recommended or alternative categories is associated with eventual failure and recommend the latter tactic.

At present there are very few clinical data to support specific strategies for changing therapy in patients who have failed the strongly recommended regimens; however, a number of theoretical considerations should guide decisions. Because of the relatively rapid mutability of HIV, viral strains with resistance to one or more agents often emerge during therapy, particularly when viral replication has not been maximally suppressed. Of major concern is the possibility of broad cross-resistance among drugs within a class. Evidence indicates that viral strains that become resistant to one PI or NNRTI often have reduced susceptibility to most or all other PIs or NNRTIs.

Table 21 summarizes some of the most important guidelines to follow when changing a patient's antiretroviral therapy. As stated above, a change in regimen because of treatment failure should ideally be guided by results of resistance testing. Dose modifications may be required to account for drug interactions when using combinations of PIs or a PI and NNRTI (Table 18). In some individuals, options may be limited because of prior antiretroviral use, toxicity or intolerance. In the clinically stable patient with detectable viremia for whom an optimal change in therapy is not possible, it may be prudent to delay changing therapy in anticipation of the availability of newer and more potent agents. It is recommended that the decision to change therapy and design a new regimen should be made with assistance from a clinician experienced in the treatment of HIV infected patients through consultation or referral.

Acute HIV Infection

It has been estimated that at least 50% and as many as 90% of patients acutely infected with HIV will experience at least some symptoms of the acute retroviral syndrome (Table 22) and can thus be identified as candidates for early therapy *(158-161)*. However, acute HIV infection is often not recognized in the primary care setting because of the similarity of the symptom complex with those of the "flu" or other common illnesses. Additionally, acute primary infection may occur without symptoms. Physicians should maintain a high level of suspicion for HIV infection in all patients presenting with a compatible clinical syndrome (Table 22) and should obtain appropriate laboratory confirmation (see below). Information regarding treatment of acute HIV infection from clinical trials is very limited. Preliminary data suggest that treatment of primary HIV infection with combination therapy has a beneficial effect on laboratory markers of disease progression as well as clinical outcome *(19, 162-164)*. Ongoing clinical trials are addressing the question of the long term clinical benefit of potent treatment regimens.

The theoretical rationale for early intervention is sixfold:

- to suppress the initial burst of viral replication and decrease the magnitude of virus dissemination throughout the body;
- to decrease the severity of acute disease;
- to potentially alter the initial viral "set point," which may ultimately affect the rate of disease progression;
- to possibly reduce the rate of viral mutation due to the suppression of viral replication;
- to possibly reduce the risk of viral transmission;
- to preserve immune function.

The physician and the patient should be fully aware that therapy of primary HIV infection is based on theoretical considerations, and the potential benefits, described above, should be weighed against the potential risks (see below). Most authorities endorse treatment of acute HIV infection based on the theoretical rationale, limited but supportive clinical trial data, and the experience of HIV clinicians.

The risks of therapy for acute HIV infection include adverse effects on quality of life resulting from drug toxicities and dosing constraints; the potential, if therapy fails to effectively suppress viral replication, for the development of drug resistance which may limit future treatment options; and the potential need for continuing therapy indefinitely. These considerations are similar to those for initiating therapy in the asymptomatic patient and were discussed in greater detail in the section "Considerations for Initiating Therapy in the Patient with Asymptomatic HIV-Infection, p. 6."

Whom to Treat During Acute HIV Infection

Many experts would recommend antiretroviral therapy for all patients who demonstrate laboratory evidence of acute HIV infection (AII). Such evidence includes detectable HIV RNA in plasma using sensitive PCR or bDNA assays together with a negative or indeterminate HIV antibody test. While measurement of plasma HIV RNA is the preferable method of diagnosis, a test for p24 antigen may be useful when RNA testing is not readily available. It should be noted, however, that a negative p24 antigen test does not rule out acute infection. When suspicion for acute infection is high, such as in a patient with a report of recent risk behavior in association with symptoms and signs listed in Table 22, a test for HIV RNA should be performed (BII). Patients diagnosed with HIV infection by HIV RNA testing should have confirmatory testing performed (Table 2). As noted earlier, individuals may or may not have symptoms of the acute retroviral syndrome. Viremia occurs acutely after infection prior to the detection of a specific immune response; an indeterminate antibody test may occur when an individual is in the process of seroconversion.

Apart from patients with acute primary HIV infection, many experts would also consider therapy for patients in who seroconversion has been documented to have occurred within the previous six

months (CIII). Although the initial burst of viremia in infected adults has usually resolved by two months, treatment during the 2-6 month period after infection is based on the likelihood that virus replication in lymphoid tissue is still not maximally contained by the immune system during this time *(165)*. 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 using the algorithm mentioned previously, see "Considerations for Patients with Established HIV Infection", see p. 6 (CIII). Except in the setting of post-exposure prophylaxis with antiretroviral agents *(166)*, no patient should be treated for HIV infection until the infection is documented. In this regard, all patients presenting without a formal medical record of a positive HIV test, such as those who have tested positive by available home testing kits, should undergo ELISA and an established confirmatory test such as the Western Blot (AI) to document HIV infection.

Treatment Regimen for Primary HIV Infection

Once the physician and patient have made the decision to use antiretroviral therapy for primary HIV infection, treatment should be implemented with the goal of suppressing plasma HIV RNA levels to below detectable levels (AIII). There are insufficient data to make firm conclusions regarding specific drug recommendations; potential combinations of agents available are much the same as those used in established infection, listed in Table 12. It is recognized that these aggressive regimens may be associated with several disadvantages, including drug toxicity, large pill burden, cost of drugs, and the possibility of developing drug resistance that may limit future options; the latter is likely 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 carefully counseled regarding these potential limitations and individual decisions made only after weighing the risks and sequelae of therapy against the theoretical benefit of treatment (see above).

Since 1) the ultimate goal of therapy is suppression of viral replication to below the level of detection, and 2) the benefits of therapy are based primarily 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 considered appropriate for treating the acutely HIV-infected individual (EIII). Additional clinical studies are needed to delineate further the role of antiretroviral therapy in 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 above in "Use of Testing for Plasma HIV RNA Levels and CD4+ T Cell Count in Guiding Decisions for Therapy, p.2" (i.e., on initiation of therapy, after 4 weeks, and every 3-4 months thereafter) (AII). Some experts feel that testing for plasma HIV RNA levels at 4 weeks is not helpful in evaluating the effect of therapy for acute infection as viral loads may be decreasing from peak viremia levels even in the absence of therapy.

Duration of Therapy for Primary HIV Infection

Once therapy is initiated many experts would continue to treat the patient with antiretroviral agents indefinitely because viremia has been documented to reappear or increase after discontinuation of therapy (CII). The optimal duration and composition of therapy are unknown and ongoing clinical trials are expected to provide data relevant to these issues. The difficulties inherent in determining the optimal duration and composition of therapy initiated for acute infection should be considered when first counseling the patient regarding therapy.

Considerations for Antiretroviral Therapy in the HIV-Infected Adolescent

HIV-infected adolescents who were infected sexually or via injection drug use during adolescence appear to follow a clinical course that is more similar to HIV disease in adults than in children. In contrast, adolescents who were infected perinatally or via blood products as young children have a unique clinical course that may differ from other adolescents and long-term surviving adults. Currently, most HIV-infected adolescents were infected sexually during the adolescent period and are in a relatively early stage of infection.

Puberty is a time of somatic growth and hormonally-mediated changes, with females developing more body fat and males more muscle mass. Although theoretically these physiologic changes could affect drug pharmacology, particularly in the case of drugs with a narrow therapeutic index that are used in combination with protein-bound medicines or hepatic enzyme inducers or inhibitors, no clinically significant impact of puberty has been noted to date with the use of NRTIs. Clinical experience with PIs and NNRTIs has been limited. Thus, it is currently recommended that medications used to treat HIV and opportunistic infections in adolescents should be dosed based on Tanner staging of puberty and not specific age. Adolescents in early puberty (Tanner I–II) should be dosed under pediatric guidelines, while those in late puberty (Tanner V) should be dosed by adult guidelines. Youth who are in the midst of their growth spurt (Tanner III females and Tanner IV males) should be closely monitored for medication efficacy and toxicity when choosing adult or pediatric dosing guidelines.

Considerations for Antiretroviral Therapy in the HIV-Infected Pregnant Woman

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 of adverse effects outweighs the expected benefit to the woman. Combination antiretroviral therapy is the recommended standard treatment for HIV-infected non-pregnant adults. Additionally, a three-part regimen of ZDV, given orally starting at 14 weeks gestation and continued throughout pregnancy, intravenously during labor and to the newborn for the first six weeks of life, reduced the risk of perinatal transmission by 66% in a randomized, double-blind clinical trial (PACTG protocol 076) *(20)* and is recommended for all pregnant women *(167)*. 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 a) potential changes in dosing requirement resulting from physiologic changes associated with pregnancy, b) potential effects of antiretroviral drugs on the pregnant woman, c) effect on the risk of perinatal HIV transmission,

and d) the potential short- and long-term effects of the antiretroviral drug on the fetus and newborn, which may not be known for many antiretroviral drugs *(167)* (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). As discussed further below, the decision to use any antiretroviral drug during pregnancy should be made by the woman following discussion with her health care provider regarding the known and unknown benefits and 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 may wish to consider delaying initiation of therapy until after 10 to 12 weeks gestation, since this is the period of organogenesis when the embryo is most susceptible to potential teratogenic effects of drugs; the risks of antiretroviral therapy to the fetus during that period are unknown. However, this decision should be carefully considered and discussed between the health care provider and the patient and should include an assessment of the woman's health status and the potential benefits and risks of delaying initiation of therapy for several weeks. If clinical, virologic or immunologic parameters were such that therapy would be recommended for nonpregnant individuals, many of the Panel members would recommend initiating therapy regardless of gestational age. Nausea and vomiting in early pregnancy affecting the ability to adequately take and absorb oral medications may 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 suggest the need for treatment if non-pregnant. When initiation of antiretroviral therapy would be considered optional based on current guidelines for treatment of non-pregnant individuals but HIV-1 RNA levels are ≥1,000 copies/mL, infected pregnant women should be counseled regarding the potential benefits of standard combination therapy and should be offered such therapy including the three-part ZDV chemoprophylaxis regimen (Table 24). 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 below 1,000 copies/mL substantially lowers the risk of perinatal transmission *(168-170)* and limits the need to consider elective cesarean delivery as an intervention to reduce transmission risk *(167)* (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).

Use of antiretroviral prophylaxis has been shown 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 ZDV prophylaxis compared to 9.8% among those receiving no antiretroviral treatment *(168)*. The time-limited use of ZDV alone during pregnancy for chemoprophylaxis of perinatal transmission is controversial. The 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, some women may wish to restrict exposure of their fetus to antiretroviral drugs during pregnancy but still wish to reduce the risk of transmitting HIV to their infant. Additionally, for women with HIV-1 RNA levels <1,000 copies/mL, time-limited use of ZDV during the second and third trimesters of pregnancy is less likely to induce the development of resistance due to the limited viral replication existing in the patient and the time-limited exposure to the antiretroviral drug. For example, the development of ZDV resistance was unusual among the healthy population of women who participated in PACTG 076 *(21)*. The use of ZDV chemoprophylaxis alone during pregnancy might be an appropriate option for these women.

When combination therapy is given principally to reduce perinatal transmission and would have been considered optional for treatment if non-pregnant, consideration may be given to discontinuing therapy postnatally, with the decision to reinstitute treatment based on standard criteria for non-pregnant individuals. If drugs are discontinued postnatally, all drugs should be stopped simultaneously. Discussion regarding the decision to continue or stop combination therapy postpartum should occur prior to initiation of therapy during pregnancy.

Some women already receiving antiretroviral therapy may recognize their pregnancy early enough in gestation that concern for potential teratogenicity may lead them to consider temporarily stopping antiretroviral therapy until after the first trimester. There are insufficient data to support or refute teratogenic risk of antiretroviral drugs in humans when administered during the first 10–12 weeks of gestation. However, treatment with EFV should be avoided during the first trimester because significant teratogenic effects in rhesus macaques were seen at drug exposures similar to those representing human exposure. Hydroxyurea is a potent teratogen in a variety of animal species and should also be avoided during the first trimester.

There is concern that temporary discontinuation of antiretroviral therapy could result in a rebound in viral levels that theoretically could be associated with increased risk of early *in utero* HIV transmission or could potentiate disease progression in the woman *(171)*. Although the effects of all antiretroviral drugs on the developing fetus during the first trimester are uncertain, many experts 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 development of resistance. Once the drugs are reinstituted, they should be introduced simultaneously for the same reason.

There are currently limited data available on the pharmacokinetics and safety of antiretroviral agents during pregnancy for drugs other than ZDV (see "Safety and Toxicity of Individual Antireroviral Agents in Pregnancy", p. 85). In the absence of data, drug choices need to be individualized based on discussion with the patient and available data from preclinical and clinical testing of the individual drugs. The FDA pregnancy classification for all currently approved antiretroviral agents and selected other information relevant to the use of antiretroviral drugs in pregnancy is shown in Table 23. It is important to recognize that the predictive value of *in vitro* and animal screening tests for adverse effects in humans is unknown. Many drugs commonly used to treat HIV infection or its consequences may have positive findings on one or more of these screening tests. For example, acyclovir is positive on some *in vitro* assays for chromosomal breakage and carcinogenicity and is associated with some fetal abnormalities in

rats; however, data on human experience from the Acyclovir in Pregnancy Registry indicate no increased risk of birth defects to date in infants with *in utero* exposure to acyclovir *(172).*

When combination antiretroviral therapy is given during pregnancy, ZDV should be included as a component of antenatal therapy whenever possible. There may be circumstances where this is not feasible, such as the occurrence of significant ZDV-related toxicity. In addition, women receiving an antiretroviral regimen that does not contain ZDV but who have HIV-1 RNA levels that are consistently very low or undetectable have a very low risk of perinatal transmission and there may be concerns that the addition of ZDV to the current regimen could compromise adherence to the regimen. Regardless of the antepartum antiretroviral regimen, intravenous intrapartum ZDV and the standard six week course of ZDV for the infant is recommended. If the woman has not received ZDV as a component of her antenatal therapeutic antiretroviral regimen, intravenous ZDV should still be administered to the pregnant woman during the intrapartum period when feasible. Additionally, in 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 development of drug resistance. Because ZDV and d4T should not be administered together due to potential pharmacologic antagonism, options for women receiving oral d4T as part of their antenatal therapy include continuation of oral d4T during labor without intravenous ZDV, or withholding the oral d4T during the period of intravenous administration during labor.

Toxicity related to mitochondrial dysfunction has been reported in infected patients receiving long-term treatment with nucleoside analogues, and may be of particular concern for pregnant women. Symptomatic lactic acidosis and hepatic steatosis may have a female preponderance *(123)*. 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 (the HELLP syndrome) that occur during the third trimester of pregnancy. Some 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 *(173, 174)*, and possibly contribute to susceptibility to antiretroviral-associated mitochondrial toxicity.

It is unclear if pregnancy augments the incidence of the lactic acidosis/hepatic steatosis syndrome reported in non-pregnant individuals receiving nucleoside analogue treatment. 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 PI or NVP) *(175)*. 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. Non-fatal cases of lactic acidosis in pregnant women have also been reported.

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 *(175)*.

The antenatal ZDV dosing regimen used in the perinatal transmission prophylaxis trial PACTG 076 was ZDV 100 mg administered five times daily, and was selected based on the standard ZDV dosage for adults at the time the study was designed in 1989 (Table 24). However, data indicate that administration of ZDV three times daily will maintain intracellular ZDV triphosphate at levels comparable with those observed with more frequent dosing *(176, 177)*. Comparable clinical response also has been observed in clinical trials among persons receiving ZDV twice daily *(178-180)*. Thus, the current standard ZDV dosing regimen for adults is 200 mg three times daily, or 300 mg twice daily. A less frequent dosing regimen would be expected to enhance maternal adherence to the ZDV perinatal prophylaxis regimen, and therefore is an acceptable alternative antenatal dosing regimen for ZDV prophylaxis.

In a short-course antenatal/intrapartum ZDV perinatal transmission prophylaxis trial in Thailand, administration of ZDV 300 mg twice daily for 4 weeks antenatally and 300 mg every 3 hours orally during labor was shown to reduce perinatal transmission by approximately 50% compared to placebo *(181)*. The lower efficacy of the short-course 2-part ZDV prophylaxis regimen studied in Thailand compared to the 3-part ZDV prophylaxis regimen used in PACTG 076 and recommended for use in the U.S. could result from the shorter antenatal duration of ZDV, oral rather than intravenous administration during labor, lack of treatment for the infant, or 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 3-part PACTG 076 ZDV 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 non-pregnant individuals. Data from untreated as well as ZDV-treated infected pregnant women indicate that HIV-1 RNA levels correlate with risk of transmission *(20, 169, 170)*. However, although the risk of perinatal transmission in women with HIV-1 RNA below the level of assay quantitation appears to be very low, transmission from mother to infant has been reported in women with all levels of maternal HIV-1 RNA. Additionally, antiretroviral prophylaxis is effective in reducing transmission even among women with low RNA levels *(20, 168)*. The mechanism by which antiretroviral prophylaxis reduces transmission is likely multifactorial. Reduction in maternal antenatal viral load is likely an important component of prophylaxis. However, in addition, pre- and post-exposure 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 following the birth process *(182)*; the extent of transplacental passage varies between antiretroviral drugs (Table 23). Additionally, while there is general correlation between plasma and genital tract viral load, discordance has also been reported *(183-185)*; in addition, differential evolution of viral sequence diversity occurs between the peripheral blood and genital tract *(185, 186)*. 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 of perinatal HIV transmission. The full ZDV chemoprophylaxis regimen, including intravenous ZDV during delivery and the administration of ZDV to the infant for the first six weeks of life, in combination with other antiretrovirals or alone in selected cases, should be discussed with and offered to all infected pregnant women regardless of their HIV-1 RNA level.

Health care providers 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 individual patients. 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 physician. 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.

Conclusion

The panel has attempted to use the advances in our understanding of the pathogenesis of HIV in the infected person to translate scientific principles and data obtained from clinical experience into recommendations that can be used by the clinician and patient to make therapeutic decisions. The recommendations are offered in the context of an ongoing dialogue between the patient and the clinician after having defined specific therapeutic goals with an acknowledgment of uncertainties. It is necessary for the patient to be entered into a continuum of medical care and services, including social, psychosocial, and nutritional services, with the availability of expert referral and consultation. In order to achieve the maximal flexibility in tailoring therapy to each patient over the duration of his or her infection, it is imperative that drug formularies allow for all FDA-approved NRTI, NNRTI, and PI as treatment options. The Panel strongly urges industry and the public/private sectors to conduct further studies to allow refinement of these guidelines. Specifically, studies are needed to optimize recommendations for first line therapy; to define second line therapy; and to more clearly delineate the reason(s) for treatment failure. The Panel remains committed to revising their recommendations as such 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

Strength of Recommendation

A: Strong, should always be offered

B: Moderate, should usually be offered

C: Optional

D: Should generally not be offered

E: Should never be offered

Quality of Evidence for Recommendation

I: At least one randomized trial with clinical endpoints

II: Clinical trials with laboratory endpoints

III: Expert opinion

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 "set point"	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, HSV, PCP, etc.) and immunizations can cause 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 such as Western blot serology performed 2-4 months after the initial indeterminate or negative test.

Table 3. Recommendations for the Use of Drug Resistance Assays

Clinical setting/Recommendation	Rationale
Recommended	
Virologic failure during HAART (see page 23)	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 initiation of antiretroviral therapy (see page 23)	Determine the role of resistance and maximize the number of active drugs in the new regimen if indicated.
Consider	
Acute HIV infection	Determine if drug resistant virus was transmitted and change regimen accordingly.
Not generally recommended	
Chronic HIV infection prior to initiation of therapy	Uncertain prevalence of resistant virus. Current assays may not detect minor drug resistant species.
After discontinuation of drugs	Drug resistance mutations may become minor species in the absence of selective drug pressure. Current assays may not detect minor drug resistant species.
Plasma viral load <1000 HIV RNA copies/mL	Resistance assays cannot be reliably performed because of low copy number of HIV RNA.

Table 4. Risks and Benefits of Delayed Initiation of Therapy and of Early Therapy in the Asymptomatic HIV-Infected Patient

Risks and benefits of delayed therapy*

Benefits of delayed therapy

- Avoid negative effects on quality of life (i.e., inconvenience)
- Avoid drug-related adverse events
- Delay in development of drug resistance
- Preserve maximum number of available and future drug options when HIV disease risk is highest

Risks of delayed therapy

- Possible risk of irreversible immune system depletion
- Possible greater difficulty in suppressing viral replication
- Possible increased risk of HIV transmission

Risks and benefits of early therapy*

Benefits of early therapy

- Control of viral replication easier to achieve and maintain
- Delay or prevention of immune system compromise
- Lower risk of resistance with complete viral suppression
- Possible decreased risk of HIV transmission†

Risks of early therapy

- Drug-related reduction in quality of life
- Greater cumulative drug-related adverse events
- Earlier development of drug resistance, if viral suppression is suboptimal
- Limitation of future antiretroviral treatment options

* See Table 6 for consensus recommendations regarding when to initiate therapy.
† The risk of 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 of Progression to AIDS Defining Illness in a Cohort of Homosexual Men Predicted by Baseline CD4+ T Cell Count and Viral Load*

CD4 ≤ 200 Plasma Viral Load (copies/ml) †				% AIDS (AIDS-defining complication) ‡			
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 Plasma Viral Load (copies/ml)			**% AIDS (AIDS-defining complication)**		
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 Plasma Viral Load (copies/ml)			**% AIDS (AIDS-defining complication)**		
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

* Data from the Multi-Center AIDS Cohort Study (MACS) adapted from reference **3** by Alvaro Muñoz, Ph.D. (personal communication.)

† MACS numbers reflect plasma HIV RNA values obtained by bDNA testing. RT-PCR values are consistently 2 – 2.5 fold higher than bDNA values, as indicated.

‡ In this study AIDS was defined according to the 1987 CDC definition and does not include asymptomatic individuals with CD4+ T cells < 200 mm^3.

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

Table 6. Indications for the Initiation of Antiretroviral Therapy in the Chronically HIV-1 Infected Patient

Clinical Category	$CD4^+$ T Cell Count	Plasma HIV RNA	Recommendation
Symptomatic (AIDS, severe symptoms)	Any value	Any value	Treat
Asymptomatic, AIDS	$CD4^+$ T cells $<200/mm^3$	Any value	Treat
Asymptomatic	$CD4^+$ T cells But $>200/mm^3$ but $<350/mm^3$	Any value	Treatment should generally be offered, though controversy exists.*
Asymptomatic	$CD4^+$ T cells $>350/mm^3$	>30,000 (bDNA) or >55,000 (RT-PCR)	Some experts would recommend initiating therapy, recognizing that the 3-year risk of developing AIDS in untreated patients is >30%. In the absence of very high levels of plasma HIV RNA, some would defer therapy and monitor the $CD4^+$ T cell count and level of plasma HIV RNA more frequently. Clinical outcomes data after initiating therapy are lacking.
Asymptomatic	$CD4^+$ T cells $>350/mm^3$	<30,000 (bDNA) or <55,000 (RT-PCR)	Many experts would defer therapy and observe, recognizing that the 3-year risk of developing AIDS in untreated patients is <15%.

* Clinical benefit has been demonstrated in controlled trials only for patients with $CD4^+$ T cells $<200/mm^3$. However, most experts would offer therapy at a $CD4^+$ T cell threshold $<350/mm^3$. All decisions to initiate therapy should be based on prognosis for disease-free survival in the absence of treatment, as determined by the $CD4^+$ T cell count and level of plasma HIV RNA shown in Table 5, the potential benefits and risks of therapy shown in Table 4, and the willingness of the patient to accept therapy. For further information, see "Considerations for Initiating Therapy in the Patient with Asymptomatic HIV Infection", p. 6 .

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

- Inform patient, 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, which the patient understands and to which he/she commits.
- Take time, multiple encounters to educate and explain goals of therapy and need for adherence.
- Establish readiness to take medication *before* first prescription is written.
- Recruit family and friends to support the treatment plan.
- Develop concrete plan for specific regimen, relation to meals, daily schedule, side effects.
- Provide written schedule and pictures of medications, daily or weekly pill boxes, alarm clocks, pagers, other mechanical aids to adherence.
- Develop adherence support groups, or add adherence issues to regular agenda of support groups.
- Develop linkages with local community-based organizations around adherence with educational sessions and practical strategies.
- Consider “pill trials” with jelly beans.

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

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

Table 9. Interventions Associated with Improved Adherence

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

Table 10. Goals of HIV Therapy and Tools to Achieve Them

Goals of Therapy

- Maximal and durable suppression of viral load
- Restoration and/or preservation of immunologic function
- Improvement of quality of life
- Reduction of HIV-related morbidity and mortality

Tools to Achieve Goals of Therapy

- Maximize adherence to the antiretroviral regimen
- Rational sequencing of drugs
- Preservation of future treatment options
- Use of resistance testing in selected clinical settings

TABLE 11. Advantages and Disadvantages of Class-Sparing Regimens

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 • Continued benefits sometimes seen despite viral breakthrough • Resistance requires multiple mutations • Targets HIV at two steps of viral replication (RT and PI)	• May be difficult to use and adhere to • Long-term side effects may 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 • Resistance primes for cross-resistance with other PIs
NNRTI-based HAART regimen (PI-sparing)	• Sparing of PI-related side effects • Generally easier to use and adhere to compared with PIs	• Comparability to PI-containing regimens with regard to clinical endpoints unknown • Resistance conferred by a single or few mutations	• Fewer drug-drug interactions compared with PIs	• Preserves PIs for later use • 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 • Sparing of PI and NNRTI side effects • Resistance to 1 NRTI does not confer cross-resistance to entire class	• Comparability to PI-containing regimens with regard to clinical endpoints unknown • Long-term virologic efficacy with high baseline plasma viral load (i.e., >100,000 copies/ml) may be suboptimal	• Generally manageable drug interaction problems	• Preserves both PI and NNRTI classes for later use • Limited cross-resistance within the NRTI class

* Some side effects being attributed to protease inhibitor therapy, such as lipodystrophy, have not been proven to be strictly associated with the use of protease inhibitor-containing regimens. Lipodystrophy has also been described uncommonly in patients on NRTIs alone and in patients on no antiretroviral therapy.

Table 12. Recommended Antiretroviral Agents for Initial Treatment of Established HIV Infection

This table provides a guide to the use of available treatment regimens for individuals with no prior or limited experience on HIV therapy. In accordance with the established goals of HIV therapy, priority is given to regimens in which clinical trials data suggest the following: sustained suppression of HIV plasma RNA (particularly in patients with high baseline viral load) and sustained increase in CD4+ T cell count (in most cases over 48 weeks), and favorable clinical outcome (i.e., delayed progression to AIDS and death). Particular emphasis is given to regimens that have been compared directly with other regimens that perform sufficiently well with regard to these parameters to be included in the "Strongly Recommended" category. Additional consideration is given to the regimen's pill burden, dosing frequency, food requirements, convenience, toxicity, and drug interaction profile compared with other regimens.

It is important to note that all antiretroviral agents, including those in the 'Strongly Recommended" category, have potentially serious toxic and adverse events associated with their use. The reader is strongly encouraged to consult tables 13-19 while formulating an antiretroviral regimen.

Antiretroviral drug regimens are comprised of one choice each from columns A and B. Drugs are listed in alphabetical, not priority, order.

Strongly Recommended	Column A Efavirenz Indinavir Nelfinavir Ritonavir + Indinavir*† Ritonavir + Lopinavir*‡ Ritonavir + Saquinavir* (SGC§ or HGC§)	Column B Stavudine + Didanosine¶ Stavudine + Lamivudine Zidovudine + Didanosine Zidovudine + Lamivudine
Recommended as Alternatives	Column A Abacavir Amprenavir Delavirdine Nelfinavir + Saquinavir-SGC Nevirapine Ritonavir Saquinavir-SGC	Column B Didanosine + Lamivudine Zidovudine + Zalcitabine
No Recommendation; Insufficient Data#	Hydroxyurea in combination with antiretroviral drugs Ritonavir + Amprenavir* Ritonavir + Nelfinavir*	
Not Recommended; Should Not Be Offered	All monotherapies, whether from column A or B** Column A Saquinavir-HGC††	Column B Stavudine + Zidovudine Zalcitabine + Didanosine Zalcitabine + Lamivudine Zalcitabine + Stavudine

* See page 16 for more information on optimizing protease inhibitor exposure with ritonavir.

† Based on expert opinion.

‡ Co-formulated as Kaletra.

§ Saquinavir-SGC, soft-gel capsule (Fortovase); Saquinavir-HGC, hard-gel capsule (Invirase).

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

\# This category includes drugs or combinations for which information is too limited to allow a recommendation for or against use.

** Zidovudine monotherapy may be considered for prophylactic use in pregnant women with low viral load and high $CD4^+$ T cell counts to prevent perinatal transmission, as discussed under "Considerations in the Pregnant Woman."

†† Use of Saquinavir-HGC (Invirase) is not recommended, except in combination with ritonavir.

Table 13. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Generic Name Trade Name	**Zidovudine** **(AZT, ZDV)** Retrovir	**Didanosine** **(ddI)** Videx	**Zalcitabine** **(ddC)** HIVID
Form	100 mg capsules 300 mg tablets 10 mg/mL IV solution 10 mg/mL oral solution	25, 50, 100, 150, 200* mg chewable/dispersible buffered tablets 100, 167, 250 mg buffered powder for oral solution 400 mg enteric coated capsules (EC)	0.375, 0.75 mg tablets
Dosing Recommendations	200 mg tid or 300 mg bid or with 3TC as Combivir†, 1 bid or with abacavir and 3TC as Trizivir‡, 1 bid	>60kg: 200 mg bid (buff. tablets), 250 mg bid (buff. powder) or 400 mg qd§ (buff. tablets or EC capsules) <60kg: 125 mg bid (buff. tablets), 167 mg bid (buff. powder) or 250 mg qd§ (buff. tablets or EC capsules)	0.75 mg tid
Food Effect	Take without regard to meals	Levels ↓ 55% Take 1/2 hour before or 2 hours after meal	Take without regard to meals
Oral bioavailability	60%	30 - 40%	85%
Serum half-life	1.1 hours	1.6 hours	1.2 hours
Intracellular half-life	3 hours	25-40 hours	3 hours
Elimination	Metabolized to AZT glucuronide (GAZT) Renal excretion of GAZT	Renal excretion 50%	Renal excretion 70%
Adverse Events	Bone marrow suppression: Anemia and/or neutropenia Subjective complaints: GI intolerance, headache, insomnia, asthenia Lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity with the use of NRTIs.	Pancreatitis¶ Peripheral neuropathy Nausea Diarrhea Lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity with the use of NRTIs.#	Peripheral neuropathy Stomatitis Lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity with the use of NRTIs.

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

† Each Combivir tablet contains 300 mg ZDV and 150 mg 3TC.

‡ Each Trizivir tablet contains 300 mg ZDV, 150 mg 3TC, and 300 mg abacavir.

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

¶ Cases of fatal and nonfatal pancreatitis have occurred in treatment-naive and treatment-experienced patients during therapy with ddI or in combination with other drugs, particularly d4T or d4T + hydroxyurea.

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

Table 13. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (NRTIs)-Cont.

Generic Name Trade Name	**Stavudine** **(d4T)** Zerit	**Lamivudine** **(3TC)** Epivir	**Abacavir** **(ABC)** Ziagen
Form	15, 20, 30, 40 mg capsules 1mg/mL for oral solution	150 mg tablets 10 mg/mL oral solution	300 mg tablets 20 mg/mL oral solution
Dosing Recommendations	>60kg: 40 mg bid <60kg: 30 mg bid	150 mg bid <50kg: 2 mg/kg bid or with ZDV as Combivir, 1 bid, or with ZDV and abacavir as Trizivir‡, 1 bid	300 mg bid or with ZDV and 3TC as Trizivir‡, 1 bid
Food Effect	Take without regard to meals	Take without regard to meals	Take without regard to meals Alcohol ↑ABC levels 41%; no effect on alcohol
Oral bioavailability	86%	86%	83%
Serum half-life	1.0 hour	3-6 hours	1.5 hours
Intracellular half-life	3.5 hours	12 hours	3.3 hours
Elimination	Renal excretion 50%	Renal excretion unchanged	Metabolized by alcohol dehydrogenase and glucuronyl transferase. Renal excretion of metabolites 82%
Adverse Events	Pancreatitis¶ Peripheral neuropathy Lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity with the use of NRTIs.#	(Minimal toxicity) Lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity with the use of NRTIs.	Hypersensitivity reaction (can be fatal) **; fever, rash, nausea, vomiting, malaise or fatigue, and loss of appetite. Respiratory symptoms may also be component (sore throat, cough, SOB). Lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity with the use of NRTIs.

‡ Each Trizivir tablet contains 300 mg ZDV, 150 mg 3TC, and 300 mg abacavir.

¶ Cases of fatal and nonfatal pancreatitis have occurred in treatment-naive and treatment-experienced patients during therapy with ddI or in combination with other drugs, particularly d4T or d4T + hydroxyurea.

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

** Patients who develop 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 re-started, 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 14. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Generic Name Trade Name	**Nevirapine** Viramune	**Delavirdine** Rescriptor	**Efavirenz** Sustiva
Form	200 mg tablets 50 mg/5 mL oral suspension	100 mg tablets 200 mg tablets	50, 100, 200 mg capsules
Dosing Recommendation	200 mg po qd x 14 days, then 200 mg po bid	400 mg po tid; 100 mg tablets can be dispersed in ≥ 3 oz water to produce slurry Separate dosing with ddI or antacids by 1 hour	600 mg po qHS
Food Effect	Take without regard to meals	Take without regard to meals	Avoid taking after high fat meals, Levels↑ 50%
Oral bioavailability	> 90%	85%	Data not available
Serum half-life	25-30 hours	5.8 hours	40-55 hours
Elimination	Metabolized by cytochrome P450 (3A inducer); 80% excreted in urine (glucuronidated metabolites, < 5% unchanged), 10% in feces	Metabolized by cytochrome P450 (3A inhibitor) 51% excreted in urine (<5% unchanged), 44% in feces	Metabolized by cytochrome P450 (3A mixed inducer/inhibitor); 14-34% excreted in urine (glucuronidated metabolites, < 1% unchanged), 16-61% in feces.
Adverse Events	Rash* Increased transaminase levels Hepatitis	Rash* Increased transaminase levels Headaches	Rash* Central nervous system symptoms† Increase transaminase levels False positive cannabinoid test Teratogenic in monkeys‡
Drug Interactions	**For information on Drug Interactions please see Table 17.**		

* In clinical trials, the NNRTI was discontinued because of rash in 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.

† May include dizziness, somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, and euphoria. The overall frequency of any of these symptoms associated with use of efavirenz was 52% compared with 26% in controls; 2.6% of those on efavirenz discontinued the drug due to these symptoms; symptoms usually subside spontaneously over 2-4 weeks.

‡ No data are available regarding teratogenicity of other NNRTIs in non-human primates.

Table 15. Characteristics of Protease Inhibitors (PIs)

Generic Name Trade Name	**Indinavir** Crixivan	**Ritonavir** Norvir	**Nelfinavir** Viracept
Form	200, 333, 400 mg capsules	100 mg capsules 600 mg/7.5 mL po solution	250 mg tablets 50 mg/g oral powder
Dosing Recommendations	800 mg q8h Separate dosing with ddI by 1 hour	600 mg q12h* Separate dosing with ddI by 2 hours	750 mg tid or 1250mg bid
Food Effect	Levels decrease 77% Take 1 hour before or 2 hours after meals; may take with skim milk or low fat meal	Levels increase 15% Take with food if possible; this may improve tolerability	Levels increase 2-3 fold Take with meal or snack
Oral bioavailability	65%	(not determined)	20 – 80%
Serum half-life	1.5-2 hours	3-5 hours	3.5-5 hours
Route of Metabolism	P450 cytochrome 3A4 inhibitor (less than ritonavir)	P450 cytochrome 3A4 > 2D6 Potent 3A4 inhibitor	P450 cytochrome 3A4 inhibitor (less than ritonavir)
Storage	Room temperature	Refrigerate capsules Oral solution should NOT be refrigerated	Room temperature
Adverse Effects	• Nephrolithiasis • GI intolerance, nausea • Lab: Increased indirect bilirubinemia (inconsequential) • Misc.: Headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, alopecia • Hyperglycemia† • Fat redistribution and lipid abnormalities‡ • Possible increased bleeding episodes in patients with hemophilia	• GI intolerance, nausea, vomiting, diarrhea • Paresthesias – circumoral and extremities • Hepatitis • Pancreatitis • Asthenia • Taste perversion • Lab.: Triglycerides increase > 200%, transaminase elevation, elevated CPK and uric acid • Hyperglycemia† • Fat redistribution and lipid abnormalities‡ • Possible increased bleeding episodes in patients with hemophilia	• Diarrhea • Hyperglycemia† • Fat redistribution and lipid abnormalities‡ • Possible increased bleeding episodes in patients with hemophilia
Drug Interactions	**For more information on Drug Interactions please see Table 17.**		

* Dose escalation for Ritonavir: Day 1-2: 300 mg bid; day 3-5: 400 mg bid; day 6-13: 500 mg bid; day 14: 600 mg bid
Combination treatment regimen with Saquinavir (400 mg po bid) plus Ritonavir (400 mg po bid)

† Cases of worsening glycemic control in patients with pre-existing 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 increasingly recognized with the use of protease inhibitors. Patients with hypertriglyceridemia or hypercholesterolemia should be evaluated for risk for cardiovascular events and pancreatitis. Possible interventions include dietary modification, lipid lowering agents, or discontinuation of PIs.

Table 15. Characteristics of Protease Inhibitors (PIs) - Cont.

Generic Name Trade Name	**Saquinavir** Invirase	 Fortovase	**Amprenavir** Agenerase	**Lopinavir + Ritonavir** Kaletra
Form	200 mg capsules	200 mg capsules	50 mg, 150 mg capsules 15 mg/mL oral solution (capsules and solution NOT interchangeable on mg per mg basis)	133.3 mg lopinavir + 33.3 mg ritonavir capsules 80 mg lopinavir + 20 mg ritonavir per ml oral solution
Dosing Recommendations	400 mg bid with ritonavir; Invirase not recommended otherwise	1,200 mg tid §	>50 kg: 1200 mg bid (capsules) 1400 mg bid (oral solution) < 50 kg: 20mg/kg bid (capsules) maximum 2400 mg daily total. <50 kg: 1.5mL/kg bid (oral solution) maximum 2800 mg daily total	400 mg lopinavir + 100 mg ritonavir bid
Food Effect	No food effect when taken with ritonavir	Levels increase 6-fold Take with large meal	High fat meal decreases AUC 21%; can be taken with or without food, but high fat meal should be avoided.	Moderate fat meal increases AUC of capsules and solution by 48% and 80%, respectively. Take with food.
Oral bioavailability	Hard gel capsule: 4% erratic	Soft gel capsule (not determined)	Not determined in humans	Not determined in humans
Serum half-life	1-2 hours	1-2 hours	7.1-10.6 hours	5-6 hours
Route of Metabolism	P450 cytochrome 3A4 inhibitor (less than ritonavir)	P450 cytochrome 3A4 inhibitor (less than ritonavir)	P450 cytochrome 3A4 inhibitor (less than ritonavir; similar to indinavir, nelfinavir)	P450 cytochrome 3A4 inhibitor
Storage	Room temperature	Refrigerate or store at room temperature (up to 3 months)	Room temperature	Refrigerated capsules stable until date on label. If stored at room temperature, stable for 2 months
Adverse Effects	• GI intolerance, nausea and diarrhea • Headache • Elevated transaminase enzymes • Hyperglycemia † • Fat redistribution and lipid abnormalities ‡ • Possible increased bleeding episodes in patients with hemophilia	• GI intolerance, nausea, diarrhea, abdominal pain and dyspepsia • Headache • Elevated transaminase enzymes • Hyperglycemia † • Fat redistribution and lipid abnormalities ‡ • Possible increased bleeding episodes in patients with hemophilia	• GI intolerance, nausea, vomiting, diarrhea • Rash • Oral paresthesias • Lab: Increase in liver function tests • Hyperglycemia† • Fat redistribution and lipid abnormalities ‡ • Possible increased bleeding episodes in patients with hemophilia • 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	• GI intolerance, nausea, vomiting, diarrhea • Asthenia • Elevated transaminase enzymes • Hyperglycemia† • Fat redistribution and lipid abnormalities‡ • Possible increased bleeding episodes in patients with hemophilia • Oral solution continues 42% alcohol
Drug Interactions	**For more information on Drug Interactions please see Table 17.**			

§ Saquinavir soft gel capsule given as 1600 bid produced lower daily exposure and trough serum concentrations compared with the standard 1200 mg tid regimen. Trends in immunologic and virologic responses favored the standard tid regimen. The clinical significance of the inferior trends observed in the bid dosing group are not known; however, until the availability of the results from longer follow-up studies, bid dosing of saquinavir soft gel capsules is not recommended.

† Cases of worsening glycemic control in patients with pre-existing 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 increasingly recognized with the use of protease inhibitors. Discontinuation of PIs may be required to reverse fat redistribution. Patients with hypertriglyceridemia or hypercholesterolemia should be evaluated for risk for cardiovascular events and pancreatitis. Possible interventions include dietary modification, lipid lowering agents or discontinuation of PIs.

Table 16. Drugs That Should Not Be Used With PI Antiretrovirals

Drug Category	Indinavir	Ritonavir*	Saquinavir	Nelfinavir	Amprenavir	Lopinavir + Ritonavir
Ca++ channel blocker	(none)	bepridil	(none)	(none)	bepridil	(none)
Cardiac	(none)	amiodarone flecainide propafenone quinidine	(none)	(none)	(none)	flecainide propafenone
Lipid Lowering Agents	simvastatin lovastatin	simvastatin lovastatin	simvastatin lovastatin	simvastatin lovastatin	simvastatin lovastatin	simvastatin lovastatin
Anti-Mycobacterial	rifampin	(none)	rifampin rifabutin	rifampin	rifampin	rifampin
Antihistamine	astemizole terfenadine	astemizole terfenadine	astemizole terfenadine	astemizole terfenadine	astemizole terfenadine	astemizole terfenadine
Gastrointestinal Drugs	cisapride	cisapride	cisapride	cisapride	cisapride	cisapride
Neuroleptic	(none)	clozapine pimozide	(none)	(none)	(none)	pimozide
Psychotropic	midazolam triazolam	midazolam triazolam	midazolam triazolam	midazolam triazolam	midazolam triazolam	midazolam triazolam
Ergot Alkaloids (vasoconstrictor)	dihydroergotamine (D.H.E. 45) ergotamine† (various forms)	dihydroergotamine (D.H.E. 45) ergotamine† (various forms)	dihydroergotamine (D.H.E. 45) ergotamine† (various forms)	dihydroergotamine (D.H.E. 45) ergotamine† (various forms)	dihydroergotamine (D.H.E. 45) ergotamine† (various forms)	dihydroergotamine (D.H.E. 45) ergotamine† (various forms)
Herbs	St. John's wort	St. John's wort	St. John's wort	St. John's wort	St. John's wort	St. John's wort

* Some of the contraindicated drugs listed are based on theoretical considerations. Thus, drugs with low therapeutic indices yet with suspected major metabolic contribution from cytochrome P450 3A, CYP2D6, or unknown pathways, are included in this table. Actual interactions may or may not occur in patients.

† This is likely a class effect.

Suggested Alternatives

Simvastatin, lovastatin: atorvastatin, pravastatin, fluvastatin, cerivastatin (alternatives should be used with caution)

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

Astemizole, terfenadine: loratadine, fexofenadine, cetirizine

Midazolam, triazolam: temazepam, lorazepam

Table 16. Drugs That Should Not Be Used With NNRTI Antiretrovirals - Cont.

Drug Category	Nevirapine	Delavirdine	Efavirenz
Ca++ channel blocker	(none)	(none)	(none)
Cardiac	(none)	(none)	(none)
Lipid Lowering Agents	(none)	simvastatin lovastatin	(none)
Anti-Mycobacterial	Insufficient data	rifampin rifabutin	(none)
Antihistamine	(none)	astemizole terfenadine	astemizole terfenadine
Gastrointestinal Drugs	(none)	cisapride H-2 blockers Proton pump inhibitors	cisapride
Neuroleptic	(none)	(none)	(none)
Psychotropic	(none)	midazolam triazolam	midazolam triazolam
Ergot Alkaloids (vasoconstrictor)	(none)	dihydroergotamine (D.H.E. 45) ergotamine† (various forms)	dihydroergotamine (D.H.E. 45) ergotamine† (various forms)

† This is likely a class effect.

Suggested Alternatives

Simvastatin, lovastatin: atorvastatin, pravastatin, fluvastatin, cerivastatin (alternatives should be used with caution)
Rifabutin: clarithromycin, azithromycin (MAI prophylaxis); clarithromycin, ethambutol (MAI treatment)
Astemizole, terfenadine: loratadine, fexofenadine, cetirizine
Midazolam, triazolam: temazepam, lorazepam

Table 17. Drug Interactions Between Antiretrovirals and Other Drugs
Protease Inhibitors (PIs)

Drug Interactions Requiring Dose Modifications or Cautious Use			
Drugs Affected	**Indinavir (IDV)**	**Ritonavir* (RTV)**	**Saquinavir† (SQV)**
ANTIFUNGALS			
Ketoconazole	Levels: IDV ↑ 68% Dose: IDV 600 mg tid	Levels: ketoconazole ↑ 3X Dose: Use with caution; do not exceed 200 mg ketoconazole daily	Levels: SQV ↑ 3X Dose: Standard
ANTI-MYCOBACTERIALS			
Rifampin	Levels: IDV ↓ 89% Contraindicated	Levels: RTV ↓ 35% Dose: No Data Increased liver toxicity possible	Levels: SQV ↓ 84% Contraindicated, unless using RTV+SQV, then use rifampin 600 mg qd or 2-3x/week
Rifabutin	Levels: IDV ↓32% Rifabutin ↑2X Dose: ↓rifabutin to 150 mg qd or 300 mg 2-3x/week IDV 1000 mg tid	Levels: Rifabutin ↑4X Dose: ↓rifabutin to 150 mg qod Or dose 3x per week RTV: Standard	Levels: SQV ↓40% No dose adjustment unless using RTV+SQV, then use rifabutin 150 mg 2-3x/week
Clarithromycin	Levels: Clarithromycin ↑ 53% No dose adjustment	Levels: Clarithromycin ↑ 77% Dose adjust for renal insufficiency	Levels: Clarithromycin ↑ 45% SQV ↑ 177% No dose adjustment
ORAL CONTRACEPTIVES	Levels: Norethindrone ↑26% Ethinylestradiol ↑24% No dose adjustment	Levels: Ethinyl estradiol ↓ 40% Use alternative or additional method	No data
LIPID LOWERING AGENTS			
Simvastatin **Lovastatin**	Levels: Potential for large increase in statin levels. Avoid concomitant use.	Levels: Potential for large increase in statin levels. Avoid concomitant use.	Levels: Potential for large increase in statin levels. Avoid concomitant use.
ANTICONVULSANTS			
Phenobarbitol **Phenytoin** **Carbamazepine**	Carbamazepine markedly ↓ IDV AUC. Consider alternative agent	Unknown Use with caution Monitor anticonvulsant levels.	Unknown but may decrease SQV levels substantially Monitor anticonvulsant levels.
Methadone	No change in methadone levels	Methadone ↓ 37%. Monitor and titrate dose if needed. May require ↑ methadone dose.	No data
Miscellaneous	Grapefruit juice ↓ IDV levels by 26% Sildenafil AUC ↑ 2-11 fold. Do not exceed 25 mg in a 48 hr. period	Desipramine ↑ 145%, reduce dose Theophylline ↓47%, monitor theo. levels. Many possible interactions Sildenafil AUC ↑ 2-11 fold. Do not exceed 25 mg in a 48 hr. period	Grapefruit juice increases SQV levels Dexamethasone decreases SQV levels Sildenafil AUC ↑ 2-11 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.

Table 17. Drug Interactions Between Antiretrovirals and Other Drugs - Cont. Protease Inhibitors (PIs)

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% Keto ↑ 44%. Combination under investigation	Levels: LPV AUC ↓ 13%. Keto ↑ 3-fold
ANTI-MYCOBACTERIALS			
Rifampin	Levels ↓ 82% Contraindicated	Levels: APV AUC ↓ 82% No change in rifampin AUC. Avoid concomitant use.	Levels: LPV AUC ↓ 75% Avoid concomitant use
Rifabutin	Levels: NFV ↓32% Rifabutin↑2X Dose: ↓rifabutin to 150 mg qd Or 300 mg 2-3x/week ↑NFV dose to 1000 mg tid.	Levels: APV AUC ↓15% Rifabutin ↑193% Dose: No change in APV dose; Decrease rifabutin to 150 mg qd or 300 mg 2-3x/week.	Levels: Rifabutin AUC ↑ 3-fold 25-O-desacetyl metabolite ↑ 47.5-fold. 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	No data
ORAL CONTRACEPTIVES	Levels: Norethindrone↓ 18% Ethinyl estradiol↓47% Use alternative or additional method	Levels: Potential for metabolic interactions; use alternative or additional method.	Levels: ethinyl estradiol ↓ 42% Use alternative or additional method
LIPID LOWERING AGENTS			
Simvastatin **Lovastatin** **Atorvastatin** **Pravastatin**	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 AUC ↑ 5.88-fold. Use with caution and monitoring. Pravastatin AUC ↑ 33%; no dosage adjustment necessary
ANTICONVULSANTS			
Phenobarbitol **Phenytoin** **Carbamazepine**	Unknown, but may decrease NFV levels substantially Monitor anticonvulsant levels.	Unknown, but may decrease APV levels substantially Monitor anticonvulsant levels.	Unknown, but may decrease LPV levels substantially. Monitor anticonvulsant levels.
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% Monitor and titrate dose if needed. May require ↑ methadone dose.
Miscellaneous	Sildenafil AUC ↑ 2-11 fold. Do not exceed 25 mg in a 48 hr period	Sildenafil AUC ↑ 2-11 fold. Do not exceed 25 mg in a 48 hr period.	Probable substantial ↑ in sildenafil AUC. Do not exceed 25 mg in a 48 hr period.

Table 17. Drug Interactions Between Antiretrovirals and Other Drugs - Cont.
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

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
ANTI-MYCOBACTERIALS			
Rifampin	Levels: NVP ↓ 37% Not recommended	Levels: DLV ↓ 96% Contraindicated	Levels: EFV ↓ 25% No dose adjustment
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 2-3x/week.* EFV: Standard
Clarithromycin	Levels: NVP ↑26%, clarithromycin ↓ 30%. No dose adjustment.	Levels: Clarithromycin ↑100%, DLV ↑ 44% Dose adjust for renal failure	Levels: Clarithromycin ↓39% Alternative recommended
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
ANTICONVULSANTS			
Phenobarbitol **Phenytoin** **Carbamazepine**	Unknown Use with caution Monitor anticonvulsant levels.	Unknown but may decrease DLV levels substantially Monitor anticonvulsant levels.	Unknown 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. Do not exceed 25 mg in a 48 hr period	Monitor warfarin when used concomitantly

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

Table 17. Drug Interactions Between Antiretrovirals and Other Drugs- Cont.
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Drug Interactions Requiring Dose Modifications or Cautious Use			
Drugs Affected	**Zidovudine (ZDV)**	**Stavudine (d4T)**	**Didanosine (ddI)**
METHADONE	No data	Levels: d4T ↓27%, methadone unchanged. No dose adjustment.	Levels: ddI ↓41%, methadone unchanged. Consider ddI dose increase.
MISCELLANEOUS	Ribavirin inhibits phosphorylation of ZDV; this combination should be avoided if possible.	No data	No data

Table 18. Drug Interactions: Protease Inhibitors
Effect of Drug on Levels (AUCs)/Dose

Drug Affected	Ritonavir	Saquinavir*	Nelfinavir	Amprenavir	Lopinavir/ Ritonavir
Indinavir (IDV)	Levels: IDV ↑ 2-5X Dose: IDV 400 mg bid + RTV 400 mg bid, or IDV 800 mg bid + RTV 100 or 200 mg bid	Levels: IDV no effect SQV ↑ 4-7x † Dose: Insufficient data	Levels: IDV ↑ 50% NFV ↑ 80% Dose: Limited data for IDV 1200 mg bid + NFV 1250 mg bid	Levels: APV AUC ↑ 33%. Dose: no change	Levels: IDV AUC and Cmin increased. Dose: IDV 600 mg bid
Ritonavir (RTV)	•	Levels: RTV no effect SQV ↑ 20x †‡ Dose: Invirase or Fortovase 400 mg bid + RTV 400 mg bid	Levels: RTV no effect NFV ↑ 1.5x Dose: RTV 400 mg bid + NFV 500-750 mg bid	Levels: APV AUC ↑ 2.5-fold. Dose: Limited data for APV 600-1200 mg bid + RTV 100-200 mg bid	Lopinavir is co-formulated with ritonavir as Kaletra.
Saquinavir (SQV)	•	•	Levels: SQV ↑ 3-5x NFV ↑ 20% † Dose: Standard NFV Fortovase 800 mg tid or 1200 mg bid	Levels: APV AUC↓32% Dose: insufficient data	Levels: SQV† AUC and Cmin increased Dose: SQV 800 mg bid, LPV/r standard
Nelfinavir (NFV)	•	•	•	Levels: APV AUC ↑ 1.5-fold. Dose: insufficient data	No data
Amprenavir (APV)	•	•	•	•	Levels: APV AUC and Cmin increased Dose: APV 600-750 mg bid, LPV/r standard

∗ 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.

† Conducted with Fortovase

‡ Conducted with Invirase

Table 18. Drug Interactions: Protease Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors - Cont.

Effect of Drug on Levels (AUCs)/Dose

Drug Affected	Nevirapine	Delavirdine	Efavirenz
Indinavir (IDV)	Levels: IDV ↓ 28% NVP no effect Dose: IDV 1000 mg q8h NVP standard	Levels: IDV ↑ >40% DLV no effect Dose: IDV 600 mg q 8h DLV: standard	Levels: IDV ↓ 31% Dose: IDV 1000mg q 8h EFV standard
Ritonavir (RTV)	Levels: RTV ↓ 11% NVP no effect Dose: Standard	Levels: RTV ↑70% DLV: no effect Dose: DLV: standard RTV: no data	Levels: RTV ↑ 18% EFV ↑ 21% Dose: RTV 600 mg bid (500 mg bid for intolerance) EFV standard
Saquinavir (SQV)	Levels: SQV ↓ 25% NVP no effect Dose: No data	Levels: SQV ↑ 5x‡ DLV no effect Dose: Fortovase 800 mg tid, DLV standard (monitor transaminase levels)	Levels: SQV ↓ 62%‡ EFV ↓ 12% Co-administration not recommended
Nelfinavir (NFV)	Levels: NFV ↑ 10% NVP no effect Dose: Standard	Levels: NFV ↑ 2x DLV↓ 50% Dose: No data (monitor for neutropenic complications)	Levels: NFV ↑ 20% Dose: Standard
Amprenavir (APV)	No data	No data	Levels:APV AUC ↓ 36% Dose: APV 1200 mg tid as single PI, or 1200 mg bid + RTV 200 mg bid EFV standard
Lopinavir/ Ritonavir (LPV/RTV)	Levels: LPV Cmin ↓ 55%. Dose: Consider LPV/r 533/133 mg bid in PI-experienced patients NVP standard	Levels: LPV levels expected to increase. Dose: Insufficient data	Levels: LPV AUC ↓ 40% EFV no change Dose: Consider LPV/r 533/133 mg bid in PI-experienced patients EFV standard
Nevirapine (NVP)	•	No data	Levels: NVP: no effect EFV: AUC ↓ 22%
Delavirdine (DLV)	No data	•	No data

‡ Conducted with Invirase

Table 19. HIV-Related Drugs with Overlapping Toxicities

Bone Marrow Suppression	Peripheral Neuropathy	Pancreatitis	Nephrotoxicity	Hepatotoxicity	Rash	Diarrhea	Ocular Effects
cidofovir cotrimoxazole cytotoxic chemotherapy dapsone flucytosine ganciclovir hydroxyurea interferon-α primaquine pyrimethamine ribavirin rifabutin sulfadiazine trimetrexate zidovudine	didanosine isoniazid stavudine zalcitabine	cotrimoxazole didanosine lamivudine (children) pentamidine ritonavir stavudine	adefovir aminoglycosides amphotericin B cidofovir foscarnet indinavir pentamidine	delavirdine efavirenz fluconazole isoniazid itraconazole ketoconazole nevirapine NRTIs protease inhibitors rifabutin rifampin	abacavir amprenavir cotrimoxa-zole dapsone NNRTIs sulfadiazine	didanosine clindamycin nelfinavir ritonavir lopinavir/ritonavir	didanosine ethambutol rifabutin cidofovir

Table 20. Drugs Available Through Treatment Investigational New Drug Protocols

Drug	**Tenofovir Disoproxil Fumarate (Tenofovir DF)**
Source	Gilead Early Access Program 1-800-GILEAD-5
Class	Nucleotide Reverse Transcriptase Inhibitor
Usual Dose	300 mg po qd
Side Effects (major)	Elevation of creatine phosphokinase, elevation of transaminases
Comments	▪ Also active against Hepatitis B
Enrollment Criteria	▪ HIV-RNA $\geq$ 10,000 copies/mL and, ▪ CD4 $\leq$ 50 cells/μL and, ▪ Failed treatment with at least 2 PIs or 1 PI + 1 NNRTI or, ▪ CD4 > 100 and $\leq$ 200 cells/μL with documented AIDS-defining OI within 90 days

Table 21. Guidelines for Changing an Antiretroviral Regimen for Suspected Drug Failure

- Criteria for changing therapy include a suboptimal reduction in plasma viremia after initiation of therapy, re-appearance of viremia after suppression to undetectable, significant increases in plasma viremia from the nadir of suppression, and declining $CD4^+$ T cell numbers. Please refer to the more extensive discussion of these on page 23.
- When the decision to change therapy is based on viral load determination, it is preferable to confirm with a second viral load test.
- Distinguish between the need to change a regimen due to drug intolerance or inability to comply with the regimen versus failure to achieve the goal of sustained viral suppression; single agents can be changed in the event of drug intolerance.
- In general, do not change a single drug or add a single drug to a failing regimen; it is important to use at least two new drugs and preferably to use an entirely new regimen with at least three new drugs. If susceptibility testing indicates resistance to only one agent in a combination regimen, it may be possible to replace only that drug; however, this approach requires clinical validation.
- Many patients have limited options for new regimens of desired potency; in some of these cases, it is rational to continue the prior regimen if partial viral suppression was achieved.
- In some cases, regimens identified as suboptimal for initial therapy are rational due to limitations imposed by toxicity, intolerance or nonadherence. This especially applies in late stage disease. For patients with no rational options who have virologic failure with return of viral load to baseline (pretreatment levels) and declining $CD4^+$ T cell count, there should be consideration for discontinuation of antiretroviral therapy.
- Experience is limited with regimens using combinations of two protease inhibitors or combinations of protease inhibitors with NNRTIs; for patients with limited options due to drug intolerance or suspected resistance these regimens provide possible alternative treatment options.

  There is limited information about the value of restarting a drug that the patient has previously received. Susceptibility testing may be useful in this situation if clinical evidence suggestive of the emergence of resistance is observed. However, testing for phenotypic or genotypic resistance in peripheral blood virus may fail to detect minor resistant variants. Thus, the presence of resistance is more useful information in altering treatment strategies than the absence of detectable resistance.
- Avoid changing from ritonavir to indinavir or vice versa for drug failure, since high level cross resistance is likely.
- Avoid changing among NNRTIs for drug failure, since high level cross resistance is likely.
- The decision to change therapy and the choice of a new regimen requires that the clinician have considerable expertise in the care of people living with HIV. Physicians who are less experienced in the care of persons with HIV infection are strongly encouraged to obtain assistance through consultation with or referral to a clinician with considerable expertise in the care of HIV-infected patients.

Table 22. Acute Retroviral Syndrome: Associated Signs and Symptoms (Expected Frequency) (ref. #159)

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

Table 23. Preclinical and Clinical Data Relevant to Use of Antiretrovirals in Pregnancy

Antiretroviral Drug	FDA Pregnancy Category*	Placental Passage [Newborn:Maternal Drug Ratio]	Long-Term Animal Carcinogenicity Studies	Rodent Teratogen
zidovudine†	C	Yes (human) [0.85]	Positive (rodent, vaginal tumors)	Positive (near lethal dose)
zalcitabine	C	Yes (rhesus) [0.30 – 0.50]	Positive (rodent, thymic lymphomas)	Positive (hydrocephalus at high dose)
didanosine	B	Yes (human) [0.5]	Negative (no tumors, lifetime rodent study)	Negative
stavudine	C	Yes (rhesus) [0.76]	Positive (rodent, liver and bladder tumors)	Negative (but sternal bone calcium decreases)
lamiduvine	C	Yes (human) [~1.0]	Negative (no tumors, lifetime rodent study)	Negative
abacavir	C	Yes (rats)	Not completed	Positive (anasarca and skeletal malformations at 1000 mg/kg [35x human exposure] during organogenesis)
saquinavir	B	Unknown	Not completed	Negative
indinavir	C	Yes (rats) ("Significant" in rats, low in rabbits)	Not completed	Negative (but extra ribs in rats)
ritonavir	B	Yes (rats) [mid-term fetus, 1.15; late-term fetus, 0.15 – 0.64]	Positive (rodent, liver tumors)	Negative (but cryptorchidism in rats)‡
nelfinavir	B	Unknown	Not completed	Negative
amprenavir	C	Unknown	Not completed	Positive (thymic elongation; incomplete ossification of bones; low body weight)
lopinavir/ ritonavir	C	Lopinavir – yes (rats) [0.08 at 6 hrs post-dose]	Lopinavir – not completed. Ritonavir – see above	Negative (but delayed skeletal ossification and increase in skeletal variations in rats at maternally toxic doses)
nevirapine	C	Yes (human) [~1.0]	Not completed	Negative
delavirdine	C	Yes (rats) [late-term fetus, blood, 0.15; late-term fetus, liver 0.04]	Positive (rodent, liver and bladder tumors)	Ventricular septal defect
efavirenz	C	Yes (cynomolgus monkeys, rats, rabbits) [~1.0]	Not completed	Anencephaly; anophthalmia; microphthalmia (cynomolgus monkeys)

* FDA Pregnancy Categories are:

A – Adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence 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 based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks;

X - Studies in 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.

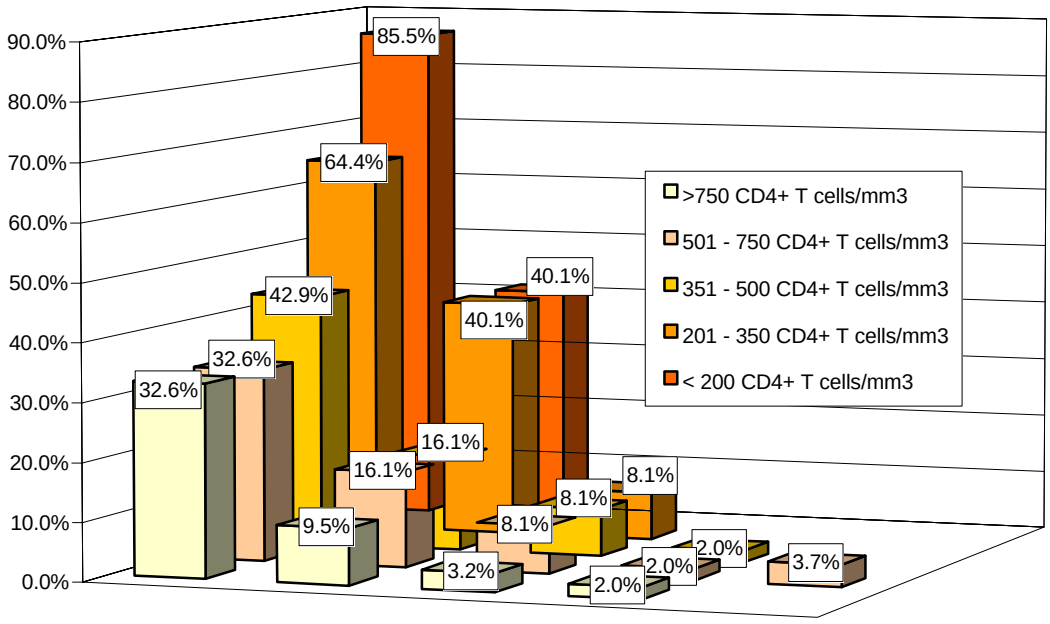
† Despite certain animal data showing potential teratogenicity of ZDV when near-lethal doses are given to pregnant rodents, considerable human data are available to date indicating that the risk to the fetus, if any, is extremely small when given to the pregnant mother beyond 14 weeks gestation. Follow-up for up to 6 years of age for 734 infants born to HIV-infected women who had in utero exposure to ZDV has not demonstrated any tumor development (184). However, no data are available on longer follow-up for late effects.

‡ These effects seen only at maternally toxic doses.

Table 24. Zidovudine Perinatal Transmission Prophylaxis Regimen

ANTEPARTUM	Initiation at 14-34 weeks gestation and continued throughout pregnancy A. PACTG 076 REGIMEN: ZDV 100 mg 5 times daily B. ACCEPTABLE ALTERNATIVE REGIMEN: ZDV 200 mg 3 times daily or ZDV 300 mg 2 times daily
INTRAPARTUM	During labor, ZDV 2 mg/kg intravenously over 1 hour, followed by a continuous infusion of 1 mg/kg intravenously until delivery.
POSTPARTUM	Oral administration of ZDV to the newborn (ZDV syrup, 2 mg/kg every 6 hours) for the first 6 weeks of life, beginning at 8-12 hours after birth.

Likelihood of Developing AIDS Within 3 Years



MACS 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)

Figure 1. Likelihood of developing an AIDS-related illness in three years. Viral load represents the actual data obtained on the specimens from the MACS cohort as well as the values showing the equivalent expected RT-PCR values. Values shown in this figure differ slightly from those in Table 5 because better discrimination of outcome was achieved by re-analysis of the data using viral load as the initial parameter for categorization followed by CD4+T lymphocyte stratification of the patients. (Adapted from reference 4)

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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 use in the treatment of certain malignancies and in 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. Depletion of the dNTP pool results in arrest of the cell cycle in the G1 phase prior to DNA synthesis; in an HIV-infected cell, incomplete reverse transcription of the viral genome also results from depletion of the dNTP pool *(1)*. Hydroxyurea preferentially depletes intracellular dATP; therefore, it has been hypothesized that the antiretroviral activity of ddI and d4T may 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.

Few data are available from controlled clinical trials that provide support for the clinical utility 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. Importantly, this trial was prematurely closed 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, and a substantial decrease in median CD4+ T cell count was observed in the hydroxyurea treatment group. 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 *(6)* and hepatotoxicity *(7)*, the drug's teratogenic properties, and the possibility of an increased risk of neuropathy. Given these concerns, more data on the potential safety and efficacy of lower doses of hydroxyurea are necessary to determine if hydroxyurea in combination with antiretroviral agents has a therapeutic role for HIV infection. 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 (DII).

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Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy

Nucleoside 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 and lamivudine, while didanosine and stavudine are under study. Zalcitabine and abacavir have not been studied in pregnant women.

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 percent of female rodents (at estimated drug concentrations three and 24 times that of human therapeutic exposure in mice and rats, respectively) *(1)*. 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 *(1)*. 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 *(2)*. 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 six 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 *(3)*. 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 *(4)*. The panel concluded that the known benefit of zidovudine in reducing

vertical transmission of HIV by nearly 70 percent (7.2 versus 21.9 percent with placebo) *(5)* 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 *(6)*. 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 animal studies

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 *(7)*.

Teratogenicity/developmental toxicity animal studies

No evidence of teratogenicity or toxicity was observed with administration of doses up to 500 to 600 mg/kg per 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 per day (near the lethal dose, and 350 times the peak human plasma concentration).

In humans, data from PACTG 076 study and the Antiretroviral Pregnancy Registry do not demonstrate an increased incidence of congenital abnormalities in infants born to women with antepartum ZDV exposure *(5, 8-10)*. In the PACTG 076 study, the incidence of minor and major congenital abnormalities were similar between zidovudine and placebo groups, and no specific pattern of defects was seen *(5, 9)*. However, definitive conclusions regarding teratogenic risk cannot be made due to the limited numbers of children that have been evaluated.

Placental and breast milk passage in humans

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 six hours *(5, 11)*. 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 four years postpartum *(12)*. Infants with *in utero* zidovudine exposure followed for nearly six years have shown no significant differences from those who received placebo in immunologic, neurologic and growth parameters *(9, 13)*; follow-up of these infants is continuing.

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 animal studies

There has been no effect of didanosine on reproduction or fertility in rodents or on preimplantation mouse embryos *(14).*

Teratogenicity/developmental toxicity animal studies

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 in humans

Placental transfer of didanosine was limited in a phase I/II safety and pharmacokinetic study (cord-to-maternal blood ratio, 0.35-0.11) *(15).* 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 six weeks postpartum *(15).* The drug was well-tolerated during pregnancy by the women and the fetuses. Preliminary analyses indicate that pharmacokinetic parameters after oral administration were not significantly affected by pregnancy, and that dose modification from the usual adult dosage is not needed.

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 animal studies

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

Teratogenicity/developmental toxicity animal studies

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

Placental and breast milk passage in humans

Lamivudine readily crosses the placenta in humans, achieving comparable cord blood and maternal concentrations *(16).* 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 one week following birth to the infants *(16)*. 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 percent that of older children, requiring a reduced dosing regimen (4 mg/kg per day in neonates compared to 8 mg/kg per day for infants older than three months). There are currently no data on the pharmacokinetics of lamivudine between two to six 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 animal studies

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 *(14)*.

Teratogenicity/developmental toxicity animal studies

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.

Placental and breast milk passage in animals

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 *(17)*. Stavudine is excreted into the breast milk of lactating rats.

Human studies in pregnancy

A phase I/II safety and pharmacokinetic study of combination stavudine and lamivudine in pregnant HIV-infected women and their infants (PACTG 332) is being conducted, but data are not yet available. In primate studies, pregnancy did not affect the pharmacokinetics of stavudine *(18)*.

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 animal studies

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 *(14)*.

Teratogenicity/developmental toxicity animal studies

Teratogenicity (hydrocephalus) occured in rats given very high doses (over 1000 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 animal studies

In primate and placental perfusion studies, zalcitabine crosses the placenta (fetal-to-maternal drug ratio approximately 0.50 to 0.60) *(19)*. In rodents, zalcitabine concentrates in the fetal kidney and a relatively small proportion (approximately 20 percent) 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.

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 animal studies

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

Teratogenicity/developmental toxicity animal studies

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). 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 per 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 in animal studies

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.

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 *(20)*. 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 *(21)*. These toxicities may be of particular concern for pregnant women and 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 *(22)*. 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 *(23-25)*. 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 *(26)*. 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 *(27, 28)*; 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 *(22)*. 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 1989-1994, the incidence of the hepatic steatosis syndrome was 0.13% per year *(29)*. However, in a report from a cohort of 964 HIV-infected individuals followed in France between 1997-1999 the incidence of symptomatic hyperlactatemia was 0.8% per year for all patients and 1.2% for patients receiving a regimen including d4T *(30)*.

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 *(31)*. Bristol-Myers Squibb has reported 3 maternal deaths due to lactic acidosis, 2 with and 1 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) *(32)*. 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 (30). 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 2 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 (9). In a large database that included 223 deaths in over 20,000 children with and without antiretroviral drug exposure who were born to HIV-infected women followed prospectively in several large cohorts in the United States, no deaths similar to those reported from France were identified (33). 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. Evaluation is ongoing to determine if there is any evidence of mitochondrial dysfunction among any of the living children in these cohorts. Data have been reviewed relating to neurologic adverse events in 1,798 children that participated in PETRA, an African perinatal trial that compared three regimens of ZDV/3TC (before, during and one week postpartum; during labor and postpartum; and during labor only) to placebo for prevention of transmission. No increased risk of neurologic events was observed among children treated with ZDV/3TC compared to placebo, regardless of the intensity of treatment (34). Echocardiograms were prospectively performed every 4 to 6 months during the first 5 years of life in 382 uninfected infants born to HIV-infected women; 9% of infants had been exposed to ZDV prenatally (35). No significant differences in ventricular function were observed between infants exposed and unexposed to ZDV.

If the association of mitochondrial dysfunction and *in utero* antiretroviral exposure proves to be real, the development of severe or fatal mitochondrial disease in these infants appears to be extremely rare, and should be compared to the clear benefit of ZDV in reducing transmission of a fatal infection by nearly 70% *(36)*. 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 animal studies

Delavirdine does not impair fertility in rodents.

Teratogenicity/developmental toxicity animal studies

Delavirdine is teratogenic in rats; doses of 50 to 200 mg/kg per day during organogenesis caused ventricular septal defects. Exposure of rats to doses approximately five 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 six times human therapeutic exposure.

Placental and breast milk passage in animal studies

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 six 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 animal studies

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 animal studies

Malformations were observed in three 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). 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 in animal studies

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 studies with efavirenz in pregnant humans are planned at this time. Because teratogenic effects were seen in primates at drug exposures similar to those representing human therapeutic exposure, pregnancy should be avoided in women receiving efavirenz.

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 animal studies

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

Teratogenicity/developmental toxicity animal studies

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 percent higher than human therapeutic exposure.

Placental and breast milk passage in humans

Nevirapine crosses the placenta and achieves neonatal blood concentrations equivalent to that in the mother (cord-to-maternal blood ratio approximately 0.90) *(37)*. 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 percent (range 54 to 104 percent) of serum levels *(37)*.

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 *(37)*. 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. Pharmacokinetic data on chronic antenatal nevirapine dosing in pregnant women are under study but not yet available. 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 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 zidovdine (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 *(38)*. 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 standard ZDV prophylaxis combined with whatever antiretroviral therapy is needed for treatment of their HIV disease; it is unknown whether adding the HIVNET 012 nevirapine regimen to standard antiretroviral prophylaxis and treatment offers any additional benefit in terms of reducing perinatal transmission. A phase III perinatal trial (PACTG 316) being conducted in the United States, Europe, the Bahamas and Brazil is evaluating this regimen in combination with standard maternal antiretroviral therapy and ZDV antiretroviral therapy and ZDV prophylaxis for the prevention of perinatal HIV transmission. Selection of nevirapine-resistant virus was found at 6 weeks postpartum in both the untreated and antiretroviral-treated pregnant women who received a single dose of nevirapine in labor in HIVNET 012 and PACTG 316. In HIVNET 012, 7 of 31 women (23%) evaluated developed genotypic resistance mutations at 6 weeks postpartum; these mutations were no longer present in 4 women studied at 13-18 months postpartum *(34, 39)*. In the antiretroviral-treated women in PACTG 316, 4 of 32 women (13%, 95% CI 4-25%) with HIV-1 RNA above 3,000 copies/mL at delivery who received nevirapine developed genotypic nevirapine resistance mutations compared to none of 38 women in the placebo arm *(36)*.

Severe, life-theatening 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 (BI physician letter). 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 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 *(40-43)*. 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 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

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 *(44)***.** Almost 80 percent 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 *(45-47)*. To evaluate the baseline rates of adverse pregnancy outcome and risk factors for such outcomes in HIV-infected pregnant women, a meta-analysis of multiple PACTG perinatal trials and cohort studies is in progress. Preliminary analyses do not indicate an elevated risk of preterm delivery among infants born to women receiving combination antiretroviral therapy with or without protease inhibitors compared to those receiving single drug or no antiretroviral therapy. 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.

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 animal studies

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

Teratogenicity/developmental toxicity animal studies

There has been no evidence of teratogenicity of indinavir in rats, rabbits or dogs. In rats, developmental toxicity manifest by 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 percent of maternal levels) or dogs (fetal exposure approximately 50 percent 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 to 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 in animals

Significant placental passage of indinavir occurs in rats and dogs, but only limited placental transfer occurs in rabbits. 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 5 women and infants *(48)*. 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 2 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 *(49)*. 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 4-fold 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 9-fold 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 animal studies

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 animal studies

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 in animals

Data on placental passage of lopinavir in animals are not available. For ritonavir, Tran placental passage has been observed in rat fetuses at mid- and late-gestation. 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 animal studies

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 animal studies

No teratogenicity or effect on fetal development by nelfinavir has been demonstrated in rodent or rabbit studies at exposures comparable to human therapeutic exposure.

Placental and breast milk passage in animals

Whether nelfinavir crosses the placenta is unknown. 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 is being conducted, but complete data are not yet available. In preliminary data from this study, the standard adult dose of nelfinavir (750 mg tid) produced drug exposures in the first 9 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 has been modified to evaluate an increased dose of nelfinavir (1250 mg) administered bid. In infants, nelfinavir was not detectable in cord blood from 4 infants born to mothers receiving 750 mg nelfinavir tid; in one additional infant, the cord blood nelfinavir concentration was 11.7% that detected in maternal blood at delivery.

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 4-fold 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 9-fold 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 animal studies

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

Teratogenicity/developmental toxicity animal studies

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 percent of human therapeutic exposure). In addition, a slight increase in cryptorchidism was also noted in rats at exposures equivalent to 22 percent 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 passage in animals

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 *(50)*. Ritonavir is excreted in the milk of lactating rats; it is unknown if it is excreted in human milk.

Human studies in pregnancy

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]; Fortovase [Soft Gel Capsule]) is classified as FDA pregnancy category B

Animal carcinogenicity studies

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

Reproduction/fertility animal studies

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 per day).

Teratogenicity/developmental toxicity animal studies

No evidence for embryotoxicity or teratogenicity of saquinavir has been found in animal studies.

Placental and breast milk transfer in animal studies

Placental transfer of saquinavir in the rat and rabbit was minimal. Saquinavir 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 386) of saquinavir in combination with ZDV and lamivudine in pregnant HIV-infected women and their infants is being conducted, but complete data are not yet available. In preliminary data from this study, the standard adult dose of saquinavir (1200 mg tid) was not sufficient to produce adequate drug exposure in the first 4 pregnant HIV-infected women enrolled in the study compared to those obtained with standard dosing in non-pregnant adults. Therefore, the study has been modified to evaluate a dose of saquinavir 800 mg combined with ritonavir 100 mg both administered bid.

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 animal studies

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 animal studies

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 in animals

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.

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 per kg of hydroxyurea (approximately 0.6 to 1.2 times the maximum recommended human oral dose on a mg per meter squared 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 animal studies

Hydroxyurea administered to male rats at doses of 60 mg per kg per day (about 0.3 times the maximum recommended human daily dose on a mg per meter squared basis) produced testicular atrophy, decreased spermatogenesis, and significantly reduced their ability to impregnate females.

Teratogenicity/developmental toxicity animal studies

Potent teratogenic effects have been observed in all animal species tested, with defects reported in multiple organ systems *(51-57)*. Administration of hydroxyurea to pregnant rats at doses as low as 180 mg per kg per day (about 0.8 times the maximum recommended human daily dose on a mg per meter squared basis) and pregnant rabbits at 30 mg per kg per day (about 0.3 times the maximum recommended human daily dose on a mg per meter squared basis) was associated with embryotoxicity and fetal malformations. In pregnant rats administered doses ranging from 185 to 1000 mg per 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 *(51, 54, 55)*. Exposure early in gestation was frequently associated with embryo death in a large percentage of cases. In pregnant rats, single doses of 375 mg per kg body weight or more (about 1.7 times the maximum recommended human daily dose on a mg per meter squared basis), were associated with growth retardation and impaired learning ability in their offspring. In hamsters, neural tube defects and cardiovascular abnormalities were produced after 50 mg of hydroxyurea was given intravenously *(52)*. In pregnant rhesus monkeys administered a cumulative dose greater than 500 mg per kg body weight, multiple skeletal, genitourinary, cardiac and ocular anomalies were found in their offspring *(54)*. Teratogenicity was also demonstrated in pregnant cats given a single oral dose of 50 or 100 mg per kg body weight *(53)*.

Placental and breast milk passage in animal studies

Hydroxyurea has been shown to cross the placenta in animals.

Placental and breast milk passage in humans

Hydroxyurea is excreted in human milk *(58)*.

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) *(59).* Doses ranged from 0.5 to 3 grams per 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 a component of antiretroviral regimen 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, 1410 Commonwealth Drive, Wilmington, NC 28403; telephone (800)-258-4263; fax (800) 800-1052.

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