January 28, 2000

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, $CD4^+$ T 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 depend on virologic and immunologic factors. In general, treatment should be offered to individuals with fewer than 500 $CD4^+$ T cells/mm^3 or plasma HIV RNA levels exceeding 10,000 copies/mL (bDNA assay) or 20,000 copies/mL (RT-PCR assay). The strength of the recommendation to treat asymptomatic patients should be based on the patient's willingness to accept therapy, the probability of adherence with the prescribed regimen (see Adherence, page 60), and the prognosis in terms of time to an AIDS-defining complication as predicted by plasma HIV RNA levels and $CD4^+$ T cell counts, which independently help to predict prognosis. 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-fold) decrease at eight weeks and no detectable virus (<50 copies/mL) at 4-6 months after initiation of treatment. Failure of therapy (i.e., plasma HIV RNA levels exceeding 50 copies/mL) 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 for which 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**)

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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; see "Considerations for Antiretroviral Therapy in the HIV-Infected Adolescent," below). 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, (**http://www.hivatis.org**).

These guidelines are intended for use by physicians and other health care providers who use antiretroviral therapy to treat HIV-infected adults and adolescents and serves as the companion document 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 physician 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 physician 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 I); 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 I). 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. It should be noted that the majority of clinical trial data available to date regarding the use of antiretroviral agents have been obtained in trials enrolling predominantly young to middle-aged males. While current knowledge indicates that women may differ from men in the absorption, metabolism and clinical effects of certain pharmacologic agents, clinical experience and data available to date would suggest that there are no significant gender differences known that would modify these guidelines. However, theoretical concerns exist. The Panel urges continuation of the current efforts to enroll more women in antiretroviral clinical trials so that the data needed to re-evaluate this issue can be gathered expeditiously.

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; special considerations for therapy in patients with advanced stage disease; 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 the 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) (See Table II). $CD4^+$ 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" (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;" 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 have recently become 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 (see Table III), and in acute HIV infection. 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" (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 (see "Considerations for Changing a Failing Regimen"). 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 witheld 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 (see below, "Considerations for Antiretroviral Therapy in the HIV-Infected Pregnant Woman " and Table XXI). 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.

Established 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 (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 (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

It has been demonstrated that antiretroviral therapy provides clinical benefit in HIV-infected individuals with advanced HIV disease and immunosuppression (24-27). Although there is theoretical benefit to treatment for patients with $CD4^+$ T cells greater than 500 cells/mm^3, no long term clinical benefit of treatment has yet been demonstrated. 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. Thus, decisions regarding treatment of asymptomatic, chronically infected individuals must balance a number of competing factors that influence risk and benefit.

Table IV summarizes some of the factors that the physician and the asymptomatic patient must consider in deciding when to initiate therapy. Factors that would lead one to initiate early therapy include the real or potential goal of maximally suppressing viral replication; preserving immune function; prolonging health and life; decreasing the risk of drug resistance due to early suppression of viral replication with potent therapy; decreasing drug toxicity by treating the

healthier patient; and possibly decreasing the risk of viral transmission. Factors weighing against early treatment in the asymptomatic stable patient include the potential adverse effects of the drugs on quality of life, including the inconvenience of most of the suppressive regimens currently available; the potential risk of developing drug resistance despite early initiation of therapy; the potential for limiting future treatment options due to cycling of the patient through the available drugs during early disease; the potential risk of transmission of virus resistant to protease inhibitors and other agents; the unknown durability of effect of the currently available therapies; and the unknown long term toxicity of some drugs. Thus, the decision to begin therapy in the asymptomatic patient 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 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 level of plasma HIV RNA (Table V 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 physician 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 that have been developed in the context of chronic treatment for other serious diseases; 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 Adherence, page 60).

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 (28) that persists with an extremely long half-life, even with prolonged suppression of plasma viremia to < 50 copies/mL (29-32). 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 VI). In fact, adoption of treatment strategies articulated in these guidelines has resulted in substantial reductions in HIV-related morbidity and mortality (33-35).

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 (36). 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 ("Criteria for Changing Therapy").

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 (37). In turn, continued viral load suppression is more likely among those who achieve higher CD4+ T cell counts during therapy (38). A favorable CD4+ T cell response can occur with incomplete viral load suppression and may not necessarily indicate a poor prognosis (39). 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 (40,41), partial normalization of perturbed T cell receptor Vβ repertoires (42), and evidence of residual thymic function in patients receiving HAART (43,44) 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 (45), 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 (46-48). 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 (49,50). Predictors of virologic success include low baseline viremia and high baseline CD4+ T cell count (49-51), rapid decline of viremia (6), decline of viremia to <50 HIV RNA copies/mL (6), adequate serum levels of antiretroviral drugs (6,52), and adherence to the drug regimen (50, 53, 54). 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. A direct correlation between adherence with antiretroviral regimens and virologic outcome has been documented in clinical studies (50, 53, 54). Numerous interventions have been proposed to improve adherence, including support from family, friends, and members of the health care team; electronic reminders; specialized pill boxes; aggressive patient education; improved access to physicians after hours; and a trusting relationship with a physician or other health care provider. In addition, some new dosing strategies with reduced pill burdens and dosing frequency have shown pharmacologic and virological equivalence with

standard, less convenient dosing schedules. For further information on adherence, consult the adherence hypertext link associated with these guidelines (see Adherence, page 60).

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 VII 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 (25-27). 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 (55) or abacavir + 2 NRTIs (56); 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 (57-60). 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 (10-12). 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").

Initiating Therapy in the Patient with Asymptomatic HIV Infection

Once the patient and physician have decided to initiate antiretroviral therapy, treatment should be aggressive, with the goal of maximal suppression of plasma viral load to undetectable levels. Tables VIII and IX summarize the recommendations regarding when to initiate therapy and what regimens to use. In general, any patient with less than 500 $CD4^+$ T cells/mm^3 or greater than 10,000 (bDNA) or 20,000 (RT-PCR) copies of HIV RNA/mL of plasma should be offered therapy (AII). This recommendation is based on the relationship between viral load, CD4+ T cell counts, and rates of HIV disease progression in men. Recent data suggest that viral load in women is approximately 50% lower compared with viral load in men for the same rate of CD4+ T cell decline and time to AIDS (61). These findings are limited to non-pregnant women who acquired HIV primarily by injection drug use, and have not been consistently observed (62). No changes in current guidelines for viral load threshold to offer treatment are recommended because these differences are within the error of the viral load assay and the applicability of these conclusions to other populations of women with HIV infection is unknown. The strength of the recommendation for therapy should be based on the readiness of the patient for treatment as well as a consideration of the prognosis for disease-free survival as determined by viral load, $CD4^+$ T cell count (Table V and Figure 1), and the slope of the $CD4^+$ T cell count decline. Note that the values for bDNA shown in Figure 1 and Table V (first line or column) are the uncorrected HIV RNA values obtained from the Multicenter AIDS Cohort Study (MACS). RT-PCR values are also shown in Table V and Figure 1; comparison of the results obtained from the RT-PCR and

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 XIX) 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, 72,73). 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 in Initiating Therapy in the Asymptomatic HIV-infected Patient."

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 XIX, a test for HIV RNA should be performed (BII).

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 values must be 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.

In current practice there are two general approaches to initiating therapy in the asymptomatic patient: a therapeutically more aggressive approach that would treat most patients early in the course of HIV infection due to the recognition that HIV disease is virtually always progressive; and a more therapeutically cautious approach in which therapy may be delayed because the balance of the risk of clinically significant progression and other factors discussed above are felt to weigh in favor of observation and delayed therapy. The aggressive approach is heavily based on the Principles of Therapy (1), particularly the Principle that one should begin treatment before the development of significant immunosuppression and one should treat to achieve undetectable viremia; thus, all patients with less than 500 $CD4^+$ T cells/mm^3 would be started on therapy as would patients with higher $CD4^+$ T cell numbers who have plasma viral load > 10,000 (bDNA) or 20,000 (RT-PCR)(Table VIII). The more conservative approach to the initiation of therapy in the asymptomatic individual would delay treatment of the patient with <500 $CD4^+$ T cells/mm^3 and low levels of viremia who have a low risk of rapid disease progression, according to the data in Table V; careful observation and monitoring would continue. Patients with $CD4^+$ T cell counts > 500/mm^3 would also be observed, except those at substantial risk of rapid disease progression because of a high viral load. For example, the patient with 60,000 (RT-PCR) or 30,000 (bDNA) copies of HIV RNA/mL, regardless of $CD4^+$ T cell count, has a high probability of progressing to an AIDS-defining complication of HIV disease within 3 years (32.6% if $CD4^+$ T cells are greater than 500/mm^3) and should clearly be encouraged to initiate antiretroviral therapy. On the other hand, a patient with 18,000 copies of HIV RNA/mL of plasma, measured by RT-PCR, and a $CD4^+$ T cell count of 410/mm^3 has a 5.9% chance of progressing to an AIDS-defining complication of HIV infection in 3 years (Table V). The therapeutically aggressive physician would recommend treatment for this patient to suppress the ongoing viral replication that is readily detectable; the therapeutically more conservative physician would discuss the possibility of initiation of therapy, but recognize that a delay in therapy due to the balance of considerations discussed above is also reasonable. In either case, the patient should make the final decision regarding acceptance of therapy following discussion with the health care provider of specific issues relevant to his/her own clinical situation.

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, or efavirenz in combination with one of several 2 NRTI combinations (Table IX). Clinical outcome data support the use of a PI in combination with 2 NRTIs (25-27) (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 (50), 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. 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. Ritonavir potentiates the levels of other PIs through its inhibition of the cytochrome P450 pathway that metabolizes PIs. The combination of ritonavir with saquinavir produces a 20-fold increase in saquinavir steady-state levels and significantly reduces the overall pill burden (63, 64). Although clinical data are too preliminary to warrant endorsement, combinations of ritonavir + indinavir (65) or ritonavir + amprenavir (66) have excellent pharmacokinetic profiles and may allow for more convenient dosing.

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 PI + 2 NRTIs in suppressing plasma viremia and increasing CD4+ T cell counts (55), 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 (56) (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, page 72).

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 X-XVI. In addition, because certain investigational new drugs are available to physicians for use in selected patients, Table XVII has been provided for the physician treating patients under investigational protocols. Particular attention should be paid to Tables XII-XV 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

Patients diagnosed with HIV infection by HIV RNA testing should have confirmatory testing performed (see Table II). 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 (74). 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 "Asymptomatic Chronic Infection" algorithm mentioned previously (CIII). Except in the setting of post-exposure prophylaxis with antiretroviral agents (75), 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 IX. 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…" i.e., on initiation of therapy, after 4 weeks, and every 3–4 months thereafter (AII). Some experts feel that

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.

Special Considerations in the Patient with Advanced Stage Disease

Some patients present with opportunistic infections, wasting, dementia or malignancy and are first diagnosed with HIV infection at this advanced stage of disease. All patients with advanced HIV disease should be treated with antiretroviral therapy. 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 IX. 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 X-XVI. 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 Tables XIV; this topic is discussed in greater detail elsewhere (67). 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 XIII-XVI. 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 association.

Class Adverse Events (See Class Adverse Events, page 74)

Several class-related adverse events have been recognized with antiretroviral drugs during the post-marketing period. For nucleoside analogue reverse transcriptase inhibitors (NRTIs), lactic acidosis with hepatomegaly and hepatic steatosis has been reported. For protease inhibitors reports of hyperglycemia/diabetes mellitus, increased bleeding episodes in patients with hemophilia, and fat redistribution with and without serum lipid abnormalities have been received. Because these events were identified based on spontaneous reports and other uncontrolled data, the actual incidence of these events and the causal association with these drugs have not been definitively established. Controlled and/or population-based epidemiologic studies evaluating these potential class adverse events are warranted.

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; remaining treatment options in terms of potency, potential resistance patterns from prior antiretroviral therapies and potential for compliance/tolerance; assessment of adherence to medications; 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

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, making them ideal candidates for early intervention.

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

Guidelines for optimal antiretroviral therapy and for initiation of therapy in pregnant HIV-infected women should be the same as those delineated for non-pregnant adults. Thus, the woman's clinical, virologic and immunologic status should be of primary importance in guiding treatment decisions. However, it must be realized that the potential impact of such therapy on the fetus and infant is unknown. 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.

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 affects 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 above). 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 reduction in plasma HIV RNA by 4 weeks following initiation of therapy, or less than a 1 log 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 IX). 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

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.

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 when administered during the first 10–12 weeks of gestation. However, a rebound in viral levels would be anticipated during the period of discontinuation and this rebound could theoretically be associated with increased risk of early in utero HIV transmission or could potentiate disease progression in the woman (76). Although the effects of all antiretroviral drugs on the developing fetus during the first trimester are uncertain, most 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.

The choice of which antiretroviral agents to use in pregnant women is subject to unique considerations. (See Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy, page 78). There are currently minimal data available on the pharmacokinetics and safety of antiretroviral agents during pregnancy for drugs other than ZDV. In the absence of data, drug choice 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 XX. It is important to recognize that the predicitive 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 (77).

Zidovudine has been shown to reduce the risk of perinatal HIV transmission when administered according to the following regimen: orally administered antenatally after 14 weeks gestation and continued throughout pregnancy, intravenously administered during the intrapartum period, and to the newborn for the first 6 weeks of life (78). This chemoprophylactic regimen was shown to

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 category 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 XVIII 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 XV). 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 XIX) and can thus be identified as candidates for early therapy (68-71). However, acute HIV infection is often not recognized in the primary care setting because of the similarity of the symptom complex with

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

Potential Benefits

- Control of viral replication and mutation; reduction of viral burden
- Prevention of progressive immunodeficiency; potential maintenance or reconstruction of a normal immune system
- Delayed progression to AIDS and prolongation of life
- Decreased risk of selection of resistant virus
- Decreased risk of drug toxicity
- Possible decreased risk of viral transmission

Potential Risks

- Reduction in quality of life from adverse drug effects and inconvenience of current maximally suppressive regimens
- Earlier development of drug resistance
- Transmission of drug resistant virus
- Limitation in future choices of antiretroviral agents due to development of resistance
- Unknown long term toxicity of antiretroviral drugs
- Unknown duration of effectiveness of current antiretroviral therapies

reduce the risk of perinatal transmission by 66% in a randomized, double blind clinical trial, pediatric (P)-ACTG 076 (20). There are insufficient data available at present to justify the substitution of any antiretroviral agent other than ZDV for the purpose of reducing perinatal HIV transmission; further research will address this question. For the time being, if combination antiretroviral drugs are administered to the pregnant woman for treatment of her HIV infection, ZDV should be included as a component of the antenatal therapeutic regimen whenever possible, and the intrapartum and neonatal ZDV components of the chemoprophylactic regimen should be administered for the purpose of reducing the risk of perinatal transmission. If a woman does not receive ZDV as a component of her antenatal antiretroviral regimen (e.g. because of prior history of non-life threatening ZDV-related severe toxicity or personal choice), intrapartum and newborn ZDV should continue to be recommended; when use of ZDV is contraindicated in the woman, the intrapartum component may be deleted but the newborn component is still recommended. ZDV and d4T should not be administered together due to potential pharmacologic antagonism. When d4T is a preferred nucleoside for treatment of a pregnant woman, it is recommended that antenatal ZDV not be added to the regimen; however, intrapartum and neonatal ZDV should still be given.

The antenatal 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 (see Table XXI). However, recent data have indicated that administration of ZDV three times daily will maintain intracellular ZDV triphosphate at levels comparable with those observed with more frequent dosing (79, 80). Comparable clinical response also has been observed in clinical trials among persons receiving ZDV twice daily (81-83). 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.

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 (84). 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.

A trial in Africa in breastfeeding HIV-infected women has shown that an intrapartum/postpartum ZDV and 3TC regimen, started during labor and continued for one week in the woman and infant, reduced transmission by 38% (85). Additionally, a study in Uganda, again in a breastfeeding population, demonstrated that a single 200 mg oral dose of nevirapine given to the mother at onset of labor combined with a single 2 mg/kg oral dose given to her infant at 48-72 hours of age reduced transmission by nearly 50% compared to a regimen of ZDV given orally during labor and to the infant for one week (86). These two studies provide potential effective

intrapartum/postpartum interventions for those women in whom the diagnosis of HIV infection is not made until very near to or during labor.

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. 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. For women in whom initiation of antiretroviral therapy for treatment of their HIV infection would be considered optional (e.g. $CD4^+$ count >500/mm^3 and plasma HIV RNA less than 10,000–20,000 RNA 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 resistance was unusual among the healthy population of women who participated in P-ACTG 076 (21). The use of ZDV chemoprophylaxis alone during pregnancy might be an appropriate option for these women. However, for women with more advanced disease and/or higher levels of HIV RNA, concerns about resistance are greater and they should be counseled that a combination antiretroviral regimen that includes ZDV for reducing transmission risk would be more optimal for their own health than use of ZDV chemoprophylaxis alone.

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, 87, 88). 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, ZDV appears to be effective in reducing transmission regardless of maternal RNA level (20). The genital tract is a distinct virologic compartment, with uncertain consequences with regard to perinatal HIV transmission. While there is general correlation between plasma and genital tract viral load, discordance has also been reported (89-91); in addition, differential evolution of viral sequence diversity occurs between the peripheral blood and genital tract (91, 92). 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. Meanwhile, the use of 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, alone or in combination with other antiretrovirals, 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

Table V. Risk of Progression to AIDS Defining Illness in a Cohort of Homosexual Men Predicted by Baseline $CD4^+$ T Cell Count and Viral Load *

CD4 ≤ 350 Plasma Viral Load (copies/ml) **				% AIDS (AIDS – defining complication) ***			
bDNA		RT-PCR		n	3 years	6 years	9 years
	≤ 500		≤ 1,500	– #	–	–	–
501	– 3,000	1,501	– 7,000	30	0	18.8	30.6
3,001	– 10,000	7,001	– 20,000	51	8.0	42.2	65.6
10,001	– 30,000	20,001	– 55,000	73	40.1	72.9	86.2
	> 30,000		> 55,000	174	72.9	92.7	95.6
CD4 351 – 500 Plasma Viral Load (copies/ml)				**% AIDS (AIDS – defining complication)**			
bDNA		**RT-PCR**		**n**	**3 years**	**6 years**	**9 years**
	≤ 500		≤ 1,500	–	–	–	–
501	– 3,000	1,501	– 7,000	47	4.4	22.1	46.9
3,001	– 10,000	7,001	– 20,000	105	5.9	39.8	60.7
10,001	– 30,000	20,001	– 55,000	121	15.1	57.2	78.6
	> 30,000		> 55,000	121	47.9	77.7	94.4
CD4 > 500 Plasma Viral Load (copies/ml)				**% AIDS (AIDS – defining complication)**			
bDNA		**RT-PCR**		**n**	**3 years**	**6 years**	**9 years**
	≤ 500		≤ 1,500	110	1.0	5.0	10.7
501	– 3,000	1,501	– 7,000	180	2.3	14.9	33.2
3,001	– 10,000	7,001	– 20,000	237	7.2	25.9	50.3
10,001	– 30,000	20,001	– 55,000	202	14.6	47.7	70.6
	> 30,000		> 55,000	141	32.6	66.8	76.3

* Data from the Multi-Center AIDS Cohort Study (MACS), reference **3**.

** 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.

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 (93).

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 I. 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 VI. 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 II. 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 III. Recommendations for the Use of Drug Resistance Assays

Clinical setting/Recommendation	Rationale
Recommended	
Virologic failure during HAART (see page 15)	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 15)	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 VII – Advantages and Disadvantages of Class-sparing regimens

Regimen	Possible Advantages	Possible Disadvantages	Drug Interaction Complications	Impact on Future Options
PI-based HAART Regimen	• 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 (protease-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 viral load 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 VIII. Indications for the Initiation of Antiretroviral Therapy in the Chronically HIV-Infected Patient

Clinical Category	$CD4^+$ T Cell Count and HIV RNA	Recommendation
Symptomatic (AIDS, thrush, unexplained fever)	Any value	Treat
Asymptomatic	$CD4^+$ T Cells < 500/mm^3 **or** HIV RNA > 10,000 (bDNA) or > 20,000 (RT-PCR)	Treatment should be offered. Strength or recommendation is based on prognosis for disease-free survival as shown in Table V and willingness of the patient to accept therapy. *
Asymptomatic	$CD4^+$ T Cells > 500/mm^3 **and** HIV RNA < 10,000 (bDNA) or < 20,000 (RT-PCR)	Many experts would delay therapy and observe; however, some experts would treat.

* Some experts would observe patients with $CD4^+$ T cell counts between 350 – 500/mm^3 and HIV RNA levels < 10,000 (bDNA) or < 20,000 (RT-PCR)

Table XIII. Drugs That Should Not Be Used With Antiretrovirals

Drug Category	Indinavir	Ritonavir *	Saquinavir	Nelfinavir	Amprenavir
Ca++ channel blocker	(none)	bepridil	(none)	(none)	bepridil
Cardiac	(none)	amiodarone flecainide propafenone quinidine	(none)	(none)	(none)
Lipid Lowering Agents	simvastatin lovastatin	simvastatin lovastatin	simvastatin lovastatin	simvastatin lovastatin	simvastatin lovastatin
Anti-Mycobacterial	rifampin	(none)	rifampin rifabutin	rifampin	rifampin
Antihistamine	astemizole terfenadine	astemizole terfenadine	astemizole terfenadine	astemizole terfenadine	astemizole terfenadine
Gastrointestinal Drugs	cisapride	cisapride	cisapride	cisapride	cisapride
Neuroleptic	(none)	clozapine pimozide	(none)	(none)	(none)
Psychotropic	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)

* 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, ethambutol (MAI treatment)
Astemizole, terfenadine: loratidine, fexofenadine, cetirizine
Midazolam,triazolam: temazepam, lorazepam

Table IX. 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 X-XVI 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.

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

* Saquinavir-SGC, soft-gel capsule (Fortovase): Saquinavir-HGC, hard-gel capsule (Invirase).

** 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 X. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Generic Name Trade Name	**Zidovudine (AZT, ZDV)** Retrovir	**Didanosine (ddI)** Videx	**Zalcitabine (ddC)** HIVID	**Stavudine (d4T)** Zerit	**Lamivudine (3TC)** Epivir	**Abacavir (ABC)** Ziagen
Form	100 mg capsules 300 mg tablets 10 mg/mL IV solution 10 mg/mL oral solution	25, 50, 100, 150, 200 mg tablets 167, 250 mg sachets	0.375, 0.75 mg tablets	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	200 mg tid or 300 mg bid or with 3TC as Combivir, 1 bid	Tablets >60kg: 200 mg bid or 400 mg qd <60kg: 125 mg bid or 250 mg qd	0.75 mg tid	>60kg: 40 mg bid <60kg: 30 mg bid	150 mg bid <50kg: 2 mg/kg bid or with ZDV as Combivir 1 bid	300 mg bid
Food Effect	Take without regard to meals	Levels ↓ 55% Take ½ hour before or 1 hour after meal	Take without regard to meals	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	60%	30 - 40%	85%	86%	86%	83%
Serum half-life	1.1 hour	1.6 hour	1.2 hour	1.0 hour	3-6 hours	1.5 hours
Intracellular half-life	3 hours	25 – 40 hours	3 hours	3.5 hours	12 hours	3.3 hours
Elimination	Metabolized to AZT glucuronide (GAZT) Renal excretion of GAZT	Renal excretion 50%	Renal excretion 70%	Renal excretion 50%	Renal excretion unchanged	Metabolized by alcohol dehydrogenase and glucuronyl transferase Renal excretion of metabolites 82%
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.	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** Lactic acidosis with hepatic steatosis is a rare but potentially life-threatening toxicity with the use of NRTIs.

* 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.

* * 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 XIII. Drugs That Should Not Be Used With 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	(none)	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: loratidine, fexofenadine, cetirizine
Midazolam,triazolam: temazepam, lorazepam

Table XI. 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	50, 100, 200 mg capsules
Dosing Recommendation	200 mg po qd x 14 days, then 200 mg po bid	400 mg po tid, or four 100 mg tablets in $\geq$ 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 systems symptoms ** Increase transaminase levels False positive cannabinoid test Teratogenic in monkeys ***
Drug Interactions	**For more information on Drug Interactions please see Table XIV.**		

* 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.

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

Table XII. Characteristics of Protease Inhibitors (PIs)

Generic Name Trade Name	**Indinavir** Crixivan	**Ritonavir** Norvir	**Nelfinavir** Viracept
Form	200, 333, 400 mg caps	100 mg caps. 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 q12 * Separate dosing with ddI by 2 hours	750 mg tid or 1250 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 • Hyperglycemia + • Fat redistribution and lipid abnormalities ++ • Possible increased bleeding episodes in patients with hemophilia	• GI intolerance, nausea, vomiting, diarrhea • Paresthesias – circumoral and extremities • Hepatitis • Asthenia • Taste perversion • Lab.: Tryglycerides 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 XIV.**		

* 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. Discontinuation of PIs may be required to reverse fat redistribution. Patients with hypertriglyceridemia or hypercholesterolemia should be evaluates for risks for cardiovascular events and pancreatitis. Possible interventions include dietary modification, lipid lowering agents, or discontinuation of PIs.

Table XIV. 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: keto. ↑ 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
Rifabutin	Levels: IDV ↓32% Rifabutin ↑2X Dose: ↓rifabutin to 150 mg qd, IDV 1000 mg tid	Levels: Rifabutin ↑4X Dose: ↓rifabutin to 150 mg qod Or dose 3x per week	Levels: SQV ↓40% Not recommended
Clarithromycin	Levels: Clari. ↑ 53% No dose adjustment	Levels: Clari. ↑ 77% Dose adjust for renal insufficiency	Levels: Clari. ↑ 45% SQV ↑ 177% No dose adjustment
ORAL CONTRACEPTIVES	Levels: Norethindrone↑26% ethinylestradiol↑24% No dose adjustment	Levels: ethinylestradiol ↓ 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**	Unknown but may decrease IDV levels substantially Monitor anticonvulsant levels.	Unknown Use with caution Monitor anticonvulsant levels.	Unknown but may decrease SQV levels substantially Monitor anticonvulsant levels.
Methadone	No data	Methadone ↓ 37%, May require dose increase	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.

* Some drug interaction studies were conducted with INVIRASE. May not necessarily apply to use with FORTOVASE.

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

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

Generic Name Trade Name	**Saquinavir** Invirase	 Fortovase	**Amprenavir** Agenerase
Form	200 mg caps	200 mg caps	50 mg, 150 mg tablets 15 mg/mL oral solution (tabs and solution NOT interchangeable on mg per mg basis)
Dosing Recommendations	400 mg bid with ritonavir; Invirase not recommended otherwise	1,200 mg tid **	1200 mg 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.
Oral bioavailability	Hard gel capsule: 4% erratic	Soft gel capsule (not determined)	Not determined in humans
Serum half-life	1 – 2 hours	1 – 2 hours	7.1 – 10.6 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)
Storage	Room temperature	Refrigerate or store at room temperature (up to 3 months)	Room temperature
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
Drug Interactions	**For more information on Drug Interactions please see Table XIV.**		

** 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 glysemic 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 evaluates for risks for cardiovascular events and pancreatitis. Possible interventions include dietary modification, lipid lowering agents, or discontinuation of PIs.

Table XIV. 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)**
ANTIFUNGALS		
Ketoconazole	No dose adjustment necessary	Levels: APV ↑ 31% Keto ↑ 44%. Combination under investigation
ANTI-MYCOBACTERIALS		
Rifampin	Levels ↓ 82% Contraindicated	Levels: APV AUC ↓ 82% No change in rifampin AUC. Avoid concomitant use.
Rifabutin	Levels: NFV ↓32% Rifabutin ↑2X Dose: ↓rifabutin to 150 mg qd. ↑NFV dose to 1000 mg tid.	Levels: APV AUC ↓15% Rifabutin ↑193% Dose: No change in APV dose; Decrease rifabutin to 150 mg qd.
Clarithromycin	No data	Levels: APV AUC ↑ 18%. No change in Clari. AUC. No dose adjustment
ORAL CONTRACEPTIVES	Levels: Norethindrone↓ 18% ethinylestradiol↓47% Use alternative or additional method	Levels: Potential for metabolic interactions; use alternative or additional method.
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.
ANTICONVULSANTS		
Phenobarbitol **Phenytoin** **Carbamazepine**	Unknown but may decrease NFV levels substantially Monitor anticonvulsant levels.	Unknown but may decrease APV levels substantially Monitor anticonvulsant levels.
Methadone	No data	No data
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.

Table XIV. 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 data for rifabutin dose	Levels: DLV ↓80% Rifabutin ↑ 100% Not Recommended	Levels: EFV unchanged; Rifabutin ↓ 35% Dose: ↑ rifabutin dose to 450 mg qd.
Clarithromycin	Levels: NVP ↑26%, clari. ↓ 30%. No dose adjustment.	Levels: clari. ↑100%, DLV ↑ 44% Dose adjust for renal failure	Levels: clari. ↓39% Alternative recommended
ORAL CONTRACEPTIVES	No data	No data	Levels: Ethinylestradiol ↑ 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	No data
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

Table XIV. 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 XVIII. 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 on these on page 14.
- 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 sub-optimal for initial therapy are rational due to limitations imposed by toxicity, intolerance or non-adherence. This especially applies in late stage disease. For patients with no rational alternative 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 XV. Drug Interactions: Protease Inhibitors and Non-nucleoside Reverse Transcriptase Inhibitors

Effect of Drug on Levels (AUCs)/Dose

Drug Affected	Ritonavir	Saquinavir *	Nelfinavir	Amprenavir
Indinavir (IDV)	Levels: IDV ↑ 2-5X Dose: Limited data for IDV 400 mg bid + RTV 400 mg bid, or IDV 600 mg bid + RTV 200 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
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: Limited data for RTV 400 mg bid + NFV 500-750 mg bid	Levels: APV AUC ↑ 2.5-fold. Dose: insufficient data
Saquinavir (SQV)	•	•	Levels: SQV ↑ 3-5x NFV ↑ 20% # Dose: Standard NFV Fortovase 800 mg tid	Levels: APV AUC↓32% Dose: insufficient data
Nelfinavir (NFV)	•	•	•	Levels: APV AUC ↑ 1.5-fold. Dose: insufficient data

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

\+ Conducted with Invirase

\# Conducted with Fortovase

Table XV. 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	Levels: IDV ↑ >40% DLV no effect Dose: IDV 600 mg q 8h DLV: standard	Levels: IDV ↓ 31% Dose: IDV 1000mg q 8h
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)
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
Nevirapine (NVP)	•	No data	No data
Delavirdine (DLV)	No data	•	No data

\+ Conducted with Invirase

Table XIX. Acute Retroviral Syndrome: Associated Signs and Symptoms (Expected Frequency) (69)

- 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-Barre syndrome
  - Brachial neuritis
  - Cognitive impairment or psychosis

Table XVI: 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-" primaquine pyrimethamine ribavirin sulfadiazine trimetrexate zidovudine	didanosine isoniazid stavudine zalcitabine	cotrimoxazole didanosine lamivudine (children) pentamidine ritonavir	adefovir aminoglycosides amphotericin B cidofovir foscarnet indinavir pentamidine ritonavir	delavirdine efavirenz fluconazole isoniazid itraconazole ketoconazole nevirapine NRTIs Protease inhibitors rifabutin rifampin	abacavir cotrimoxa-zole dapsone NNRTIs Protease inhibitors	didanosine clindamycin nelfinavir ritonavir	didanosine ethambutol rifabutin cidofovir

Table XVII. Drugs Available Through Treatment Investigational New Drug Protocols

Drug	Adefovir (Preveon) *	Tenofovir Disoproxil Fumarate (Tenofovir DF)	ABT-378/ritonavir (ABT-378/r)
Source	Gilead 800-GILEAD-5	Gilead Compassionate Access Study 1-800-GILEAD-5 or 1-800-276-0231	Abbott Early Access Program 1-888-711-7193
Class	Nucleotide RT Inhibitor	Nucleotide Reverse Transcriptase Inhibitor	Protease Inhibitor
Usual Dose	60 mg po qd or 120 mg po qd + L-carnitine 500 mg po qd	300 mg po qd	(ABT-378 400mg + ritonavir 100mg) po bid
Side Effects (major)	Proximal renal tubular dysfunction, nausea, elevated LFTs	elevation of creatine phosphokinase, elevation of transaminases	nausea, diarrhea, skin rash, hyperlipidemia, elevation of transaminases
Comments	Activity vs. HBV, CMV, HSV	▪ Eligibility of patients with prior history of adefovir-induced nephrotoxicity will be determined on a case by case basis ▪ Also active against Hepatitis B	▪ Concomitant use with amprenavir, indinavir, nelfinavir, or saquinavir allowed ▪ Concomitant use with ritonavir and delavirdine prohibited
Enrollment Criteria	Failure or intolerance with current therapy; absence of clinically significant renal dysfunction and no concurrent use of nephrotoxic drugs	▪ HIV-RNA $\geq$ 10,000 copies/mL ▪ CD4 $\leq$ 50 cells/μL or, ▪ CD4 > 50 and $\leq$ 200 cells/μL with documented AIDS-defining OI within 90 days ▪ Serum creatinine < 1.5 mg/dL ▪ No concomitant nephrotoxic drugs	▪ Documented failure and/or intolerance to $\geq$ 2 PI ▪ HIV-RNA $\geq$ 10,000 copies/mL within 3 months ▪ CD4 $\leq$ 200 cells/μL within 3 months

* No longer in development

Table XX. 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]	Not completed	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]	Not completed	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)
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]	Not completed	Ventricular septal defect
efavirenz	C	Yes (cynomolgus monkeys, rats, rabbits) [~1.0]	Not completed	Anencephaly; anophthalmia; microphthalmia (cynomalgus 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.

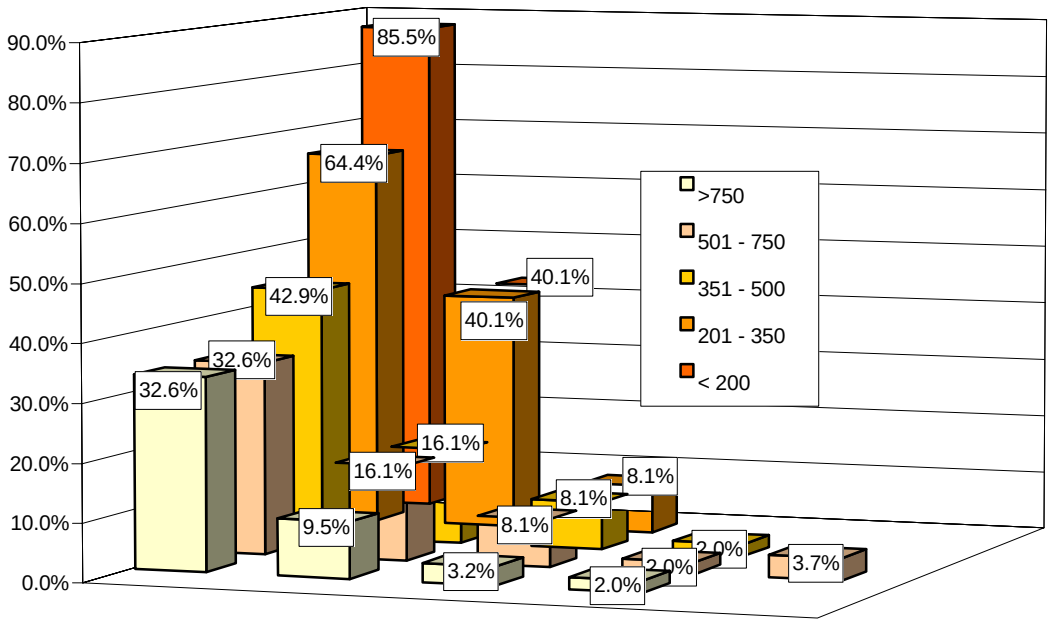
** Despite certain animal data showing potential teratogenicity of ZDV when near-lethal doses are given to pregnant rodents, considerable human data are available to date indicating that the risk to the fetus, if any, is extremely small when given to the pregnant mother beyond 14 weeks gestation. Follow-up 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 (93). However, no data is available on longer follow-up for late effects.

† These effects seen at only at maternally toxic doses.

Table XXI. 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 V 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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Adherence to Potent Antiretroviral Therapy

I. Introduction

The Guidelines for the Treatment of HIV Infected Adults and Adolescents call for most people living with HIV, many of whom are asymptomatic, to be treated with highly active antiretroviral therapy (HAART) for the rest of their lives.(1) The ability of the patient to adhere to the regimen is essential to the potential benefit of treatment. Poor adherence will lead to the development of drug resistance, limiting the effectiveness of therapy. The determinants, measurements, and interventions to improve adherence to HAART are poorly characterized and understood, and more research on this critical topic is needed. In particular, clarification of the degree of adherence to HAART necessary to prevent resistance is urgently needed. The Panel reviewed the available literature on adherence and offers this summary and recommendations. A citation of recent literature is appended.

II. The Science of Adherence

A. Adherence in other disease states

a. Determinants

The medical literature is clear that it is difficult for patients to adhere to even the simplest treatment regimens. In the hypertension literature, one-third of patients take medications as directed, one-third take little or no medication, and one-third are intermittently adherent (2). Age, race, sex, educational level, socioeconomic status, and a past history of alcoholism or drug use are not reliable predictors of poor adherence (3). On the other hand, active drug use or alcoholism have been associated with poor adherence in numerous studies (4,5). Regimen simplicity affects adherence in hypertension; once daily therapy is associated with rates of 90% adherence, twice daily with 80%, and three or more times daily with 65% (6). Other factors shown to be associated with better adherence to medications include more severe symptoms or illness and belief in efficacy of treatment (7). Factors associated with poor adherence include unstable housing, mental illness, and major life crises (8).

b. Measurements

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 (7). Physician estimation of a patient's likelihood of adherence is a poor predictor (4). Each of several aids to measure adherence, such as pill counts, pharmacy records, smart pill bottles with computer chips recording each opening

("Memscaps"), and other devices may be of use, though each requires comparison to patient self-reports (9).

c. Interventions

No single intervention to improve adherence is considered best. A menu of options is needed, one or more of which may prove useful in a given patient (10). The practical strategies which have been shown to improve adherence are varied, with a few consistent themes. A trusting physician-patient relationship is clearly associated with improved adherence (7). Time and energy spent on educating the patient regarding the goals of therapy and the consequences of good and poor adherence are valuable. Adherence results from a negotiated treatment plan, rather than a dictated course from physician to patient; hence the preference for the term "adherence" over "compliance." Recruitment of family and friends to support the therapeutic plan and its implementation is associated with improved outcomes. Simplification of the regimen, i.e., with reduced pill numbers and frequencies, is associated with better adherence, as is the reduction and treatment of adverse events.

B. Adherence in HIV Disease

Recent studies found an association between poor adherence and adverse virologic outcomes. In San Francisco, non-adherence in patients on HAART was the strongest predictor of failure to achieve viral suppression below the level of detection (11). In the INCAS Study, patients who missed doses of antiretroviral drugs on 28 or more days during the 52 week study had a significantly lower likelihood of achieving durable viral suppression to both the 500 copies/ml level and the 50 copies/ml level (12).

Regarding HAART-taking behavior, two recent surveys showed that one-third of patients missed doses within three days of the survey (9, 13). Factors associated with poor adherence included active alcohol or drug use and lack of advanced disease. 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. The instability of homelessness may lead to poor adherence, but not without exception (14); one recent program achieved a 70% adherence rate among the homeless utilizing flexible clinic hours, accessible clinical staff, and incentives (15).

The response to the problem of adherence in special populations has not been well-studied. 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. Obviously, not all injecting drug users (IDUs) or homeless persons are alike; physicians should employ an individualized case-by-case assessment of their patients and act accordingly to ensure and improve adherence (see below).

III. Adherence to HAART: Approach to the Patient

A. Patient-related strategies

Suggestions for strategies to improve adherence are noted in Tables I-IV. The first principle is to negotiate a treatment plan which the patient understands and to which he/she commits (10). Before the first prescription is written, patient "readiness" to take medication should be clearly established (16). Such negotiation takes time, commonly two or three office visits, and patience. Specific education should include the goals of therapy, including reviews of expected outcomes based on baseline viral load and CD4+ T cell counts, such as 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 physician 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 are offering "dry runs" with jelly beans in order to familiarize the patient with the rigors of HAART. Daily or weekly pill boxes, timers with alarms, pagers and other devices may be useful. The development of side effects can affect the ability to adhere to treatment. Physicians should inform patients in advance about possible side effects and when they are likely to occur; treatment information should be included in the first prescription along with instructions on the appropriate response and the possible need to contact the physician.

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.

B. Physician and health team-related strategies

As above, the first principle is for the physician to negotiate a treatment plan which the patient understands and to which he/she commits. Suggestions for strategies for the physicians and health team are noted in Tables III and IV. A trusting relationship is essential. The physician should commit to a feasible mechanism for communication between clinic visits, to ongoing monitoring of adherence, and to substantive 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. Specific training on HAART and adherence should be offered and updated regularly.

Monitoring may identify periods of poor adherence. Reasonable responses 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 (17). 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, such as 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 two month exacerbation of chronic depression.

C. Regimen-related strategies

To the extent possible, HAART 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. Recent evidence on alternate dosing strategies of HAART regimens may allow more user-friendly dosing and should be closely watched by physicians for further validation from clinical trials. Comparative clinical trials of simplified dosing schedules for didanosine, nelfinavir, and saquinavir-soft gel capsules are currently underway. Based on preliminary results from these trials, it appears that didanosine given as a single 400mg daily dose, and nelfinavir given as 1,250 mg twice daily resulted in similar area under the concentration-time curves and similar virologic and immunologic responses when compared to their approved dosing schedules. Saquinavir soft-gel capsule given as 1,600 mg twice daily produced lower daily exposure and trough serum concentrations compared with the standard 1,200 mg TID regimen. At up to 32 weeks, these two dosing schedules resulted in similar overall virologic responses; however, the twice daily regimen was inferior in the subgroup of NRTI-experienced patients. In addition, a trend favoring the TID regimen was evident when CD4+ T cell responses were analyzed. 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. In a comparative trial of indinavir 1,200 mg q12h vs 800mg q8h in anti-retroviral naïve patients, significantly fewer patients in the q12h group achieved HIV-RNA < 400 copies/mL compared with the q8h group (64% vs 91%) at week 24. When indinavir is used as the sole protease inhibitor, q12h dosing regimen should not be prescribed.

Regimens should be chosen with food requirements to which the patient has agreed. 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.

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Table I. Strategies to Improve Adherence: 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

Table II. Strategies to Improve Adherence: Patient-Related

- 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 CBOs around adherence with educational sessions & practical strategies.
- Consider “pill trials” with jelly beans.

Table III. Strategies to Improve Adherence: Physician-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 IDUs.
- Consider impact of new diagnoses on adherence, e.g. depression, liver disease, wasting, recurrent chemical dependency, and include adherence intervention in management.

Table IV. Strategies to Improve Adherence: Health Team-Related

- 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 PAT and adherence.
- Add adherence interventions to job descriptions of HIV support team members; add continuity of care role to improve patient access.

Hydroxyurea

Hydroxyurea is indicated for use in the treatment of certain malignancies and in sickle cell anemia, and has been used investigationally for 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 has 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 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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Class Adverse Events

I. Class Adverse Events

Several class-related adverse events have been recognized with antiretroviral drugs during the post-marketing period. For nucleoside analogue reverse transcriptase inhibitors (NRTIs), lactic acidosis with hepatomegaly and hepatic steatosis has been reported. For protease inhibitors reports of hyperglycemia/diabetes mellitus, increased bleeding episodes in patients with hemophilia, and fat redistribution with and without serum lipid abnormalities have been received. Because these events were identified based on spontaneous reports and other uncontrolled data, the actual incidence of these events and the causal association with these drugs have not been definitively established. Controlled and/or population-based epidemiologic studies evaluating these potential class adverse events are warranted.

II. NRTIs

A. Lactic Acidosis/Hepatic Steatosis

The occurrence of lactic acidosis and severe hepatomegaly with steatosis during use of nucleoside analogue reverse transcriptase inhibitors (NRTIs) appears to occur at a low frequency, but with a high case fatality rate. 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. There are no data to suggest that the toxicity occurs more often with any particular nucleoside analogue reverse transcriptase inhibitor or combination. The initial clinical manifestations of lactic acidosis are variable and may include nonspecific gastrointestinal symptoms without dramatic elevation of hepatic enzymes, and in some cases dyspnea. Fatalities have been reported despite intensive supportive treatment; in other cases the adverse event has resolved after discontinuation of NRTIs. Treatment should be suspended if clinical or laboratory manifestations suggestive of lactic acidosis or otherwise unexplained pronounced hepatotoxicity occur (BIII).

III. NNRTIs

A. 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.

IV. Protease Inhibitors

Fat redistribution, hyperlipidemia, and insulin resistance have been associated with protease inhibitor use with variable frequency. These changes may occur together or as isolated observations. The etiologic role of PIs is not considered established by some and the long term consequences are generally unclear. Recommendations for monitoring and intervention are also unclear at the present time.

A. Hyperglycemia/Diabetes Mellitus

Hyperglycemia, new onset diabetes mellitus, diabetic ketoacidosis, and exacerbation of existing diabetes mellitus in patients receiving protease inhibitors have been reported (1-3). Among these reports, symptom onset occurred a median of 63 days (range 2 – 390 days) following initiation of protease inhibitor therapy. Hyperglycemia resolved in some patients who discontinued protease inhibitor therapy; however, the reversibility of these events is currently unknown due to limited data. Some patients continued protease inhibitor therapy and initiated treatment with oral hypoglycemic agents or insulin. Clinicians are advised to monitor HIV-infected patients with pre-existing diabetes closely when protease inhibitors 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 authorities recommend routine fasting blood glucose measurements at 3-4 month intervals during treatment (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 highly active antiretroviral therapy in the absence of severe, life-threatening diabetes (BIII).

B. Fat Redistribution and Lipid Abnormalities

Changes in body fat distribution, sometimes referred to as "lipodystrophy syndrome" or "pseudo-Cushing's syndrome" have been observed in patients receiving protease inhibitors. Clinical findings include central obesity and peripheral fat wasting. The changes may include visceral fat accumulation, dorsocervical fat accumulation ("buffalo hump"), extremity wasting with venous prominence, facial thinning, and breast enlargement (4-8). Some patients may have a cushingoid appearance despite the absence of confounding medications (i.e., corticosteroids) or adrenal function laboratory abnormalities. It is unclear whether the various clinical manifestations represent distinct entities with different etiologies, or whether they occur as a result of a single pathologic process. Similar findings have also been reported in HIV infected patients not receiving protease inhibitors (5); however, the number of reports has increased concomitant with the widespread use of protease inhibitor-containing antiretroviral regimens. There are sparse data on management recommendations,

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although dose reduction of PIs is not recommended. Discontinuation of PI therapy has been successful in the resolution of symptoms in some cases.

C. Hyperlipidemia

Changes in triglycerides and/or cholesterol have occurred with or without the clinical findings of fat redistribution. In clinical studies, all PIs have been implicated, but ritonavir has been shown to produce substantial increases in triglycerides and cholesterol most frequently. Although the long-term consequences of fat redistribution 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, and cholelithiasis in patients receiving PI therapy. Some authorities recommend monitoring of serum levels of cholesterol and triglycerides at 3-4 month intervals during PI therapy (*CIII*). 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). The effectiveness of dietary modification and lipid lowering drugs such as gemfibrozil and niacin is not clear. Some patients have had resolution of serum lipid abnormalities with discontinuation of PIs; however, this decision requires a risk-benefit analysis.

D. 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. 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.

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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) [21]. 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 [20]. A French group reported 8 cases of uninfected infants with in utero and/or neonatal exposure to either ZDV/3TC (4 infants) or ZDV alone (4 infants) who developed indications of mitochondrial dysfunction after the first few months of life [22]. 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 a large database that included 353 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 [23]. 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 3 regimens of ZDV/3TC (before, during and 1 week postpartum; during labor and postpartum; and during labor only) to placebo for prevention of transmission. No increased risk of neurologic events were observed among children treated with ZDV/3TC compared to placebo, regardless of intensity of treatment [24]. If the association of mitochondrial dysfunction and in utero antiretroviral exposures 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% [25]. These data emphasize the importance of the existing Public Health Service recommendation for long-term follow-up for any infant 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) (26). 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 (26).

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 (26). 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 zidovudine (600 mg orally to the mother at the onset of delivery and 300 mg every 3 hours until delivery, and 4 mg/kg orally twice daily for the first 7 days of life to the neonate). In this study, nevirapine lowered the risk of HIV transmission by nearly 50% during the first 14-16 weeks of life compared with zidovudine (27). 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.

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 (28-31). 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 (32)**.** 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 (33-35). 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, data are not yet available regarding drug dosage, safety, and tolerance of the protease inhibitors in pregnancy or in neonates. Amprenavir, a recently approved protease inhibitor, has 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 in combination with ZDV and 3TC in pregnant HIV-infected women is being conducted, but data are not yet available.

Certain side effects of indinavir seen in adults (hyperbilirubinemia, nephrolithiasis) could be problematic for the newborn if placental passage occurs in humans. It is unknown if administration of indinavir to the mother during the perinatal period will exacerbate physiologic hyperbilirubinemia in neonates. Because the half-life of indinavir in adults is short, these concerns may only be relevant if the drug is administered near the time of delivery.

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 zidovudine and lamivudine in pregnant HIV-infected women and their infants is being conducted, but data are not yet available.

Ritonavir (Norvir) is classified as FDA pregnancy category B

Animal carcinogenicity studies

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

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 (36). 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 (Fortovase) 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 zidovudine and lamivudine in pregnant HIV-infected women and their infants is being conducted, but data are not yet available.

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 (37-43). 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 (37, 40, 41). 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 (38). 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 (40). Teratogenicity was also demonstrated in pregnant cats given a single oral dose of 50 or 100 mg per kg body weight (39).

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 (44).

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) (45). 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, 115 N. 3rd Street, Suite 306, Wilmington, NC 28401; telephone (800)-258-4263; fax (800) 800-1052, US and Canada. International calls (910) 251-0689.

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