**June 17, 1998**

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

***These Guidelines were developed by the Panel on Clinical Practices for Treatment of HIV Infection convened by the Department of Health and Human Services (DHHS) and the Henry J. Kaiser Family Foundation. Leadership of the Panel consists of Anthony S. Fauci, National Institutes of Health, Bethesda, MD (co-chair); John G. Bartlett, Johns Hopkins University, Baltimore, MD (co-chair); Eric P. Goosby, DHHS (convener); Mark D. Smith, California HealthCare Foundation, San Francisco, CA, formerly of the Henry J. Kaiser Foundation, (convener.) Succeeded by Sophia W. Chang, Henry J. Kaiser Foundation.***

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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 with particular emphasis on measurement of plasma levels of HIV RNA. 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. Like the treatment of most chronic diseases, antiretroviral regimens are complex, have major side effects, pose difficulty with compliance, and carry serious potential consequences with the risk of resistance from 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 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, 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 goal is maximum viral suppression for as long as possible. Results of clinical trials to date indicate that this may currently be best achieved with a potent protease inhibitor (PI) in combination with two nucleoside analogue reverse transcriptase inhibitors (NRTIs). Another option is the combination of saquinavir plus ritonavir combined**

**with one or two NRTIs. Other currently available regimens may be used in selected settings, but are considered by many to be less likely to produce maximum viral suppression. 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 (<500 copies/ml) at 4-6 months after initiation of treatment. Failure of therapy (i.e. plasma HIV RNA levels exceeding 500 copies/mL) at 4–6 months may be ascribed to non-adherence, inadequate potency of drugs or suboptimal levels of antiretroviral agents, resistance, and other factors that are poorly understood. Patients whose therapy fails should change to at least two new agents that are not likely to show cross-resistance with drugs given previously; ideally, the regimen should be changed to a completely new regimen devoid of anticipated cross-resistance and with clinical trial data supporting a high probability of viral response. Rational 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 the optimal virologic goal.**

**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).**

**June 17, 1998**

# 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 antiretoviral 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 will address pediatric-specific issues related to antiretroviral therapy.

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. The recommendations in this document are presented in the context of and with reference to the Principles of Therapy contained in the companion document. 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, will meet several times a year to review new data as it becomes available; recommendations for changes in this document will then be submitted to the Panel and incorporated as appropriate. Copies of this document and all updates are available from the HIV/AIDS Treatment Information Service (1–800–448–0440; Fax 301–519–6616) and on the ATIS Web site (http://www.hivatis.org). They are also available from the CDC National AIDS Clearinghouse (1–800–458–5231; TTY 1–800–243–7012) and are posted on the Clearinghouse Web site (http://www.cdcnac.org) These recommendations are not intended to substitute for the judgment of a physician who is 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 (1). 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 for 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; 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. As discussed in Principle 2, results of the two laboratory tests gives the physician important information about the virologic and immunologic status of the patient and the risk of disease progression to AIDS. It should be noted that HIV viral load testing has been approved by the FDA only for the RT-PCR assay (Roche) and only for determining disease prognosis. However, data presented at an FDA Advisory Committee for the Division of Antiviral Drug Products (July 14–15, 1997, Silver Spring, MD) provide further evidence for the utility of viral RNA testing in monitoring therapeutic responses. 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 4–8 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 (~0.5 to 0.75 $\log_{10}$) in viral load by 4–8 weeks. The viral load should continue to decline over the following weeks and in most individuals becomes below detectable levels (currently defined as <500 RNA copies/ml) by 12–16 weeks. The speed of viral load decline and the movement toward undetectable are affected by the baseline $CD4^+$ T cell count, the initial viral load, potency of the regimen, adherence, 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 500 copies of HIV RNA per ml of plasma (2). If HIV RNA remains detectable in plasma after 6 months 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). More sensitive viral load assays are in development that can quantify HIV RNA down to approximately 50 copies/ml. Preliminary 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. However, the clinical significance of these findings is currently unclear.

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. Consistent with Principle 2, 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 (3,4). 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 (5). Such discordance can complicate decisions regarding antiretroviral therapy and may be due to a number of factors that affect plasma HIV RNA testing (see Principle 2). 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.

## *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 $\geq$ 2 weeks) including AIDS, defined according to the 1993 CDC classification system (6). 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” (1) (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 (7–11). Although there is theoretical benefit to treatment for patients with $CD4^+$ T cells greater than 500 cells/$mm^3$ (see Principle 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 III summarizes some of the factors that the physician and the asymptomatic patient must consider in deciding when to initiate therapy (see also Principle 3). 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; and decreasing drug toxicity by treating the healthier patient. 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 maximally 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 IV and Figure 1; see also Principles document); 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 characteristic judged by some to lend itself to noncompliance. 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.

## 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 V and VI 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). However, 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 IV 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 IV (first line or column) are the uncorrected HIV RNA values obtained from the Multicenter AIDS Cohort Study (MACS). It had previously been thought that these values, obtained on stored heparinized plasma specimens, should be multiplied by a factor of two to adjust for an anticipated two-fold loss of RNA ascribed to the effects of heparin and delayed processing on the stability of RNA. However, more recent analysis suggests that the reduction ascribed to these factors is $\leq$ 0.2 log, so that no significant correction factor is necessary (Mellors J, personal communication, October 1997). RT-PCR values are also shown in Table IV and Figure 1; comparison of the results obtained from the RT-PCR and bDNA assays using the manufacturer's controls consistently indicate that the HIV-1 RNA values obtained by RT-PCR are approximately two times higher than those obtained by the bDNA assay (12). 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, 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 that 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 V). 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 IV; 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 IV). 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 naive to antiretroviral therapy, one should begin with a regimen that is expected to reduce viral replication to undetectable levels (AIII). Based on the weight of experience, the preferred regimen to accomplish this is 2 nucleoside analogues (NRTIs) and one potent protease inhibitor (PI) (Table VI). Alternative regimens have been employed; these include ritonavir and saquinavir (with one or two nucleoside analogues) or nevirapine as a substitute for the protease inhibitor. Ritonavir and saquinavir (hard gel capsule) dual PI therapy (without an NRTI) appears to be potent in suppressing viremia below detectable levels, and has convenient BID dosing; however, the safety of this combination has not been fully established according to FDA guidelines. In addition, this regimen has not been directly compared to the proven regimens of 2 NRTIs and a PI, and thus the Panel recommends that at least one additional NRTI be used when the physician elects to use 2 PIs as initial therapy. Substituting nevirapine for the PI, or using 2 NRTIs alone, does not achieve the goal of suppressing viremia to below detectable levels as

consistently as does combination treatment with 2 NRTIs and a PI and should be used only if more potent treatment is not possible. It should be noted, however, that some experts feel that there are currently insufficient data to choose between a three drug regimen containing a protease inhibitor and one containing nevirapine in the drug-naive patient; further studies are pending. Likewise, other regimens using two PIs or a PI and a non-nucleoside reverse transcriptase inhibitor (NNRTI) as initial therapy are currently in clinical trials with data pending. ~~Of the two available NNRTIs, clinical trials support a preference for nevirapine over delavirdine based on results of viral load assays.~~ Although 3TC is a potent NRTI when used in combination with another NRTI, in situations in which suppression of virus replication is not complete, resistance to 3TC develops rapidly (13,14). Therefore, the optimal use for this agent is as part of a three or more drug combination that has a high chance of complete suppression of virus replication. Other agents in which a single genetic mutation can confer drug resistance, such as the NNRTIs nevirapine and delavirdine, should also be used in this manner. 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.

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

## Initiating Therapy in Advanced HIV Disease

All patients diagnosed with advanced HIV disease, which is defined as any condition meeting the 1993 CDC definition of AIDS (6) 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, such as 2 NRTIs and a protease inhibitor, should be used, as indicated in Table VI. 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 VII–XII. 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 VIII–XI; this topic is discussed in greater detail elsewhere (15). 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. Some of these PIs and NNRTIs (ritonavir, indinavir, saquinavir, nelfinavir and delavirdine) inhibit the CYP450 pathway; others (nevirapine) induce CYP450 metabolism. 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 the hard gel capsule formulation of saquinavir) as well as contribute an additive antiviral effect; however, these interactions can also result in life threatening drug toxicity, as indicated in Tables X–XII. 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 risk 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.

## *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 (see Principle 4).

## *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 (see Principle 7). Failure of a regimen may occur for many reasons, including initial viral resistance to one or more agents, altered absorption or metabolism of the drug, multi-drug pharmacokinetics that adversely affect therapeutic drug levels, and poor patient adherence to a regimen due to either poor compliance or inadequate patient education about the therapeutic agents. In this regard, it is important to carefully assess patient compliance 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. Optimally and when possible, the regimen should be changed entirely to drugs that have not been taken previously. With triple combinations of drugs, at least two and preferably three new drugs must be used; this is based on the current understanding of strategies to prevent drug resistance (see Principles 4 and 5). Assays to determine genotypic resistance are commercially available; however, these have not undergone field testing to demonstrate clinical utility and are not FDA-approved. The Panel does not recommend these assays for routine use at the present time.

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 including a protease inhibitor and whose viremia was initially suppressed to undetectable levels but has again become detectable; and 3) individuals who have been on potent combination therapy including a protease inhibitor and whose viremia was never suppressed to below detectable limits. While these groups of individuals should have treatment regimens changed in order to maximize the chances of durable, maximal viral RNA suppression, the first group may have more treatment options as they are protease inhibitor naive.

## 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 <500 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., 500–5000 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 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 preferred category (Table VI). Prior experience indicates that most of these patients on double nucleoside therapy will eventually have virologic failure with a frequency that is subtantially greater compared to patients treated with the preferred regimens.

- *Persistently declining $CD4^+$ T cell numbers, as measured on at least two separate occasions (see Principle 2 for significant decline) (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 (see Principle 7). This may influence the physician to be somewhat more conservative when deciding to change therapy. Consideration of alternative options should include potency of the substituted regimen and probability of tolerance of or adherence to the alternative regimen. Clinical trials have shown that partial suppression of virus is superior to no suppression of virus. On the other hand, some physicians and patients may prefer to suspend treatment in order to preserve future options or because a sustained antiviral effect cannot be achieved. Referral to or consultation with an experienced HIV clinician is appropriate when one is considering a change in therapy. When possible, patients requiring a change in an antiretroviral regimen but without treatment options using currently approved drugs should be referred for consideration for inclusion in an appropriate clinical trial.

## Therapeutic Options When Changing Antiretroviral Therapy

Recommendations for changes in treatment differ according to the indication for the change. If the desired virologic objectives have been achieved in patients who have intolerance or toxicity, there should be substitution for the offending drug, preferably using an agent in the same class with a different toxicity or tolerance profile. If virologic objectives have been achieved, but the patient is receiving a regimen not in the preferred category (such as two NRTIs or monotherapy), there is the option to continue treatment with careful monitoring of viral load or to add drugs to the current regimen to comply with preferred treatment regimens. As discussed above, most authorities feel that treatment with regimens not in the preferred 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 preferred regimens that include PIs; 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 recent evidence of broad cross-resistance among the class of PIs. Evidence indicates that viral strains that become resistant to one PI will have reduced susceptibility to most or all other PIs. Thus, the likelihood of success of a subsequently administered PI + 2 NRTI regimen, even if all drugs are different from the initial regimen, may be limited, and many experts would include 2 new PIs in the subsequent regimen.

Table XIV summarizes some of the most important guidelines to follow when changing a patient's antiretroviral therapy. Table XV outlines some of the treatment options

available when a decision has been made to change the antiretroviral regimen. As noted in the footnote to the Table, there are extremely limited data to suggest that any of these alternative regimens will be effective, and careful monitoring and consultation with an expert in the care of such HIV-infected patients is desirable**.** As stated above, a change in regimen because of treatment failure should ideally involve complete replacement of the regimen with different drugs to which the patient is naive. This typically would include the use of 2 new NRTIs and one new PI or NNRTI, two PIs with one or two new NRTIs, or a PI combined with an NNRTI. Dose modifications may be required to account for drug interactions when using combinations of PIs or a PI and NNRTI (Table XII). In some individuals, these options are not possible 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 XVI) and can thus be identified as candidates for early therapy (16–19). However, acute HIV infection is often not recognized in the primary care setting because of the similarity of the symptom complex with those of the "flu" or other common illnesses. Additionally, acute primary infection may occur without symptoms. Physicians should maintain a high level of suspicion for HIV infection in all patients presenting with a compatible clinical syndrome (Table XVI) and should obtain appropriate laboratory confirmation (see below). Information regarding treatment of acute HIV infection from clinical trials is very limited. There is evidence for a short term effect of therapy on viral load and $CD4^+$ T cell counts (20), but there are as yet no outcome data demonstrating a clinical benefit of antiretroviral treatment during primary HIV infection. Clinical trials completed to date have also been limited by small sample sizes, short duration of follow up and often by the use of treatment regimens that have suboptimal antiviral activity by current standards. Nevertheless, these studies generally support antiretroviral treatment of acute HIV infection. Ongoing clinical trials are addressing the question of the long term clinical benefit of more potent treatment regimens.

The theoretical rationale for early intervention, as provided in Principle 10, is fourfold:

- 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;
- and to possibly reduce the rate of viral mutation due to the suppression of viral replication.

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 XVI**,** a test for HIV RNA should be performed (BII). (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 whom 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. 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 (21), 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). The weight of current experience suggests that the therapeutic regimen for acute HIV infection should include a combination of two nucleoside reverse transcriptase inhibitors and one potent protease inhibitor (AII). Although most experience to date with protease inhibitors in the setting of acute HIV infection has been with ritonavir, indinavir or nelfinavir (2, 22–24), 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 VI. 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 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). However, some experts would treat for one year and then re-evaluate the patient with $CD4^+$ T cell determinations and quantitative HIV RNA measurements. 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.

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## *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 (see Principle 8). 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 antiretoviral drug during pregnancy should be made by the woman following discussion with her health care provider regarding the known and unknown benefits and risks to her and her fetus. Long-term follow-up is recommended for all infants born to women who have received antiretroviral drugs during pregnancy.

Women who are in the first trimester of pregnancy and who are not receiving antiretroviral therapy may wish to consider delaying initiation of therapy until after 10 to 12 weeks gestation, since this is the period of organogenesis when the embryo is most susceptible to potential teratogenic effects of drugs; the risks of antiretroviral therapy to the fetus during that period are unknown. However, this decision should be carefully considered and discussed between the health care provider and the patient and should include an assessment of the woman's health status and the potential benefits and risks of delaying initiation of therapy for several weeks. If clinical, virologic or immunologic parameters are 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 (25). 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 Principle 8). 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 will 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 XVII. It is important to recognize that the predictive value of *in vitro* and animal screening tests for adverse effects in humans is unknown. Many drugs commonly used to treat HIV infection or its consequences may have positive findings on one or more of these screening tests. For example, acyclovir is positive on some *in vitro* assays for chromosomal breakage and carcinogenicity and is associated with some fetal abnormalities in rats; however, data on human experience from the Acyclovir in Pregnancy Registry indicate no increased risk of birth defects to date in infants with *in utero* exposure to acyclovir (26).

Of the currently approved nucleoside analogue antiretroviral agents, the pharmacokinetics of only ZDV and 3TC have been evaluated in infected pregnant women to date (27,28). Both appear to be well tolerated at the usual adult doses and cross the placenta, achieving concentrations in cord blood similar to those observed in maternal blood at delivery. All the nucleosides except ddI have preclinical animal studies that indicate potential fetal risk and have been classified as FDA pregnancy category C (defined in Table XVII); ddI has been classified as category B. In primate studies, all the nucleoside analogues appear to cross the placenta, but ddI and ddC appear to have significantly less placental transfer (fetal to maternal drug ratios of 0.3 to 0.5) than do ZDV, d4T and 3TC (fetal to maternal drug ratios >0.7)(29).

Of the non-nucleoside reverse transcriptase inhibitors, only nevirapine administered once at the onset of labor has been evaluated in pregnant women. The drug was well-tolerated after a single dose, and crossed the placenta and achieved neonatal blood concentrations equivalent to those in the mother. The elimination of nevirapine administered during labor in the pregnant women in this study was prolonged (mean half-life following a single dose, 66 hours) compared to non-pregnant individuals (mean half-life following a single dose, 45 hours)**.** Data on multiple dosing during pregnancy are not yet available. Delavirdine has not been studied in Phase I pharmacokinetic and safety trials in pregnant women. In premarketing clinical studies, outcomes of 7 unplanned pregnancies were reported. Three of these were ectopic pregnancies, and three resulted in healthy live births. One infant was born prematurely with a small ventricular septal defect to a patient who received approximately 6 weeks of treatment with delavirdine and ZDV early in the course of pregnancy.

Although studies of combination therapy with protease inhibitors in pregnant infected women are in progress, there are currently no data available regarding drug dosage, safety and tolerance in pregnancy. In mice, indinavir has significant placental passage, but in rabbits, little placental passage was observed. Ritonavir has been shown to have

some placental passage in rats**.** There are some special theoretical concerns regarding the use of indinavir late in pregnancy. Indinavir is associated with side effects (hyperbilirubinemia and renal stones) that theoretically could be problematic for the newborn if transplacental passage occurs and the drug is administered shortly before delivery. This is because the immaturity of the metabolic enzyme system of the neonatal liver would likely be associated with prolonged drug half-life leading to extended drug exposure in the newborn which could lead to potential exacerbation of physiologic neonatal hyperbilirubinemia. Additionally, due to immature neonatal renal function and the inability of the neonate to voluntarily ensure adequate hydration, high drug concentrations and/or delayed elimination in the neonate could result in a higher risk for drug crystallization and renal stone development than observed in adults. These concerns are theoretical and such effects have not been reported; because the half-life of indinavir in adults is short, these concerns may only be relevant if drug is administered near the time of labor. Gestational diabetes is a pregnancy-related complication that can develop in some women; administration of any of the four currently available protease inhibitors has been associated with new onset diabetes mellitus, hyperglycemia or exacerbation of existing diabetes mellitus in HIV-infected patients (30)**.** Pregnancy is itself a risk factor for hyperglycemia and it is unknown if the use of protease inhibitors will exacerbate this risk**.** Health care providers caring for infected pregnant women who are receiving protease inhibitor therapy should be aware of this possibility, and closely monitor glucose levels in their patients as well as instruct their patients in recognizing the early symptoms of hyperglycemia**.**

To date, the only drug that has been shown to reduce the risk of perinatal HIV transmission is ZDV 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 (31). This chemoprophylactic regimen was shown to reduce the risk of perinatal transmission by 66% in a randomized, double-blind clinical trial, pediatric ACTG 076 (32). 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 XVIII). 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 (33,34). Comparable clinical response also has been observed in clinical trials among persons receiving ZDV twice daily (35–37). 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 recent 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 (38). 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.**

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 Pediatric (P)-ACTG 076 (**39**). 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**.** Transmission of HIV from mother to infant can take place at all levels of maternal HIV-1 RNA. In untreated women, higher HIV-1 RNA levels correlate with increased transmission risk. However, in ZDV-treated women this relationship is markedly attenuated (32). ZDV is effective in reducing transmission regardless of maternal HIV RNA level. Therefore, the use of the full ZDV chemoprophyaxis 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 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, Post Office Box 13398, Research Triangle Park, NC 27709–3398; telephone 919–483–9437 or 1–800–258–4263; fax 1–800–800–1052.

## *Conclusion*

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

recommendations for first line therapy; to define second line therapy; and to more clearly delineate the reason(s) for treatment failure. The Panel remains committed to revising their recommendations as such new data become available.

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

**June 17, 1998**

## Table I. Rating Scheme for Clinical Practice Recommendations

**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 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 pts. not on therapy | Changes in viral load | Decision to start therapy |
| 4–8 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 pts. on therapy | Durability of anti-retroviral 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 increases 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.
HIV RNA should be measured using the same laboratory and the same assay.

** 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. 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 reconstitution 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

**Potential Risks**

Reduction in quality of life from adverse drug effects and inconvenience of current maximally suppressive regimens

Earlier development of drug resistance

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

# Table IV. 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 | ≤1500 | -## | - | - | - |
| 501–3000 | 1501–7000 | 30 | 0 | 18.8 | 30.6 |
| 3001–10,000 | 7001–20,000 | 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** | | **% AIDS (AIDS-defining complication)** | | | |
| **Plasma Viral Load (copies/ml)** | | | | | |
| bDNA | RT-PCR | n | 3 years | 6 years | 9 years |
| ≤500 | ≤1500 | - | - | - | - |
| 501–3000 | 1501–7000 | 47 | 4.4 | 22.1 | 46.9 |
| 3001–10,000 | 7001–20,000 | 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** | | **% AIDS (AIDS-defining complication)** | | | |
| **Plasma Viral Load (copies/ml)** | | | | | |
| bDNA | RT-PCR | n | 3 years | 6 years | 9 years |
| ≤500 | ≤1500 | 110 | 1.0 | 5.0 | 10.7 |
| 501–3000 | 1501–7000 | 180 | 2.3 | 14.9 | 33.2 |
| 3001–10,000 | 7001–20,000 | 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 12.

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

# 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.

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

# Table V. 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/$mm^3$<br>or<br>HIV RNA>10,000 (bDNA)<br>or >20,000 (RT-PCR) | Treatment should be offered. Strength of recommendation is based on prognosis for disease-free survival as shown in Table IV and willingness of the patient to accept therapy.* |
| Asymptomatic | $CD4^+$ T Cells >500/$mm^3$<br>and<br>HIV RNA<10,000 (bDNA)<br>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 VI. Recommended Antiretroviral Agents for Treatment of Established HIV Infection

**Preferred:** Strong evidence of clinical benefit and**/**or sustained suppression of plasma viral load (2,**40**,**41**), One choice each from column A and column B. Drugs are listed in random, not priority, order:

| **Column A** | **Column B** |
|---|---|
| Indinavir (AI) | ZDV + ddI (AI) |
| Nelfinavir (AII) | d4T + ddI (AII) |
| Ritonavir (AI) | ZDV + ddC (AI) |
| Saquinavir-SGC* (All) | ZDV + 3TC[#] (AI) |
| Ritonavir + Saquinavir SGC or HGC**(BII) | d4T + 3TC[#] (AII) |

**Alternative:** Less likely to provide sustained virus suppression; **(42**, **43)**
1 NNRTI + 2 NRTIs (Column B, above) *** (BII)

**Not generally recommended:**
Strong evidence of clinical benefit but initial virus suppression is not sustained in most patients (**44–47**).

2 NRTIs (Column B, above) (CI)
**Saquinavir-HGC + 2 NRTIs (Column B, above)[II] (CI)**

**Not recommended:** Evidence against use, virologically undesirable, or overlapping toxicities

All monotherapies[##] (DI)
d4T + ZDV (DI)
ddC + ddI[###] (DII)
ddC + d4T[###] (DII)
ddC + 3TC (DII)

***** Virologic data and clinical experience with **saquinavir-SGC** (Fortovase) are limited in comparison with other protease inhibitors.

** Use of ritonavir**,** 400 mg b.i.d. with saquinavir-**SGC** (Fortovase) 400 mg b.i.d. results in similar **drug exposure** and antiretroviral activity as when using 400 mg b.i.d. of **saquinavir-HGC (**Invirase**)** in combination with ritonavir. However, this combination with Fortovase has not been extensively studied**,** and gastrointestinal toxicity may be greater when using Fortovase.

*** The only combination of **1 N**NRTI + **2** NRTI**s** that has been shown to suppress viremia to undetectable levels in the majority of patients **remaining on treatment for >28 weeks are** ZDV + ddI + nevirapine **and ZDV + 3TC + delavirdine**. **Use of nevirapine or delavirdine may result in resistance that precludes efficacy of new NNRTIs such as efavirenz.**

[#] High level resistance to 3TC develops within 2–4 weeks in partially suppressive regimens; optimal use is in 3-drug antiretroviral combinations that reduce viral load to **undetectable levels.**

[II] **Use of saquinavir-HGC (Invirase) is generally not recommended, except in combination with ritonavir.**

[##] **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."

[###] This combination of NRTIs is not recommended based on lack of clinical data using the combination and/oroverlapping toxicities.

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

| **Generic Name**<br>*Trade Name* | **Zidovudine (AZT, ZDV)**<br>*Retrovir* | **Didanosine (ddI)**<br>*Videx* | **Zalcitabine (ddC)**<br>*HIVID* | **Stavudine (d4T)**<br>*Zerit* | **Lamivudine (3TC)**<br>*Epivir* |
|---|---|---|---|---|---|
| **Dosing Recommendations** | 200 mg tid or<br>300 mg bid or with 3TC as Combivir, 1 bid | Tablets<br>>60kg: 200 mg bid<br><60 kg: 125 mg bid | 0.75 mg tid | >60 kg: 40 mg bid<br>< 60 kg: 30 mg bid | 150 mg bid<br><50kg: 2 mg/kg bid or with ZDV as Combivir 1 bid |
| **Oral bioavailability** | 60% | Tablet: 40%<br>Powder: 30% | 85% | 86% | 86% |
| **Serum half-life** | 1.1 hour | 1.6 hour | 1.2 hour | 1.0 hour | 3–6 hours |
| **Intracellular half-life** | 3 hours | 25–40 hours | 3 hours | 3.5 hours | 12 hours |
| **Elimination** | Metabolized to AZT glucuronide (GAZT)<br>Renal excretion of GAZT | Renal excretion<br>50% | Renal excretion<br>70% | Renal excretion<br>50% | Renal excretion<br>unchanged |
| **Adverse Events** | Bone marrow suppression:<br>Anemia and/or neutropenia<br>Subjective complaints: GI intolerance, headache, insomnia, asthenia | Pancreatitis<br>Peripheral neuropathy<br>nausea<br>diarrhea | Peripheral neuropathy<br>Stomatitis | Peripheral neuropathy | (Minimal toxicity) |

## Table VIII. Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

| **Generic Name**<br>*Trade Name* | **Nevirapine**<br>*Viramune* | **Delavirdine**<br>*Rescriptor* |
|---|---|---|
| **Form** | 200 mg tabs | 100 mg tabs |
| **Dosing Recommendations** | 200 mg po qd x 14 days,<br>then 200 mg po bid | 400 mg po tid<br>(Four 100 mg tabs in ≥ 3 oz water to produce slurry) |
| **Oral bioavailability** | > 90% | 85% |
| **Serum half-life** | 25–30 hrs | 5.8 hrs |
| **Elimination** | Metabolized by cytochrome p450;<br>80% excreted in urine (glucuronidated metabolites, < 5% unchanged), 10% in feces | Metabolized by cytochrome p450<br>51% excreted in urine (< 5% unchanged), 44% in feces |
| **Drug interactions** | Induces cytochrome p450 enzymes<br>• The following drugs have suspected interactions that require careful monitoring if co-administered with nevirapine: rifampin, rifabutin, oral contraceptives, protease inhibitors, triazolam and midazolam | Inhibits cytochrome p450 enzymes<br>• Not recommended for concurrent use: terfenadine, astemizole, alprazolam, midazolam, cisapride, rifabutin, rifampin, triazolam, ergot derivatives, amphetamines, nifedipine, anticonvulsants (phenytoin, carbamazepine, phenobarbitol)<br>• Delavirdine increases levels of clarithromycin, dapsone, quinidine, warfarin, indinavir, saquinavir<br>• Antacids **or** didanosine: separate **delavirdine** administration by ≥ 1 hr |
| **Adverse Events** | Rash<br>Increased transaminase levels<br>Hepatitis | Rash<br>Headaches |

# Table IX. Characteristics of Protease Inhibitors (PIs)

| **Generic Name**<br>*Trade name* | **Indinavir**<br>*Crixivan* | **Ritonavir**<br>*Norvir* | **Saquinavir**<br>*Invirase* | <br>*Fortovase* | **Nelfinavir**<br>*Viracept* |
|---|---|---|---|---|---|
| **Form** | 200,400 mg caps | 100 mg caps<br>600mg/7.5ml po solution | 200 mg caps | 200-mg caps | 250 mg tablets<br>50mg/g oral powder |
| **Dosing Recommendations** | 800 mg q8h<br>Take 1 hr before or 2 hrs after meals; may take with skim milk or low fat meal | 600 mg q12h*<br>Take with food if possible | 600 mg TID*<br>Take with large meal | 1,200 mg TID<br>Take with large meal | 750 mg TID<br>Take with food (meal or light snack) |
| **Oral Bioavailability** | 65% | (not determined) | hard gel capsule:<br>4%, erratic | soft-gel capsule<br>(not determined**)** | 20–80% |
| **Serum half-life** | 1.5–2 hours | 3–5 hours | 1–2 hours | 1–2 hours | 3.5–5 hours |
| **Route of Metabolism** | P450 cytochrome 3A4 | P450 cytochrome 3A4> 2D6 | P450 cytochrome 3A4 | P450 cytochrome 3A4 | P450 cytochrome 3A4 |
| **Storage** | Room temperature | Refrigerate capsules; refrigeration for oral solution is preferred but not required if used within 30 days | Room temperature | Refrigerate or store at room temperature (up to 3 mos.) | Room temperature |

| **Generic Name**<br>*Trade name* | **Indinavir**<br>*Crixivan* | **Ritonavir**<br>*Norvir* | **Saquinavir**<br>*Invirase* | <br>*Fortovase* | **Nelfinavir**<br>*Viracept* |
|---|---|---|---|---|---|
| **Adverse Effects** | • Nephrolithiasis<br>• GI intolerance, nausea<br>• Lab: Increased indirect bilirubinemia (inconsequential)<br>• Misc: Headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia<br>• Hyperglycemia+ | • GI intolerance, nausea, vomiting, diarrhea<br>• Paresthesias — circumoral and extremities<br>• Hepatitis<br>• Asthenia<br>• Taste perversion<br>• Lab: Triglycerides increase>200%, transaminase elevation, elevated CPK and uric acid<br>• Hyperglycemia+ | • GI intolerance, nausea and diarrhea<br>• Headache<br>• Elevated transaminase enzymes<br>• Hyperglycemia+ | • GI intolerance, nausea, diarrhea, abdominal pain and dyspepsia<br>• Headache<br>• Elevated transaminase enzymes<br>• Hyperglycemia+ | • Diarrhea<br>• Hyperglycemia+ |

| **Generic Name**<br>*Trade name* | **Indinavir**<br>*Crixivan* | **Ritonavir**<br>*Norvir* | **Saquinavir**<br>*Invirase* | **Saquinavir**<br>*Fortovase* | **Nelfinavir**<br>*Viracept* |
|---|---|---|---|---|---|
| **Drug Interactions** | • Inhibits cytochrome P450 (less than ritonavir)<br>• Not recommended for concurrent use: rifampin, terfenadine, astemizole, cisapride, triazolam, midazolam, ergot alkaloids<br>• Indinavir levels increased by: ketoconazole***, delavirdine, nelfinivir<br>• Indinavir levels reduced by: rifampin, rifabutin, grapefruit juice, nevirapine<br>• Didanosine: reduces indinavir absorption unless taken > 2 hrs apart | • Inhibits cytochrome P450 (potent inhibitor)<br>• Ritonavir increases levels of multiple drugs that are not recommended for concurrent use**<br>• Didanosine: may cause reduced absorption of both drugs; should be taken $\geq$ 2 hours apart<br>• Ritonavir decreases levels of ethinyl estradiol, theophylline, sulfamethoxazole and zidovudine<br>• Ritonavir increases levels of clarithromycin and desipramine | • Inhibits cytochrome P450<br>• Saquinavir levels increased by: ritonavir, ketoconazole, grapefruit juice, nelfinavir, delavirdine<br>• Saquinavir levels reduced by: rifampin, rifabutin and possibly the following: phenobarbital, phenytoin, dexamethasone and carbamezepine, nevirapine<br>• Not recommended for concurrent use: rifampin, rifabutin, terfenadine, astemizole, cisapride, ergot alkaloids**, triazolam, midazolam** | • Inhibits cytochrome P450<br>• Saquinavir levels increased by: ritonavir, ketoconazole, grapefruit juice, nelfinavir, delavirdine<br>• Saquinavir levels reduced by: rifampin, rifabutin and possibly the following: phenobarbital, phenytoin, dexamethasone and carbamezepine, nevirapine<br>• Not recommended for concurrent use: rifampin, rifabutin, terfenadine, astemizole, cisapride, ergot alkaloids**, triazolam, midazolam** | • Inhibits cytochrome P450 (less than ritonavir)<br>• Nelfinavir levels reduced by rifampin, rifabutin.<br>• Contraindicated for concurrent use: triazolam, midazolam, ergot alkaloids terfenadine, astemizole, cisapride<br>• Nelfinavir decreases level of ethinyl estradiol and norethindrone<br>• Nelfinavir increases levels of rifabutin, saquinavir, and indinavir<br>• Not recommended for concurrent use: rifampin |

* 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 (400–600 mg po bid) plus Ritonavir (400–600 mg po bid)

** Drugs contraindicated for concurrent use with Ritonavir: amiodarone (Cordarone), astemizole (Hismanal), bepridil (Vascar), bupropion (Wellbutin), cisapride (Propulsid), clorazepate (Tranxene), clozapine (Clozaril), diazepam (Valium), encainide (Enkaid), estazolam (ProSom), flecainide (Tambocor), flurazepam (Dalmane), meperidine (Demerol), midazolam (Versed), piroxicam (Feldene), propoxyphene (Darvon), propafenone (Rythmol), quinidine, rifabutin, terfenadine (Seldane), triazolam (Halcion), zolpidem (Ambien), ergot alkaloids.

***Decrease indinavir to 600 mg q8h.

+ Cases of new onset hyperglycemia have been reported in association with the use of all protease inhibitors (ref **48–50**).

# Table X. Drugs That Should Not Be Used With Protease Inhibitors

| **Drug Category** | **Indinavir** | **Ritonavir*** | **Saquinavir** ***(given as Invirase or Fortovase)*** | **Nelfinavir** | **Alternatives** |
|---|---|---|---|---|---|
| Analgesics | (none) | meperidine<br>piroxicam<br>propoxyphene | (none) | (none) | ASA<br>oxycodon<br>acetaminophen |
| Cardiac | (none) | amioderone<br>encainide<br>flecainide<br>propafenone<br>quinidine | (none) | (none) | limited experience |
| Anti-Mycobacterial | rifampin | rifabutin** | rifampin<br>rifabutin | rifampin | For rifabutin ( as alternative for MAI treatment): clarithromycin, ethambutol (treatment, not prophylaxis), or azithromycin |
| Ca++ channel blocker | (none) | bepridil | (none) | (none) | limited experience |
| Antihistimine | astemizole<br>terfenadine | astemizole<br>terfenadine | astemizole<br>terfenadine | astemizole<br>terfenadine | loratadine |
| GI | cisapride | cisapride | cisapride | cisapride | limited experience |
| Antidepressant | (none) | bupropion | (none) | (none) | fluoxetine<br>desipramine |
| Neuroleptic | (none) | clozapine<br>pimozide | (none) | (none) | limited experience |
| Psychotropic | midazolam<br>triazolam | clorazepate<br>diazepam<br>estazolam<br>flurazepam<br>midazolam<br>triazolam<br>zolpidem | midazolam<br>triazolam | midazolam<br>triazolam | temazepam<br>lorazepam |
| Ergot Alkaloids (vasoconstrictor) | **dihydroer-gotamine (D.H.E. 45)<br>ergotamine*** (various firm)** | dihydroergotamine (D.H.E. 45)<br>ergotamine*** (various forms) | **dihydroer-gotamine (D.H.E. 45)<br>ergotamine*** (various firm**) | dihydroer-gotamine (D.H.E. 45),<br>ergotamine*** (various forms) | **limited experience** |

***** 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.

** Reduce rifabutin dose to one quarter of the standard dose.

*** This is likely a class effect.

# Table XI. Drug Interactions Between Protease Inhibitors And Other Drugs

## Drug Interactions Requiring Dose Modifications

| | Indinavir | Ritonavir | Saquinavir* | Nelfinavir |
|---|---|---|---|---|
| **Fluconazole** | No dose change | No dose change | No data | No dose change |
| **Ketoconazole and Itraconazole** | Decrease dose to 600 mg q8h | Increases ketoconazole >3 fold; dose adjustment required | Increases saquinavir levels 3-fold; no dose change** | No dose change |
| **Rifabutin** | Reduce rifabutin to half dose: 150 mg qd | Consider alternative drug or reduce **rifabutin** dose to one quarter | Not Recommended with either Invirase or Fortovase | Reduce rifabutin to half dose: 150 mg qd |
| **Rifampin** | Contraindicated | Unknown*** | Not recommended either Invirase or Fortovase | Contraindicated |
| **Oral Contraceptives** | Modest increase in Ortho-Novum levels; no dose change | Ethinyl estradiol levels decreased; use alternative or additional contraceptive method | No data | Ethinyl estradiol and norethindrone levels decreased; use alternative or additional contraceptive method |
| **Miscellaneous** | Grapefruit juice reduces indinavir levels by 26% | -Desipramine increased 145%: reduce dose<br>- Theophylline levels decreased: dose increase | Grapefruit juice increases saquinavir levels** | |

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.

Rifampin reduces ritonavir 35%. Increased ritonavir dose or use of ritonavir in combination therapy is strongly recommended. The effect of ritonavir on rifampin is unknown. Used concurrently, there may be increased liver toxicity. Therefore, patients on ritonavir and rifampin should be monitored closely.

# Table XII. Drug Interactions: Protease Inhibitors and Non-Nucleoside Reverse Transcriptase Inhibitors

## Effect of Drug on Levels/Dose

| Drug Affected | Indinavir | Ritonavir | Saquinavir* | Nelfinavir | Nevirapine | Delavirdine |
|---|---|---|---|---|---|---|
| **Indinavir (IDV)** | • | No data | Levels: IDV no effect; SQV ↑4–7x[#]<br>Dose: No data | Levels: IDV ↑50%; NFV ↑80%<br>Dose: No data | Levels: IDV ↓28%<br>Dose: Standard | Levels: IDV ↑40%<br>Dose: IDV 600 mg q 8h |
| **Ritonavir (RTV)** | No data | • | Levels: RTV no effect; SQV ↑20x[+#]<br>Dose: Invirase or Fortovase 400 mg bid + RTV: 400 mg bid | Levels: RTV no effect; NFV ↑1.5x<br>Dose: No data | Levels: RTV ↓11%<br>Dose: Standard | Levels: RTV ↑70%<br>Dose: No data |
| **Saquinavir (SQV)** | Levels: SQV ↑4–7x; IDV no effect[#]<br>Dose: No data | Levels: SQV ↑20x[+#] RTV no effect<br>Dose: Invirase or Fortovase 400 mg bid+RTV 400 mg bid | • | Levels: SQV ↑3–5x; NFV ↑20%[#]<br>Dose: Standard NFV Fortovase 800mg tid | Levels: SQV ↓25%[+]<br>Dose: No data | Levels: SQV ↑5x[+]<br>Dose: Standard for Invirase<br>Monitor transaminase levels |
| **Nelfinavir (NFV)** | Levels: NFV ↑80% IDV ↑50%<br>Dose: No data | Levels: NFV ↑1.5x RTV no effect<br>Dose: No data | Levels: NFV ↑20%; SQV ↑3–5x[#]<br>Dose: Standard NFV Fortovase 800mg tid | • | Levels: NFV ↑10%<br>Dose: Standard | Levels: NFV ↑2x DLV ↓50%<br>Dose: Standard (monitor for neutropenic complications) |
| **Nevirapine (NVP)** | Levels: IDV ↓28%<br>Dose: Standard | Levels: RTV ↓11%<br>Dose: Standard | Levels: SQV ↓25%[+]<br>Dose: No data | Levels: NFV ↑10%<br>Dose: Standard | • | Do not use together |
| **Delavirdine (DLV)** | Levels: IDV ↑40%<br>Dose: IDV 600 q 8h | Levels: RTV ↑70%<br>Dose: No data | Levels: SQV ↑5x[+]<br>Dose: Standard for Invirase. Monitor transaminase levels | Levels: NFV ↑2x DLV ↓50%<br>Dose: Standard (monitor for neutropenic complications) | Do not use together | • |

* 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 XIII: Drugs Available Through Treatment Investigational New Drugs Protocols

| Drug | Adefovir (Preveon) | Efavirenz (DMP-266; Sustiva) | Abacavir (1592-U89) |
|---|---|---|---|
| **Source** | Gilead<br>800–GILEADS | DuPont-MERCK<br>800–998–6854 | Glaxo-Wellcome<br>800–501–4672 |
| **Class** | Nucleotide RT Inhibitor | Non-nucleoside RT Inhibitor | Nucleoside RT Inhibitor |
| **Usual Dose** | 120 mg po qd | 600 mg po QD | 300 mg po bid |
| **Side Effects (major)** | Renal failure (dose-related and infrequent) | Dizziness and "disconnected," usually resolves after 2 weeks | Hypersensitivity: 2–5% usually in first 4 weeks (fever, nausea, vomiting, morbilliform rash)<br>Do not re-challenge |
| **Comments** | Activity vs. HBV, CMV, HSV | Induces and inhibits cytochrome P450 enzymes | Good CNS penetration |
| **Enrollment Criteria** | CD4<50;<br>viral load >30,000;<br>failure with 2 NRTIs + PI | CD4  400 at any point in the patient's history, viral load (any), failure or intolerant of current therapy | CD4<100; viral load  30,000 |

# Table XIV. Guidelines for Changing an Antiretroviral Regimen for Suspected Drug Failure

- Criteria for changing therapy include a suboptimal reduction in plasma viremia after initiation of therapy, re-appearance of viremia after suppression to undetectable, significant increases in plasma viremia from the nadir of suppression, and declining $CD4^+$ T cell numbers. Please refer to the more extensive discussion of these on page 11.

- 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 or dose reduced 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.

- 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 a 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 nevirapine or delavirdine; 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. The experience with zidovudine is that resistant strains are often replaced with "wild-type" zidovudine sensitive strains when zidovudine treatment is stopped, but resistance recurs rapidly if zidovudine is restarted. While there is preliminary evidence that this occurs with indinavir, it is not known if similar problems apply to other nucleoside analogues, protease inhibitors, or NNRTIs, but a conservative stance is that they probably do.

- Avoid changing from ritonavir to indinavir or vice versa for drug failure, since high level cross resistance is likely.

- Avoid changing from nevirapine to delavirdine or vice versa 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. Possible Regimens For Patients Who Have Failed Antiretroviral Therapy: A Work in Progress*#

| Prior Regimen | New Regimen (Not listed in priority order) |
|---|---|
| 2 NRTIs + | 2 new NRTIs + |
| Nelfinavir | RTV; or IDV; or SQV + RTV; or NNRTI## + RTV; or NNRTI + IDV** |
| Ritonavir | SQV + RTV** ; NFV + NNRTI; or NFV + SQV |
| Indinavir | SQV + RTV; NFV + NNRTI; or NFV + SQV |
| Saquinavir | RTV + SQV; or NNRTI + IDV |
| 2 NRTIs + NNRTI | 2 new NRTIs + a protease inhibitor |
| 2 NRTIs | 2 new NRTIs + a protease inhibitor<br>2 new NRTIs + RTV + SQV<br>1 new NRTI + 1 NNRTI + a protease inhibitor<br>2 protease inhibitors + NNRTI |
| 1 NRTI | 2 new NRTIs + a protease inhibitor<br>2 new NRTIs + NNRTI<br>1 new NRTI + 1 NNRTI + a protease inhibitor |

* These alternative regimens have not been proven to be clinically effective and were arrived at through discussion by the Panel of theoretically possible alternative treatments and the elimination of those alternatives with evidence of being ineffective. Clinical trials in this area are urgently needed.

\# RTV = ritonavir, IDV = indinavir, SQV = saquinavir, NVP = nevirapine, NFV = nelfinavir**,** DLV = delavirdine

** There are some clinical trials with viral burden data to support this recommendation

## ~~Of the two available NNRTIs, clinical trials support a preference for nevirapine over delavirdine based on results of viral load assays. These two agents have opposite effects on the CYP450 pathway.~~ **Nevirapine induces and delavirdine inhibits CYP450 enzymes,** and this must be considered in combining these drugs with other agents.

## Table XVI. Acute Retroviral Syndrome: Associated Signs and Symptoms (Expected Frequency)(19)

- 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 XVII. Preclinical and Clincal 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) |
| **Lamivudine** | C | Yes (human) [~1.0] | Negative (no tumors, lifetime rodent study) | Negative |
| **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 |
| **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 detect |

* 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 (**51**). However, no data is available on longer follow-up for late effects.

† These effects seen at only at maternally toxic doses.

# TABLE XVIII. 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.**

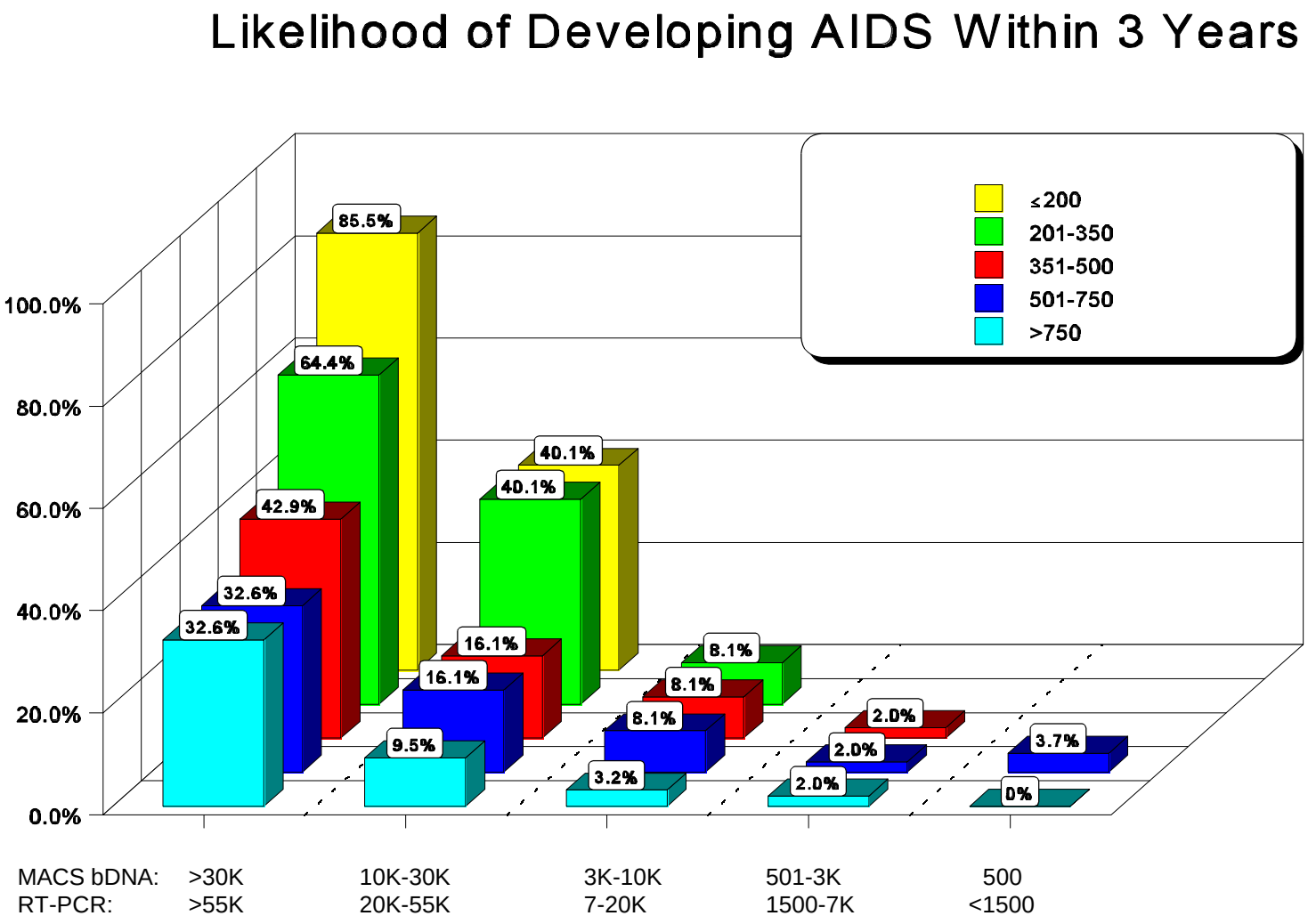


FIGURE LEGEND:

Figure 1. Likelihood of developing an AIDS-related illness in three years. Viral load values represent 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 IV 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 12.)

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