CONSENSUS STATEMENT

Antiretroviral Therapy in Adults
Updated Recommendations of the International AIDS Society–USA Panel

Charles C. J. Carpenter, MD
David A. Cooper, MD, DSc
Margaret A. Fischl, MD
Jose M. Gatell, MD, PhD
Brian G. Gazzard, MA, MD
Scott M. Hammer, MD
Martin S. Hirsch, MD
Donna M. Jacobsen, BS
David A. Katzenstein, MD
Julio S. G. Montaner, MD
Douglas D. Richman, MD
Michael S. Saag, MD
Mauro Schechter, MD, PhD
Robert T. Schooley, MD
Melanie A. Thompson, MD
Stefano Vella, MD
Patrick G. Yeni, MD
Paul A. Volberding, MD

Objective To update recommendations for antiretroviral therapy for adult human immunodeficiency virus type 1 (HIV-1) infection, based on new information and drugs that are available.

Participants A 17-member international physician panel with antiretroviral research and HIV patient care experience initially convened by the International AIDS Society–USA in December 1995.

Evidence Available clinical and basic science data including phase 3 controlled trials; data on clinical, virologic, and immunologic end points; research conference reports; HIV pathogenesis data; and panel expert opinion. Recommendations were limited to therapies available (US Food and Drug Administration approved) in 1999.

Consensus Process The panel assesses new research reports and interim results and regularly meets to consider how the new data affect therapy recommendations. Recommendations are updated via full-panel consensus. Guidelines are presented as recommendations if the supporting evidence warrants routine use in the particular situation and as considerations if data are preliminary or incomplete but suggestive.

Conclusions The availability of new antiretroviral drugs has expanded treatment choices. The importance of adherence, emerging long-term complications of therapy, recognition and management of antiretroviral failure, and new monitoring tools are addressed. Optimal care requires individualized management and ongoing attention to relevant scientific and clinical information in the field.

The International AIDS Society–USA Panel on antiretroviral therapy use in adult human immunodeficiency virus type 1 (HIV-1) infection consists of physicians experienced in antiretroviral drug–related research and care of patients with HIV infection. The panel has broadened its international representation. Recommendations herein represent the panel's consensus opinion as of December 1999, based on clinical and basic science data, where available, and expert opinions.

Scientific Rationale for Updated Recommendations

The panel was initially convened in 1995 when several advances in knowledge regarding HIV biology, monitoring, and treatment were emerging. The benefits of potent antiretroviral combinations were subsequently demonstrated and a theoretical basis for HIV eradication proposed, leading to recommendations for early and aggressive treatment.

The concept of eradication was based on assumptions that complete suppression of viral replication was achievable and the half-life of chronically infected cells was on average 10 to 14 days, suggesting the possibility of eradication within 2 to 3 years. Newer data indicated that low-level, ongoing replication may occur with plasma HIV RNA levels below detection (<50 copies/mL), and the apparent decay half-life of resting memory CD4+ lymphocytes with latent HIV provirus is calculated to be at least 6 months and as long as 44 months. Thus, HIV eradication with antiretroviral therapy alone would take a decade or more and is not presently a realistic goal.

Whether the immune system could be restored with control of viral replication was also in question. Destruction of lymphoid tissue combined with loss of HIV-specific CD4+ cell clones suggested that treatment would not restore significant immune function once immune competence was lost. Newer data show that clinically significant immune reconstitution (eg, return of pathogen- and HIV-specific lymphocytes) ...
proliferative responses and gradual increase in naive CD4+ cells) may be achieved with potent therapy.19,20

There is a growing appreciation of difficulties with use of potent regimens. Even in clinical trials therapies do not achieve levels of HIV RNA below 50 copies/mL in a substantial number of patients. This issue, in addition to those concerning treatment complexity, monitoring, adherence, and long-term complications, together with Food and Drug Administration approval of 3 antiretroviral drugs (efavirenz, abacavir, and amprenavir) in the past year, warrant refinements in antiretroviral management recommendations. The foundation of HIV therapeutics is now long-term management of a chronic infection. The challenge to clinicians is to chart a strategic therapeutic course for individual patients such that drugs are used to maximize effectiveness over time. The principles for initiating, monitoring, and changing antiretroviral therapy are addressed herein.

When to Initiate Antiretroviral Therapy

Rationale for Treatment in Established HIV Infection. Potent therapy can at least partially restore pathogen-specific immunity to recall antigens.21 Memory CD4+ cells increase early following treatment due to their redistribution from lymphoid tissue to the circulation.22 In comparison with primary HIV infection, restoration of HIV-specific immune responses in patients with established HIV infection has generally not been seen, even with potent therapy.19,23 Naive CD4+ cells, crucial for response to new antigenic challenges, can be restored gradually with prolonged virus suppression.21 Attaining CD4+ cell counts in the normal range occurs more quickly in patients having higher CD4+ cell counts at treatment initiation.21

Offsetting perceived benefits of early treatment of established HIV infection is growing concern about the long-term adverse effects of therapy. Apart from adherence problems, impact on quality of life, drug-drug interactions, and viral resistance, the potential for metabolic abnormalities raises important long-term concerns, including possible premature cardiovascular disease.24-26 These concerns suggest caution but should not obscure the dramatic changes in HIV-related morbidity and mortality resulting from therapy in advanced disease.27,28

Physicians and patients must weigh the risks and benefits of starting antiretroviral therapy and make individualized informed decisions. When to initiate therapy and what regimen to choose are crucial decisions; otherwise, future options may be severely compromised. Ultimate long-term success may also be a function of the aggregate effectiveness of sequential therapies.30

Clinical, Virologic, and Immunologic Parameters. Plasma HIV RNA levels and CD4+ cell counts are, in general, independent predictors of clinical outcome.31,32 Plasma HIV RNA level is the stronger predictor of progression rate, except in patients having low CD4+ cell counts. Since the disease process is a continuum, HIV RNA and CD4+ cell threshold levels for therapeutic decision making are somewhat arbitrary, but are useful guides.

Therapy is generally recommended for patients with a confirmed plasma HIV RNA level above 30 000 copies/mL, irrespective of CD4+ cell count, and for patients with CD4+ cell counts below 350 × 10^6/L (350/μL), irrespective of HIV RNA level (TABLE 1).31 Treatment is also recommended for patients with both plasma HIV RNA levels in the 5000 to 30 000 copies/mL range and CD4+ cell counts between 350 and 500 × 10^6/L. Therapy should be considered at CD4+ cell counts above 500 × 10^6/L with confirmed HIV RNA levels in the 5000 to 30 000 copies/mL range, based on risks of progression at higher viral load levels.31 Treatment effects on survival at higher CD4+ cell counts is not documented, and it is unlikely that such studies will be conducted.

Persons having CD4+ cell counts above 500 × 10^6/L and HIV RNA levels below 5000 copies/mL are at low risk of near-term (3-year) clinical progression. Thus, concerns regarding treatment complexities and adherence, quality of life, adverse effects, possible emergence of resistance, and limitation of future options must be balanced against potential durable viral suppression and the consequent immunologic and clinical benefits. It is reasonable to defer treatment initiation but continue monitoring these patients.33 Viral load in women appears to be lower than in men early in infection but as immune deficiency advances, sex differences generally disappear.34,36 Thus, treatment recommendations are not different for women.

Therapy is recommended for all patients with symptomatic established HIV infection.37 Acute treatment of a serious opportunistic infection may take precedence over antiretroviral therapy initiation. In situations of adverse drug-drug interactions (e.g., rifampin and protease inhibitors), it may be wise to defer antiretroviral treatment temporarily until the opportunistic infection is controlled.

Antiretroviral therapy should be discussed with all HIV-infected persons. The strength of a recommendation for initiating therapy depends on patients' clinical, virologic, and immunologic status, and their commitment to therapy and willingness to adhere to a complex regimen.

Rationale for Treatment in Primary HIV Infection. Primary HIV infection is defined as the period from the ini-
tial infection to complete seroconversion and is often symptomatic (acute HIV syndrome). The rationale for early treatment of primary infection is to diminish numbers of infected cells, maintain or re-
store HIV-specific immune responses, and possibly lower the viral "set point" to im-
prove the subsequent course of disease. 

Early intervention in primary infection can lead to restoration of HIV-specific im-

Table 2. Pharmacokinetic (PK) Interactions and Dose Recommendations

<table>
<thead>
<tr>
<th>Affected Drug</th>
<th>Indinavir</th>
<th>Ritonavir</th>
<th>Saquinavir SGC</th>
<th>Nelfinavir</th>
<th>Amprenavir</th>
<th>Nevirapine</th>
<th>Delavirdine</th>
<th>Efavirenz</th>
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<td>Dose not established</td>
<td>Dose not established</td>
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<td>Ritonavir</td>
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<td>TAUC 15%[20]</td>
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</tr>
<tr>
<td>Amprenavir</td>
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<td>No data</td>
<td>TAUC 20%</td>
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<td>No effect[20]</td>
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<td>TAUC 20%</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
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</tr>
<tr>
<td>Efavirenz</td>
<td>...</td>
<td>No effect[20]</td>
<td>TAUC 20%</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
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<td>Dose change</td>
<td>Dose change</td>
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</table>

*Table displays pharmacokinetic effect of the drugs listed in the vertical column (interacting drug) on the drugs listed horizontally (affected drug) and possible dose changes as follows: ritonavir 100 mg or 200 mg bid + indinavir 800 mg bid or ritonavir 400 mg bid + indinavir 400 mg bid; indinavir 1200 mg bid + nefinavir 1250 mg bid; indinavir 600 mg bid + delavirdine 400 mg bid; indinavir 1000 mg tid + efavirenz 600 mg once daily bid; ritonavir 400 mg bid + saquinavir SGC 400 mg or bid + ritonavir 100 mg bid + saquinavir SGC 1200 mg bid; ritonavir 400 mg bid + nefinavir 500-750 mg bid; saquinavir SGC 1200 mg bid + nefinavir 1250 mg bid; and nefinavir 1250 mg bid + delavirdine 600 mg bid. There are minimal data on combinations of 3 drugs with cytochrome P-450 3A4 interactions: ritonavir 200 mg bid + ampravin 1200 mg bid + efavirenz 600 mg qd; ritonavir 400 mg bid + saquinavir 400 mg bid + delavirdine 600 mg bid; and nefinavir 750 mg bid + saquinavir SGC 600 mg bid + delavirdine 600 mg bid. Ellipses indicate data not applicable; bid, 2 times/d; tid, 3 times/d; decrease, PI, protease inhibitor; SGC, soft-gel capsule.
tages (Table 3). Initial regimens of 2 nucleoside reverse transcriptase inhibitors (nRTIs) and a protease inhibitor (or 2 protease inhibitors) or 2 nRTIs and a nonnucleoside reverse transcriptase inhibitor (NNRTI) are recommended. Regimens of 3 nRTIs are being evaluated. 65,66 Although 3-nRTI regimens offer potential advantages, there is concern about their relative potency in patients with high baseline HIV RNA levels. 65,66 Regimens including drugs from all 3 classes are also being assessed.

Patients at high short-term risk for disease progression (eg, CD4+ cell count <5 × 10^6/L or HIV RNA >100 000 copies/mL) have a lower rate of successful HIV suppression with 3-drug regimens. 67 Although the effectiveness of more aggressive initial therapy (eg, 4-drug regimen of drugs from all 3 classes or regimens with dual protease inhibitors) for these patients is uncertain, these more potent combinations may be considered. Issues of adherence, drug-drug interactions, and adverse effects are important considerations.

Nucleoside Reverse Transcriptase Inhibitors. Available nRTIs include zidovudine, didanosine, zalcitabine, stavudine, lamivudine, and abacavir. Dual nRTIs are used in most 3- or 4-drug regimens. Choice of nRTIs should be based on convenience, adverse effects (Appendix), and patient preference. Possible nRTI combinations include (not in preferred order) zidovudine with didanosine, zalcitabine, or lamivudine; or stavudine with didanosine or lamivudine.

There are no current data regarding preferred sequencing of nRTIs; however, zidovudine and stavudine should not be used together because of drug-drug antagonism. Combining zalcitabine with didanosine or stavudine is not recommended because of overlapping toxicities, or with lamivudine because it has not been well studied. Lamivudine should be reserved for regimens that maximally suppress replication, as the rapid emergence of the M184V mutation results in loss of lamivudine activity.

Abacavir is a potent drug in treatment-naive patients. 68 Progressive accumulation of mutations, especially after zidovudine-lamivudine use, results in loss of abacavir’s effectiveness. Thus, it is less likely to be effective for patients with extensive prior exposure to antiretrovirals. Abacavir will likely be useful in initial regimens, but its effectiveness with nRTI combinations other than zidovudine and lamivudine is not well characterized. Long-term data are needed to define its optimal role.

Nonnucleoside Reverse Transcriptase Inhibitors. Three NNRTIs are currently approved in the United States: nevirapine, delavirdine, and efavirenz. There are no direct comparisons of effectiveness with nRTI combinations other than zidovudine and lamivudine is not well characterized. Long-term data are needed to define its optimal role.

Abacavir is a potent drug in treatment-naive patients. 68 Progressive accumulation of mutations, especially after zidovudine-lamivudine use, results in loss of abacavir’s effectiveness. Thus, it is less likely to be effective for patients with extensive prior exposure to antiretrovirals. Abacavir will likely be useful in initial regimens, but its effectiveness with nRTI combinations other than zidovudine and lamivudine is not well characterized. Long-term data are needed to define its optimal role.

Table 3. Advantages and Disadvantages of Possible Initial Antiretroviral Regimens*

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
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<tbody>
<tr>
<td>Protease inhibitor + 2 nRTIs</td>
<td>Clinical data</td>
<td>Complexity and high pill burden</td>
</tr>
<tr>
<td></td>
<td>Longest experience for viral suppression</td>
<td>Compromises future protease inhibitor regimens</td>
</tr>
<tr>
<td>NNRTI + 2 nRTIs</td>
<td>Defers protease inhibitor</td>
<td>Limited long-term data</td>
</tr>
<tr>
<td></td>
<td>Low pill burden</td>
<td>Compromises future NNRTI regimens</td>
</tr>
<tr>
<td>2 Protease inhibitors + 2 nRTIs</td>
<td>High potency</td>
<td>High pill burden with some regimens</td>
</tr>
<tr>
<td></td>
<td>Convenient dosing</td>
<td>Long-term toxicities unknown</td>
</tr>
<tr>
<td>Regimens Under Evaluation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 nRTIs</td>
<td>Defers protease inhibitor and NNRTI</td>
<td>Lower potency than 2-nRTI and protease inhibitor regimen in patients with high baseline viral loads</td>
</tr>
<tr>
<td></td>
<td>Low pill burden</td>
<td>Limited long-term data</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Compromises future nRTI regimens</td>
</tr>
<tr>
<td>Protease inhibitor + NNRTI + nRTI</td>
<td>High potency</td>
<td>Complexity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Compromises future regimens</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multiple-drug toxicity</td>
</tr>
</tbody>
</table>

*nRTI indicates nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor.
Potential for high-level resistance as a result of a single reverse transcriptase mutation suggests that NNRTIs should be used only in regimens designed to maximally suppress HIV. The NNRTIs generally will not be active if resistance to a previous NNRTI has emerged. Since this class of drugs is metabolized by the cytochrome P450 system, drug-drug interactions with protease inhibitors and other drugs should be considered.

**Protease Inhibitors.** Five protease inhibitors are approved in the United States and include 2 formulations of saquinavir (hard-gel and soft gel), ritonavir, indinavir, nelfinavir, and amprenavir. Long-term (>48 week) virologic data on 3-drug regimens including ritonavir, indinavir, or nelfinavir show persistent HIV suppression and warrant their continued use in initial regimens. 75-77 Full-dose ritonavir has adverse effects that limit long-term adherence and its future use is likely to be in combination with other protease inhibitors. The ritonavir soft-gel formulation may be more tolerable than the liquid formulation.

Indinavir is taken 3 times a day on an empty stomach or with a light meal; oral absorption is variable. Nelfinavir is taken twice daily with food. Hard-gel saquinavir should not be used as part of 3-drug regimens (ie, with 2 nRTIs) because of poor oral bioavailability. Soft-gel saquinavir appears to have improved oral bioavailability. Although there are limited data regarding long-term HIV suppression, this formulation can be considered. Soft-gel saquinavir is most effectively used with ritonavir to optimize its pharmacologic profile; this combination is recommended in a twice-daily regimen. Amprenavir, which may be considered, is taken as eight 150-mg pills twice daily; its long-term responses and adverse effects in initial regimens are not well defined. 78

**Dual Protease Inhibitor Combinations.** Dual protease inhibitor regimens are increasingly being used because of pharmacokinetic advantages of low-dose ritonavir (100 or 200 mg 2 times/d) in inhibiting cytochrome P450 enzymes. This improves the pharmacokinetic profiles of saquinavir, indinavir, or amprenavir given twice daily. Ritonavir also increases the plasma levels of lopinavir (ABT-378), an investigational protease inhibitor available through expanded access that may be active against protease inhibitor resistant virus. These combinations may offer increased potency and reduced pill burden, dose frequency, cost, and food restrictions. Although long-term benefit and toxicity are unknown, these combinations may offer pharmacologic and adherence benefits and improved efficacy.

**Monitoring Antiretroviral Therapy **

**Adherence.** Adherence should be routinely assessed and reinforced. In 1 study, an adherence rate of 95% was reported to be necessary for optimal results. 79 Adherence barriers such as number and timing of doses, number and size of pills, food restrictions, and particularly, adverse effects should be weighed in selecting regimens and considered for designing programs to enhance adherence. Before starting treatment, patients should be questioned about daily activities to identify regularly occurring events as triggers for taking medication. Patients should be given clear written instructions. Forms with pictures of relevant pills and daily activities can communicate directly how many and when certain pills are to be taken. Devices such as pill organizers or pill alarms may be useful.

Adherence can be enhanced by stressing at each visit the need to use drugs as prescribed. The most practical adherence assessments are made via use of nonjudgmental questions or a patient-completed questionnaire about medication use in the past several days. Asking about how medications fit into daily activities and which doses are the hardest to remember is more useful and allows for a more reasonable adherence estimate than asking if the patient has missed doses. 80 Fear of long- and short-term adverse effects can affect adherence; thus, adherence may be improved with reassurance that some adverse effects will be mild or transitory. Furthermore, explaining that a variety of regimens is available can help reassure patients that alternate regimens can be used if adherence is problematic.

The primary care provider should be personally committed to supporting adherence; other personnel also play an essential role.

**Monitoring Therapy.** Both CD4+ cell and HIV RNA levels are important tools for judging when to start therapy and evaluating treatment response. Available HIV RNA assays have lower limits of detection of about 40 to 50 copies/mL. A minimum of 2 CD4+ cell counts and 2 HIV RNA measurements should be obtained, preferably from the same laboratory and on 2 separate visits, before initiating or changing therapy. 81

The HIV RNA levels should decrease rapidly after therapy is initiated; a minimum 1.5- to 2.0-log decline should occur by 4 weeks. The nadir response correlates with response durability. 82,83 Also, achieving an early response (by week 4 or 8) is predictive of subsequent HIV suppression. 84 In patients having higher baseline HIV RNA levels (eg, >100 000 copies/mL), maximal suppression may take longer. Failure to achieve the target level of less than 50 copies/mL by 16 to 24 weeks should raise concern and prompt consideration of poor adherence, inadequate drug absorption, or drug resistance. Precise data are not available regarding optimal frequency, but in general, HIV RNA levels should be monitored within 1 month of therapy initiation or change, monthly until the goal of therapy (levels below detection) is reached, and every 2 to 3 months thereafter. Monitoring HIV RNA levels proximal to intercurrent illnesses, treatment lapses, and vaccinations should be avoided because of associated transient viral rebound. Because of biologic and assay variation at low HIV RNA levels (eg, around detection limits), there may be intermittently detectable virus; thus, any significant rebound in HIV RNA should be confirmed with a second test before changing treatment. 85,86,87 The CD4+ cell count increases during therapy reflect at least partial immune system reconsti-
tution. Progressive CD4+ cell count increases may occur throughout the first several years of therapy. Also, persistent immunologic benefits (eg, continued increases in or stabilization of CD4+ cell counts) may be noted in some patients following viral rebound. Close CD4+ cell count monitoring should continue in such situations.

**Drug Level Monitoring.** The role of drug level monitoring in clinical practice has not been determined. Trough plasma drug levels of protease inhibitors correlate with magnitude and durability of viral suppression. Because of high individual variability of protease inhibitor metabolism, therapeutic drug level monitoring to optimize drug dosing may be useful in the future, but prospective controlled studies are needed.

Drug levels for estimating adherence are seldom practical for patient management, because of short drug half-lives. However, drug levels may be useful in establishing adequate absorption and in validating patient report of medication use.

**Drug Resistance Testing.** Resistance emergence is highly predictive of loss of antiretroviral activity. Testing for HIV drug resistance is available, and accurate and correctly interpreted test information may improve patient treatment and reduce antiretroviral cost and toxicity by identifying which drugs are less likely to be effective. Currently, use of drug resistance testing is limited by cost, quality assurance documentation, and lack of clinical information about optimal use of tests and interpretation of the results.

There are limitations and pitfalls in resistance testing. Importantly, testing should be performed in laboratories with documented quality control programs. Only information on current predominant mutations or levels of resistance in actively replicating virus is provided, which may not satisfactorily reflect resistance in latent or minority populations due to temporally distant drug exposure. Thus, resistance testing may be useful in predicting which drug may not be active, but absence of phenotypic or genotypic evidence of resistance will not provide satisfactory assurance that a drug will be active.

**Changing Therapy**

Major reasons for changing an antiretroviral regimen are drug failure, adverse effects, or regimen inconvenience that may compromise adherence. A decision to change therapy must be balanced by consideration of the likelihood that another regimen will achieve control of viral replication or be better tolerated.

**Drug Failure.** Drug failure has been defined broadly as inadequate viral suppression (virologic failure, defined as a confirmed detectable HIV RNA), unsatisfactory increase in CD4+ cell count, or clinical progression (excluding clinical signs and symptoms related to immune reconstitution). Attention has been increasingly focused on failure to achieve or maintain viral suppression. The presence of detectable plasma HIV RNA should be confirmed. Whether a regimen change is necessary, however, should be assessed independently. There are few data that provide the optimal point (eg, any detectable viral load, >500 copies/mL, >1000 copies/mL) at which therapy should be changed in terms of long-term clinical outcome. The major short-term risk of any level of viral replication in the presence of antiretroviral therapy is emergence of resistance. Levels of HIV RNA between 50 and 500 copies/mL are associated with a higher risk of resistance than levels below 50 copies/mL. There is little evidence that low-level replication constitutes a major acute risk for immunologic damage; immunologic parameters may continue to improve for some time after replication resumes. Resistant variants emerge incrementally, and susceptibility to 1 or more drugs in a regimen may be initially maintained. The primary goal of monitoring for suboptimal viral suppression is preservation of therapeutic options.

The initial approach to virologic failure is to assess adherence. If adherence problems are present, the reasons for lapses should be addressed. Loss of regimen potency due to adverse drug-drug interactions or pharmacologic factors also should be considered.

Delayed plasma HIV RNA clearance raises questions about drug exposure adequacy, potency, adherence, and resistance emergence. If the HIV RNA level continues to fall toward the lower assay detection limit as a patient completes 16 weeks of therapy, it is reasonable to continue monitoring the patient without change in therapy. If the HIV RNA level has fallen to near detection levels by week 24 but is not yet below detection, it is not yet clear whether an attempt to change or add to (ie, intensify) the regimen is the wisest strategy. Since lack of adherence to a complete regimen is often the primary reason for virologic failure, alteration of a failing regimen may not directly address the underlying problem.

Although the median rise in CD4+ cell count in patients with HIV RNA levels below detection limit is about 150 × 10^3/L during the first year, less robust CD4+ cell responses may occur. A CD4+ cell count decline may also occur. Most clinicians would not recommend a therapy change based solely on the CD4+ cell response, which is likely a function of the extent of both viral suppression and immunologic reserve. If the patient is tolerating a successful antiretroviral regimen, it is not clear that a more satisfactory CD4+ cell response would be seen with another successful regimen. Also, a later rise in CD4+ cells may occur if durable HIV control is achieved. A hydroxyurea-containing regimen will also dampen the CD4+ cell response.

A CD4+ cell count rise or stabilization in absence of optimal HIV control is the most common "discordant" response. Although patients usually do well clinically for many months and might maintain the CD4+ cell count increase for some time, a progressive rise in HIV RNA levels as resistance emerges usually occurs, and a subsequent decline in CD4+ cell count may be expected. Although a CD4+ cell count above 200 × 10^3/L gives some breathing room in considering therapy change, the clinical benefits are probably temporary and disease progression likely. In patients with few remaining therapeutic options,
a period of clinical stability may provide
time for other options to emerge. If alter-
atives are available, it is usually prefer-
able to change therapy before higher
levels of resistance or broader cross-
resistance develop.

In some patients, localized inflammatory responses to opportunistic infec-
tions (eg, cytomegalovirus and myco-
bacterial infections) have occurred early in therapy with significant CD4+ cell
count increases. Since these responses
reflect immune reconstitution rather than
HIV replication, a change in the antiret-
roviral regimen is not indicated.

Drug Toxicity and Inconvenience. Increased durability of current regi-
mens has led to greater awareness of
longer-term adverse effects of therapy. If an individual drug in a
regimen is changed to reduce toxicity or
for patient convenience, the full regi-
men must be reviewed regarding po-
tency, residual resistance, and drug-
drug interactions. If a successful regimen is
unacceptable because of inconven-
ience, change in therapy can be con-
sidered if regimen simplification in-
creases adherence likelihood.

Changing the Regimen

Once the decision is made to change
therapy, selection of a new regimen
should be driven by the underlying
reason for the change and available
options.

Changing in the Absence of Virol-
ologic Failure. For adverse effects or in-
tolerance to an otherwise successful regi-
men (eg, HIV RNA level below detection
limits), substitution for an individual
identifiable offending drug is reason-
able102 (Table 4). However, there is little
direct experience with comparative antiret-
roviral drug potency, even within drug
classes, and changes in a success-
ful regimen should be approached cau-
tiously. In cases of NNRTI-induced rash,
substitutions of other NNRTIs must be
carefully monitored because of risk of
shared toxicity. Temporary discontinu-
ation of all drugs, before restarting with
a modified regimen, is an alternative to
individual drug substitution, particu-
larly when the offending drug is not
identified. Data suggest that this strat-
egg will usually result in successful re-
suppression.103

In cases of suspected abacavir hyper-
sensitivity (Table 4), the drug should be
discontinued and rechallenge should
not be attempted because this has re-
sulted in severe toxicity and death.

Changing Therapy Because of Vi-
rologic Failure. Virologic failure is not
always associated with resistance,94,95
particularly with initial rebound follow-
ing suppression to below detection lev-
els or if virus remains detectable at low
levels after 12 to 16 weeks of therapy.
If adherence is the problem, limiting
temporal discontinuation of all drugs, before restarting with
a modified regimen, is an alternative to
cross-resistance among protease inhibi-

<table>
<thead>
<tr>
<th>Table 4. Potential Options for Changing Therapy*</th>
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<tbody>
<tr>
<td>Reason for Change</td>
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<tr>
<td>-------------------</td>
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<tr>
<td>Toxicity or intolerance</td>
</tr>
<tr>
<td>HIV RNA suppressed below target</td>
</tr>
<tr>
<td>HIV RNA suppressed but still above target, and fewer than 8-16 wk+ with therapy</td>
</tr>
<tr>
<td>HIV RNA above target, more than 8-16 wk+ on therapy or prior success§</td>
</tr>
<tr>
<td>Difficulty with adherence</td>
</tr>
<tr>
<td>HIV RNA suppressed below target, but adherence problems present</td>
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<tr>
<td>HIV RNA above target, but less than 8-16 wk with therapy</td>
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<tr>
<td>HIV RNA above target, more than 8-16 wk+ with therapy or prior success§</td>
</tr>
<tr>
<td>Virologic failure</td>
</tr>
<tr>
<td>Failure to reach target viral load within 8-16 wk of therapy</td>
</tr>
<tr>
<td>Failure to reach target viral load within 24-36 wk of therapy</td>
</tr>
<tr>
<td>Prior success§ but now confirmed drug failure</td>
</tr>
</tbody>
</table>

*HIV indicates human immunodeficiency virus.
†Actual time to achieve target viral load level (eg, HIV RNA <50 copies/mL) varies depending on factors such as pretreat-
ment HIV RNA level and regimen potency.
‡Attempts should be made to manage toxicity, but if unsuccessful, substitution of equally potent drug is appropriate. (Do
not attempt this with suspected abacavir toxicity.)
§Prior success refers to patients who previously achieved target viral load but now have confirmed viral load above that
target.
¶For patients treated for 8-16 wk with substantial reduction and continued decline in viral load (>1.5 log decrease) but still
not reaching target viral load, intensification may be an option. Before using an intensification strategy, adherence must be
carefully assessed.

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tors increases with duration of viral replication in drug presence. Although specific protease inhibitor sequencing has been successful in some patients (eg, from nelfinavir to a ritonavir-saquinavir combination\(^1\))\(^6\), recommendations about optimal sequencing cannot be reliably made based on antiretroviral history alone. Cross-resistance among nRTIs may be due to shared resistance mutations conferred by one drug or to unique pathways of multidrug resistance.\(^1\)\(^5\) Optimizing benefit of a new nRTI is further complicated by potential for increased or decreased susceptibility to one drug that may be conferred by resistance to another.\(^1\)\(^6\)\(^-\)\(^10\) Given the high rate of class cross-resistance, a drug from a new class should be introduced, when possible.

The predominant virus replicating during treatment failure may not be resistant to all drugs in the failing regimen.\(^9\)\(^-\)\(^10\) Resistance testing may assist in selecting which drugs should be changed and which could remain. However, it is not known how such a drug-sparing strategy compares with complete change of therapy for virologic success.

Another consideration in choosing subsequent regimens is the potential for pharmacologic drug enhancement (Table 2); optimal dose needs to be determined for each protease inhibitor. Combining efavirenz with certain protease inhibitors should be done cautiously because of potential reductions in bioavailability (eg, saquinavir and amprenavir). Pharmacologic enhancement of antiviral activity of didanosine (Table 2); optimal dose needs to be increased antiviral activity of didanosine (Table 2); optimal dose needs to be increased antiviral activity of didanosine (Table 2); optimal dose needs to be increased antiviral activity of didanosine (Table 2); optimal dose needs to be increased antiviral activity of didanosine (Table 2); optimal dose needs to be increased antiviral activity of didanosine (Table 2); optimal dose needs to be increased antiviral activity of didanosine (Table 2); optimal dose needs to be increased antiviral activity of didanosine (Table 2); optimal dose needs to be increased antiviral activity of didanosine (Table 2); optimal dose needs to be increased antiviral activity of didanosine (Table 2); optimal dose needs to be increased antiviral activity of didanosine (Table 2); optimal dose needs to be increased antiviral activity of didanosine (Table 2); optimal dose needs to be increased antiviral activity of didanosine (Table 2); 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