

Antiretroviral Therapy in Adults

Updated Recommendations of the International AIDS Society–USA Panel

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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.¹⁻³ 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 knowl-

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.

JAMA. 2000;283:381-390

www.jama.com

edge regarding HIV biology, monitoring, and treatment were emerging.^{1,4-8} The benefits of potent antiretroviral combinations^{9,10} were subsequently demonstrated and a theoretical basis for HIV eradication proposed,¹¹ leading to recommendations for early and aggressive treatment.^{2,12}

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.^{11,13} Newer data indicated that low-level, ongoing replication may occur with plasma HIV RNA levels below detection (<50 copies/mL),¹⁴⁻¹⁶ and the apparent decay half-life of resting memory CD4⁺ lymphocytes with latent HIV provirus is cal-

culated to be at least 6 months¹⁴ and as long as 44 months.¹⁷ Thus, HIV eradication with antiretroviral therapy alone would take a decade or more and is not presently a realistic goal.^{14,17}

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.¹⁸ Newer data show that clinically significant immune reconstitution (eg, return of pathogen- and HIV-specific lympho-

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Table 1. Ranges of CD4⁺ Cell Count and Viral Load Levels for Therapy Initiation

CD4 ⁺ Cells, ×10 ⁶ /L	Plasma HIV RNA Level, Copies/mL*		
	<5000	5000-30 000	>30 000
<350	Recommend therapy	Recommend therapy	Recommend therapy
350-500	Consider therapy	Recommend therapy	Recommend therapy
>500	Defer therapy†	Consider therapy†	Recommend therapy†

*HIV indicates human immunodeficiency virus.

†See "Clinical, Virologic, and Immunologic Parameters" section.

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.²⁷⁻²⁹

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

× 10⁶/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 × 10⁶/L. Therapy should be considered at CD4⁺ cell counts above 500 × 10⁶/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 × 10⁶/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 (eg, 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 restore HIV-specific immune responses, and possibly lower the viral “set point” to improve the subsequent course of disease.³⁸ Early intervention in primary infection can lead to restoration of HIV-specific immune responses and durable virologic response.^{19,38} However, clinical benefits of potent therapy in primary infection have not been definitively established.

Given the many unanswered questions, referral to a clinical trial is recommended for all patients with primary infection. In the absence of access to a clinical trial, potent therapy should be discussed and offered, with careful review of important caveats (eg, long-term toxicity risk and unknown ultimate clinical benefit).

Initial Therapy

There are no definitive data regarding superiority of one acceptably potent initial regimen over another, and recom-

mendations for specific combinations of individual drugs cannot be made. Choice of a regimen should be individualized based on the strength of supporting data and on regimen potency, tolerability, adverse effect profile (Appendix, available at <http://www.jama.com>), likely drug-drug interactions (TABLE 2), convenience and adherence likelihood, potential for alternative treatment options if the initial regimen fails, and possibly, baseline resistance testing results. Each possible regimen for initial therapy has advantages and disadvan-

Table 2. Pharmacokinetic (PK) Interactions and Dose Recommendations*

Interacting Drug	Affected Drug							
	Indinavir	Ritonavir	Saquinavir SGC	Nelfinavir	Amprenavir	Nevirapine	Delavirdine	Efavirenz
Indinavir	...	No effect ³⁹⁻⁴¹ Dose change	↑AUC 620% at 800 mg ^{42,43} 364% at 1200 mg ^{42,43} Dose not established	↑AUC 83% (single dose PK study) ⁴⁴ No effect (multiple dose PK study) ⁴⁵ Dose change ⁴⁵	↑AUC 22%-64% ⁴⁶ Dose not established	No effect ⁴⁷ Dose change	No effect ^{48,49} Dose change	No effect ⁵⁰ Dose change
Ritonavir	↑AUC 480% ³⁹ Dose change ^{40,41}	...	↑AUC 121% ⁴³ Dose change	↑AUC 152% (single dose PK study) ⁴⁴ Effect on metabolite varies by dose Dose change ^{51,52}	No data	No effect ⁴⁷	No effect ^{48,49,53}	↑AUC 21% ⁵⁴
Saquinavir SGC	No effect ⁴² Dose not established	No effect ⁴³ Dose change	...	↑AUC 18% Dose change ⁵⁵	↓AUC 36% ⁴⁶	No effect ⁵⁶	No data	↓AUC 12% ⁵⁴ Warning: Do not use with saquinavir as only PI ⁵⁴
Nelfinavir	↑AUC 51% (single dose PK study) ⁴⁴ Dose change ⁴⁵	No effect ⁴⁴ Dose change	↑AUC 392% ⁵⁷ Dose change ⁵⁵	...	No effect ⁴⁶	No effect ⁵⁸	↓AUC 30-40% ^{59,60} Dose change ⁶⁰	No effect ^{61,62}
Amprenavir	↓AUC 38% (multiple dose PK study) ⁴⁶ Dose not established ⁴⁶	No data	↓AUC 18% ⁴⁶	↑AUC 15% ⁴⁶	...	No data	No data	↑AUC 15% Warning: Do not use with amprenavir as only PI ⁴⁶
Nevirapine	↓AUC 28% Dose change ⁴⁷	No effect ⁴⁷	Dose not established for SGC	↑AUC 8% ⁵⁸	No data	...	No data	No data
Delavirdine	↑AUC 2x Dose change ^{48,49,63}	No effect ⁴⁹	Dose not established for SGC	↑AUC 2x ↓AUC metabolite 50% ⁵⁹	No data	No data	...	No data
Efavirenz	↓AUC 31% ⁵⁰ Dose change	↑AUC 0%-18% ⁵⁴	↓AUC 62% Warning: Do not use with saquinavir-SGC as only PI ⁵⁴	↑AUC 20% ↓AUC metabolite 37% ^{61,62}	↓AUC 36% Warning: Do not use with amprenavir as only PI ⁴⁶	No data	No data	...

*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 + nelfinavir 1250 mg bid; indinavir 600 mg tid + delavirdine 400 mg tid; indinavir 1000 mg tid + efavirenz 600 mg once daily (qd); ritonavir 400 mg bid + saquinavir SGC 400 mg bid or ritonavir 100 mg bid + saquinavir SGC 1200 mg bid; ritonavir 400 mg bid + nelfinavir 500-750 mg bid; saquinavir SGC 1200 mg bid + nelfinavir 1250 mg bid; and nelfinavir 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 + amprenavir 1200 mg bid + efavirenz 600 mg qd; ritonavir 400 mg bid + saquinavir 400 mg bid + delavirdine 600 mg bid⁶⁴; and nelfinavir 750 mg tid + saquinavir 800 mg tid + delavirdine 600 mg bid.⁶⁴ Ellipses indicate data not applicable; bid, 2 times/d; ↑, increase; AUC, area under the plasma concentration–curve; 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 <50 × 10⁶/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-naïve 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 potencies of the 3 drugs. The choice of a particular NNRTI should be based on

supporting evidence, convenience, and potential for adverse effects.

Efavirenz-lamivudine-zidovudine-produced HIV suppression and CD4⁺ cell count elevation is at least comparable to that with indinavir-lamivudine-zidovudine.⁶⁹ A retrospective analysis showed similar responses in patients with pretreatment HIV RNA levels above or below 100 000 copies/mL.⁷⁰ Efavirenz is taken as 3 tablets once-daily. It is contraindicated in the first trimester of pregnancy.

Nevirapine-zidovudine-didanosine was superior to didanosine-zidovudine in suppressing HIV at 48 weeks.⁷¹ Virologic and CD4⁺ cell count results of a study comparing nevirapine-didanosine-stavudine with indinavir-didanosine-stavudine were similar at 24 weeks.⁷² Whether a triple combination including nevirapine is equally effective in suppressing HIV at high and low pretreatment viral loads is not known. Nevirapine is approved for twice-daily dosing, but pharmacokinetic data indicate that adequate blood levels are maintained with once-daily dosing.⁷³

Delavirdine-zidovudine-lamivudine produced superior HIV RNA and CD4⁺ cell responses at 48 weeks vs zidovudine-lamivudine alone,⁷⁴ but there are no available data comparing delavirdine plus 2 nRTIs with dual nRTI/protease inhibitor regimens. Delavirdine is taken as two 200-mg tablets, 3 times a day.

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

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

*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 phar-

macokinetic 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.^{6,14,81} 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.⁸⁵ 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.⁸⁶ Testing for HIV drug resistance is available, and accurate and correctly interpreted test information may improve patient treatment⁸⁶⁻⁸⁹ 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.⁸⁶

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.⁹⁰ 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.⁸³ 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.⁹¹⁻⁹³ Resistant variants emerge incrementally, and susceptibility to 1 or more drugs in a regimen may be initially maintained.⁹⁴⁻⁹⁶ 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 $150 \times 10^6/L$ during the first year, less robust CD4⁺ cell responses may occur.⁹⁷ 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.⁹¹⁻⁹³ 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 $200 \times 10^6/L$ gives some breathing room in considering therapy change, the clinical benefits are probably temporary and disease progression likely.^{7,8} In patients with few remaining therapeutic options,

a period of clinical stability may provide time for other options to emerge. If alternatives are available, it is usually preferable to change therapy before higher levels of resistance or broader cross-resistance develop.

In some patients, localized inflammatory responses to opportunistic infections (eg, cytomegalovirus and mycobacterial infections) have occurred early in therapy with significant CD4⁺ cell count increases.⁹⁸ Since these responses reflect immune reconstitution rather than HIV replication, a change in the antiretroviral regimen is not indicated.

Drug Toxicity and Inconvenience. Increased durability of current regimens has led to greater awareness of longer-term adverse effects of therapy.⁹⁹⁻¹⁰¹ If an individual drug in a regimen is changed to reduce toxicity or for patient convenience, the full regimen must be reviewed regarding potency, residual resistance, and drug-drug interactions. If a successful regimen is unacceptable because of inconvenience, change in therapy can be considered if regimen simplification increases 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 Virologic Failure. For adverse effects or intolerance to an otherwise successful regimen (eg, HIV RNA level below detection limits), substitution for an individual, identifiable offending drug is reasonable¹⁰² (TABLE 4). However, there is little direct experience with comparative antiretroviral drug potency, even within drug classes, and changes in a successful regimen should be approached cautiously. In cases of NNRTI-induced rash, substitutions of other NNRTIs must be carefully monitored because of risk of shared toxicity. Temporary discontinuation of all drugs, before restarting with a modified regimen, is an alternative to individual drug substitution, particularly when the offending drug is not

identified. Data suggest that this strategy will usually result in successful re-suppression.¹⁰³

In cases of suspected abacavir hypersensitivity (Table 4), the drug should be discontinued and rechallenge should not be attempted because this has resulted in severe toxicity and death.

Changing Therapy Because of Virologic Failure. Virologic failure is not always associated with resistance,^{94,95} particularly with initial rebound following suppression to below detection levels or if virus remains detectable at low levels after 12 to 16 weeks of therapy. If adherence is the problem, limiting changes to a responsible drug may be sufficient, but only if a drug of similar or increased potency is available.

In patients having detectable, but low-level, HIV RNA after a few months of potent therapy and without identified resistance to drugs in their current regimen, addition of a new drug (ie, intensification) could be an alternative to a complete change, after other treatment failure causes are ruled out. However, an

intensification strategy may add to the complexity of the regimen and may jeopardize future treatment options. Moreover, if failure is due to adherence difficulties, intensification is likely to exacerbate the problem.

In patients having high-level persistent viremia with continued drug presence, emergence of resistance is likely. Once the decision to change treatment is made, a change of all regimen components is usually preferred. The alternative regimen must be carefully chosen, since responses are often disappointing.⁹⁷ A drug regimen with highest predicted potency, tolerability, and adherence should be chosen. However, no data exist regarding preferred sequence of drugs within a class, and the choice of alternative drugs should be based on least potential for cross-resistance. Risk of cross-resistance is high among NNRTIs, and use of a new NNRTI is not recommended as an alternative for a failing NNRTI-containing regimen. The likelihood and extent of cross-resistance among protease inhibi-

Table 4. Potential Options for Changing Therapy*

Reason for Change	Change
Toxicity or intolerance	
HIV RNA suppressed below target	Change the offending drug (if discernible)
HIV RNA suppressed but still above target, and fewer than 8-16 wk† with therapy‡	Change the offending drug (if discernible)
HIV RNA above target, more than 8-16 wk† on therapy or prior success§	Change entire regimen
Difficulty with adherence	
HIV RNA suppressed below target, but adherence problems present	Change to simplified regimen with equal potency; may substitute single drug if the offending drug identifiable
HIV RNA above target, but less than 8-16 wk with therapy	Change to simplified regimen with equal potency; may substitute single drug if the offending drug identifiable
HIV RNA above target, more than 8-16 wk† with therapy or prior success§	Change entire regimen
Virologic failure	
Failure to reach target viral load within 8-16 wk† of therapy	Continue current regimen; assess adherence; consider intensification
Failure to reach target viral load within 24-36 wk of therapy	Change entire regimen
Prior success§ but now confirmed drug failure	Change entire regimen

*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 pretreatment 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.

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 combination¹⁰⁴), 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.¹⁰⁵ 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.¹⁰⁶⁻¹⁰⁹ 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.⁹⁴⁻⁹⁶ 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 at the level of nucleoside pools is at least in part responsible for the increased antiviral activity of didanosine in the presence of hydroxyurea. Hydroxyurea use should be monitored carefully for pancreatitis.

Multiple Virologic Failures. Drug intolerance and resistance limit alternatives in this setting. Adding 1 new drug generally will not have a profound and durable virologic effect and will likely select for additional resistance; this approach should be avoided. When a therapy change cannot be delayed until more drugs are available (eg, low CD4⁺ cell counts [$<50 \times 10^6/L$] or clinical

symptoms), 6 or more drugs recycled from the 3 different classes have variable short-term antiretroviral activity and may represent an option.^{110,111} These regimens are most effective for NNRTI-naïve patients and are fraught with adherence, drug-drug interaction, intolerance, cost, and toxicity problems. Multiple drug therapy might be simplified by use of resistance testing to exclude less effective regimen components, but this has not been well evaluated. Furthermore, presence of drug-associated mutations does not necessarily mean that the regimen lacks any antiretroviral activity. Some data suggest a temporary (1 or 2 months) treatment interruption prior to initiation of a new, multidrug regimen.¹¹² About two thirds of patients had an apparent reversion toward genotypically wild-type virus. A potential limitation of the treatment interruption strategy is the profound drop in CD4⁺ cell counts that often occurs.¹¹² More research is needed before a recommendation can be made.

Should Therapy Be Stopped? Based on clinical and immunologic benefit despite continued viremia in patients with advanced disease and few or no remaining antiretroviral options,^{92,97} it is reasonable to continue treatment as long as possible. However, in this setting, drug interruption, dose reduction, or substitution of 1 or more drugs in a complex regimen may be necessary because of toxicity. The CD4⁺ cell count and HIV RNA levels should be monitored after drug discontinuation to detect worsening of values.

Postexposure Prophylaxis

If risk associated with occupational exposure¹¹³ warrants therapy, immediate initiation of individualized therapy is recommended. Issues related to postexposure prophylaxis in occupational and nonoccupational settings have been previously discussed in detail.³

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Appendix. Selected Adverse Effects of Antiretroviral Drugs by Drug Class (Effects in Bold Are Potentially Life-threatening)

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

All drugs in this class may cause lactic acidosis with **hepatic steatosis**. Potential explanation can be mitochondrial toxicity. Cases of fat loss and fat accumulation have also been observed in patients treated exclusively with NRTIs. Dyslipidemia and changes in body fat distribution (often termed *lipodystrophy*) have been associated with the prolonged use of NRTI regimens. Drug-specific adverse effects include:

Zidovudine	Didanosine	Zalcitabine	Stavudine	Lamivudine	Abacavir
Neutropenia	Hyperamylasemia	Peripheral neuropathy	Peripheral neuropathy	Not significant	Hypersensitivity reactions*
Anemia	Pancreatitis	Mouth ulcers			
Nausea	Peripheral neuropathy	Rash			
Vomiting	Diarrhea				
Headache	Nausea				
Myopathy	Vomiting				
Nail pigmentation	Sicca syndrome				

*Although the hypersensitivity reaction is rare (3%), it is progressive and difficult to diagnose and, if suspected, necessitates discontinuation of the drug. The multisystem syndrome generally includes fever and 1 or more of the following: rash, nausea or vomiting, malaise, diarrhea, pruritis, headache, fatigue, myalgia, chills, mouth or throat symptoms. In cases of suspected abacavir hypersensitivity, the drug should be stopped. **Rechallenge should not be attempted as it has been associated with life-threatening toxicity and death.**

Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)

All drugs in this class (nevirapine, delavirdine, and, to some extent, efavirenz) may cause rash. Most cases of rash are mild or moderate; grade 1 and 2 rashes may be treated through and may improve if antihistamines or corticosteroids are added. Rash is potentially preventable if antihistamines are added during initial 2 weeks of therapy. The reaction is generally self-limited. Cases of Stevens-Johnson syndrome are exceptional. All NNRTIs may cause elevations of aminotransferases; rare cases of fatal hepatitis have been reported. Efavirenz may cause transient central nervous system disturbances that manifest as a complex of sleep and mood disturbances and may include 1 or more of the following: dizziness, somnolence, insomnia, abnormal dreams, confusion, agitation, depersonalization, or hallucinations. These symptoms may develop in up to 25% of patients within the first 4 weeks of therapy but are generally transient so that therapy needs to be discontinued in less than 3% of patients. Nevirapine and efavirenz may cause withdrawal symptoms in patients receiving methadone maintenance.

Protease Inhibitors

Dyslipidemia and/or changes in body fat distribution are associated with use of protease inhibitor—containing regimens. Symptoms include peripheral fat loss and central fat accumulation, often associated with hypercholesterolemia, hypertriglyceridemia, insulin resistance, and, rarely, hyperglycemia. Overall cumulative incidence may be 30% to 60% after 1 to 2 years of therapy and increases with the duration of therapy. **All drugs in this class may cause bleeding episodes in people with hemophilia.**

Drug-specific adverse effects include the following:

Saquinavir (Hard- and soft-gel formulations)	Ritonavir	Indinavir	Nelfinavir	Amprenavir
Gastrointestinal intolerance	Gastrointestinal intolerance	Nephrolithiasis	Diarrhea	Diarrhea
Headache	Taste disturbances	Crystal nephropathy		Rash
Elevated aminotransferase	Elevated creatine phosphokinase and uric acid	Gastrointestinal intolerance		Paresthesias
	Paresthesias	Hyperbilirubinemia		
	Hepatitis	Dry skin		