Reprinted from JAMA ® The Journal of the American Medical Association January 19, 2000 Volume 283

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.

JAMA. 2000;283:381-390 www.jama.com

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 knowledge 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 calculated to be at least 6 months[14] 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-

Author Affiliations and **Financial Disclosures** are listed at the end of this article.
Corresponding Author and Reprints: Charles C. J. Carpenter, MD, Brown University School of Medicine, The Miriam Hospital, 164 Summit Ave, Providence, RI 02906 (e-mail: Charles_Carpenter@brown.edu).

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

	Plasma HIV RNA Level, Copies/mL*		
CD4+ Cells, $\times 10^6$/L	<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 $\times 10^6$/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 $\times 10^6$/L. Therapy should be considered at CD4+ cell counts above 500 $\times 10^6$/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 $\times 10^6$/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 (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 recommendations 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 bid[64]; 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 $<50 \times 10^6$/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 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 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.[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 treatment[86-89] 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 delectable 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 150×10^6/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 200×10^6/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 reasonable[102] (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 resuppression.[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 combination[104]), 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-naive 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 exposure[113] 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]

Author Affiliations: Brown University School of Medicine, Providence, RI (Dr Carpenter); University of New South Wales, Sydney, Australia (Dr Cooper); University of Miami School of Medicine, Miami, Fla (Dr Fischl); University of Barcelona, Barcelona, Spain (Dr Gatell); Chelsea and Westminster Hospital, London, England (Dr Gazzard); Columbia University College of Physicians and Surgeons, New York, NY (Dr Hammer); Harvard Medical School, Boston, Mass (Dr Hirsch); The International AIDS Society–USA, San Francisco, Calif (Ms Jacobsen); Stanford University Medical Center, Stanford, Calif (Dr Katzenstein); St Paul's Hospital, Vancouver, British Columbia (Dr Montaner); University of California, San Diego, and San Diego Veterans Affairs Medical Center (Dr Richman); University of Alabama at Birmingham (Dr Saag); Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil (Dr Schechter); University of Colorado School of Medicine, Denver (Dr Schooley); AIDS Research Consortium of Atlanta, Atlanta, Ga (Dr Thompson); Istituto Superiore di Sanità, Rome, Italy (Dr Vella); Hôpital Bichat-Claude Bernard, X. Bichat Medical School, Paris, France (Dr Yeni); and University of California, San Francisco (Dr Volberding).
Financial Disclosures: All authors except Ms Jacobsen were speakers, advisory board members, and/or consultants, and/or had stock ownership, research grants, or honoraria involving 1 or more of the following: Abbott, Agouron, Biochem Pharma, Boehringer Ingelheim, Bristol-Myers Squibb, Chiron, DuPont Pharmaceuticals, Gilead Sciences, Glaxo Wellcome, Hoffmann-La Roche, Merck Frosst Laboratories, Merck Sharp & Dohme, Merck, Novirio, Pharmacia & Upjohn, Roche, Roxane, Schering Plough, Triangle, Trimeris, Vertex, ViroLogic, or Visible Genetics.
Funding/Support: This work was supported by the International AIDS Society–USA, San Francisco, Calif.
Acknowledgment: We thank Demia Sundra and Barbara Ryan for editorial assistance in manuscript preparation and panel meetings.

REFERENCES

1. Carpenter CC, Fischl MA, Hammer SM, et al. Antiretroviral therapy for HIV infection in 1996. *JAMA*. 1996;276:146-154.
2. Carpenter CC, Fischl MA, Hammer SM, et al. Antiretroviral therapy for HIV infection in 1997. *JAMA*. 1997;277:1962-1969.
3. Carpenter CC, Fischl MA, Hammer SM, et al. Antiretroviral therapy for HIV infection in 1998. *JAMA*. 1998;280:78-86.
4. Wei X, Ghosh SK, Taylor ME, et al. Viral dynamics in HIV-1 infection. *Nature*. 1995;373:117-122.
5. Ho DD, Neumann AU, Perelson AS, et al. Rapid turnover of plasma virions and CD4+ lymphocytes in HIV-1 infection. *Nature*. 1995;373:123-126.
6. Saag MS, Holodniy M, Kuritzkes DR, et al. HIV viral load markers in clinical practice. *Nat Med*. 1996;2:625-629.
7. Delta Coordinating Committee. Delta: a randomized double-blind controlled trial comparing combinations of zidovudine plus didanosine or zalcitabine with zidovudine alone in HIV-infected individuals. *Lancet*. 1996;348:283-291.
8. Hammer SM, Katzenstein DA, Hughes MD, et al. Trial comparing nucleoside monotherapy with combination therapy in HIV-infected adults with CD4+ cell counts from 200 to 500 per cubic millimeter. *N Engl J Med*. 1996;335:1081-1090.
9. Hammer SM, Squires KE, Hughes MD, et al. Controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200/mL or less. *N Engl J Med*. 1997;337:725-733.
10. Gulick RM, Mellors JW, Havlir D, et al. Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy. *N Engl J Med*. 1997;337:734-739.
11. Perelson AS, Essunger P, Cao Y. Decay characteristics of HIV-1 infected compartments during combination therapy. *Nature*. 1997;387:188-191.
12. US Department of Health and Human Services Panel on Clinical Practices for Treatment of HIV Infection. Guidelines for the use of antiretroviral agents in HIV-1

infected adults and adolescents. *MMWR Morb Mortal Wkly Rep*. 1998;47(RR-5):42-82.
13. Perelson AS, Neumann AU, Markowitz M, et al. HIV-1 dynamics in vivo. *Science*. 1996;271:1582-1586.
14. Zhang L, Ramratnam B, Tenner-Racz K, et al. Quantifying residual HIV-1 replication in patients receiving combination antiretroviral therapy. *N Engl J Med*. 1999; 340:1605-1613.
15. Hockett RD, Kilby JM, Derdeyn CA, et al. Constant mean viral copy number per infected cell in tissues regardless of high, low, or undetectable plasma HIV RNA. *J Exp Med*. 1999;189:1545-1559.
16. Gunthard HF, Frost SD, Leigh-Brown AJ, et al. Evolution of envelope sequences of human immunodeficiency virus type 1 in cellular reservoirs in the setting of potent antiviral therapy. *J Virol*. 1999;73:9404-9412.
17. Finzi D, Blankson J, Siliciano JD, et al. Latent infection of CD4+ T cells provides a mechanism for lifelong persistence of HIV-1, even in patients on effective combination therapy. *Nat Med*. 1999;5:512-517.
18. Fauci AS. Multifactorial nature of human immunodeficiency virus disease. *Science*. 1993;262:1011-1018.
19. Rosenberg ES, Billingsley JM, Caliendo AM, et al. Vigorous HIV-1-specific CD4+ T cell responses associated with control of viremia. *Science*. 1997;278:1447-1450.
20. Komanduri KV, Viswanathan MN, Wieder ED, et al. Restoration of cytomegalovirus-specific CD4+ T-lymphocyte responses after ganciclovir and highly active antiretroviral therapy in individuals infected with HIV-1. *Nat Med*. 1998;4:953-956.
21. Autran B, Carcelain G, Tubiana R, et al. Effects of antiretroviral therapy on immune reconstitution. From: 6th Conference on Retroviruses and Opportunistic Infections; January 31–February 4, 1999; Chicago, Ill. Abstract S44.
22. Bucy RP, Rockett RD, Derdeyn CA, et. al. Initial increase in blood CD4(+) lymphocytes after HIV antiretroviral therapy reflects redistribution from lymphoid tissues. *J Clin Invest*. 1999;103:1391-1398.
23. Plana M, Garcia F, Gallart T, et al. Lack of T-cell proliferative response to HIV-1 antigens after one year of highly active antiretroviral therapy in early HIV-1 disease. *Lancet*. 1998;352:1194-1195.
24. Dong KL, Bausserman LL, Flynn MM, et al. Changes in body habitus and serum lipid abnormalities in HIV-positive women on highly active antiretroviral therapy (HAART). *J Acquir Immune Defic Syndr*. 1999;21:107-113.
25. Carr A, Samaras K, Thorisdottir A, et al. Diagnosis, prediction, and natural course of HIV-1 protease inhibitor-associated lipodystrophy, hyperlipidemia and diabetes mellitus. *Lancet*. 1999;353:2093-2099.
26. Henry K, Melroe H, Huebsch J, et al. Severe premature coronary artery disease with protease inhibitors [letter]. *Lancet*. 1998;351:1328.
27. Palella FJ, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med*. 1998;338:853-860.
28. Hogg RS, O'Shaughnessy MV, Gataric N, et al. Decline in deaths from AIDS due to new antiretrovirals [letter]. *Lancet*. 1997;349:1294.
29. Hogg RS, Heath KV, Yip B, et al. Improved survival among HIV-infected individuals following initiation of antiretroviral therapy. *JAMA*. 1998;279:450-454.
30. Schechter M, Struchiner CJ, Harrison LH. Protease inhibitors as initial therapy for individuals with an intermediate risk of HIV disease progression. *AIDS*. 1999; 13:97-102.
31. Mellors J, Munoz AM, Giorgi JV. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med*. 1997;126:946-954.
32. Marschner IC, Collier AC, Coombs RW, et al. Use of changes in plasma levels of human immunodeficiency virus type 1 RNA to assess the clinical benefit of antiretroviral therapy. *J Infect Dis*. 1998;177:40-47.
33. Lyles R, Munoz A, Bazmi H, et al. Natural history of HIV-1 viremia after seroconversion in the Multicenter AIDS Cohort Study. From: 6th Conference on Retroviruses and Opportunistic Infections; January 31–February 4, 1999; Chicago, Ill. Abstract 273.
34. Farzadegan H, Hoover DR, Astemborski J. Sex differences in HIV-1 viral load and progression to AIDS. *Lancet*. 1998;352:1510-1514.
35. Anastos K, Gange SJ, Lau B, et al. Gender specific differences in quantitative HIV-1 RNA levels. From: 6th Conference on Retroviruses and Opportunistic Infections; January 31–February 4, 1999; Chicago, Ill. Abstract 274.
36. Sterling TR, Lyles CM, Vlahov D, et al. Sex differences in longitudinal human immunodeficiency virus type 1 RNA levels among seroconverters. *J Infect Dis*. 1999; 180:666-672.
37. Centers for Disease Control and Prevention. 1993 Revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. *MMWR Morb Mortal Wkly Rep*. 1992;41(RR-17):1-19.
38. Markowitz M, Jin X, Ramratnam B, et al. Virologic and immunologic profiles of newly infected individuals electing discontinuation of HAART after approximately three years of apparently suppressive therapy. From: 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; September 26-29, 1999; San Francisco, Calif. Abstract LB-16.
39. Hsu A, Granneman GR, Cao G, et al. Pharmacokinetic interaction between ritonavir and indinavir in healthy volunteers. *Antimicrob Agents Chemother*. 1998;42:2784-2791.
40. Saah AJ, Winchell G, Seniuk M, Deutsch P. Multiple-dose pharmacokinetics (PK) and tolerability of indinavir (IDV) ritonavir (RTV) combinations in healthy volunteers. From: 6th Conference on Retroviruses and Opportunistic Infections; January 31–February 4, 1999; Chicago, Ill. Abstract 362.
41. Burger DM, Hugen PWH, Prins JM, et al. Pharmacokinetics of an Indinavir/Ritonavir 800/100 mg BID regimen. From: 6th Conference on Retroviruses and Opportunistic Infections; January 31–February 4, 1999; Chicago, Ill. Abstract 363.
42. McCrea J, Buss N, Stone J, et al. Indinavir-saquinavir single dose pharmacokinetic study. From: 4th Conference on Retroviruses and Opportunistic Infections; January 22-26, 1997; Washington, DC. Abstract 608.
43. Buss N, and the Fortovase Study Group. Saquinavir soft gel capsule (Fortovase). From: 5th Conference on Retroviruses and Opportunistic Infections; February 1-5, 1998; Chicago, Ill. Abstract 354.
44. Yuen G, Kerr B, Lee C, et al. Overview of in-vitro and in-vivo drug interaction studies of nelfinavir mesylate (NFV), a new HIV-1 protease inhibitor. From: 4th Conference on Retroviruses and Opportunistic Infections; January 22-26, 1997; Washington, DC. Abstract 373.
45. Squires K, Riddler S, Havlir D, et al. Coadministration of indinavir (IDV) 1200 mg with nelfinavir (NFV) 1250 mg in a twice daily regimen. From: 6th Conference on Retroviruses and Opportunistic Infections; January 31–February 4, 1999; Chicago, Ill. Abstract 364.
46. Sadler B, Gillotin C, Chittick GE, et al. Pharmacokinetic drug interactions with amprenavir. From: 12th World AIDS Conference; June 28–July 3, 1998; Geneva, Switzerland. Abstract 12389.
47. Murphy R, Gagnier P, Lamson M, et al. Effect of nevirapine on pharmacokinetics of indinavir and ritonavir in HIV-1 patients. From: 4th Conference on Retroviruses and Opportunistic Infections; January 22-26, 1997; Washington, DC. Abstract 374.
48. Ferry JJ, Herman BD, Cox SR, et al. Delavirdine and indinavir. From: 4th Conference on Retroviruses and Opportunistic Infections; January 22-26, 1997; Washington, DC. Abstract 392.
49. Ferry JJ, Schneck DW, Carlson GF, et al. Evaluation of the pharmacokinetic interaction between ritonavir and delavirdine in healthy volunteers. From: 4th Conference on Retroviruses and Opportunistic Infections; January 22-26, 1997; Washington, DC. Abstract 372.
50. Fiske WD, Mayers D, Wagner KF. Pharmacokinetics of DMP 266 and indinavir multiple oral doses in HIV-1 infected individuals. From: 4th Conference on Retroviruses and Opportunistic Infections; January 22-26, 1997; Washington, DC. Abstract 568.
51. Flexner C, Hsu A, Kerr B. Steady-state pharmacokinetic interactions between ritonavir, nelfinavir, and the nelfinavir active metabolite M8 (AG 1402). From: 12th World AIDS Conference; June 28–July July 3, 1998; Geneva, Switzerland. Abstract 42265.
52. Gallant JE, Raines C, Sun E, et al. A Phase II study of ritonavir-nelfinavir combination therapy. From: 6th Conference on Retroviruses and Opportunistic Infections; January 31–February 4, 1999; Chicago, Ill. Abstract 393.
53. Shelton M, Hewitt RG, Adams JM, et al. Delavirdine mesylate pharmacokinetics during combination therapy with ritonavir. From: 37th Interscience Conference on Antimicrobial Agents and Chemotherapy; September 28–October 1, 1997; Toronto, Ontario. Abstract A-63.
54. Efavirenz [package insert]. Wilmington, Del: DuPont Pharmaceuticals Co; 1998.
55. Slater L, Sension M, Feinberg J, et al. Fortovase BID regimens in HIV-1 infected patients. From: 6th Conference on Retroviruses and Opportunistic Infections; January 31–February 4, 1999; Chicago, Ill. Abstract 390.
56. Sahai J, Cameron W, Salgo M, et al. Drug interaction study between saquinavir and nevirapine. From: 4th Conference on Retroviruses and Opportunistic Infections; January 22-26, 1997; Washington, DC. Abstract 614.
57. Kravcik S, Sahai H, Kerr B, et al. Nelfinavir mesylate increases saquinavir soft-gel capsule exposure in HIV-positive patients. From: 4th Conference on Retroviruses and Opportunistic Infections; January 22-26, 1997; Washington, DC. Abstract 371.
58. Skowron G, Leoung G, Kerr B, et al. Lack of pharmacokinetic interaction between nelfinavir and nevirapine. *AIDS*. 1998;12:1243-1244.
59. Cox SR, Schneck DW, Herman BD, et al. Delavirdine (DLV) and nelfinavir (NFV). From: 5th Conference on Retroviruses and Opportunistic Infections; February 1-5, 1998; Chicago, Ill. Abstract 345.
60. Wathen L, Slater L, Kuritzkes D, et al. Significant decreases in viral burden with twice daily dosing of delavirdine in combinations with nelfinavir, didanosine, and stavudine. *Antiviral Ther*. 1998;3(suppl 5):95-96.
61. Fiske WD, Benedek EH, White SJ, et al. Pharmacokinetic interaction between DMP 266 and nelfinavir mesylate in healthy volunteers. From: 37th Interscience Conference on Antimicrobial Agents and Chemotherapy; September 28–October 1, 1997; Toronto, Ontario. Abstract I-174.
62. Fiske WD, Benedek LH, White SJ, et al. Pharmacokinetic interaction between efavirenz (EFV) and nelfinavir mesylate (NFV) in healthy volunteers. From: 5th Conference on Retroviruses and Opportunistic Infections; February 1-5, 1998; Chicago, Ill. Abstract 349.
63. Eron J, Walmsley S, Wathen L, et al. Sustained viral suppression with delavirdine and indinavir combination therapies. From: 6th Conference on Retroviruses and Opportunistic Infections; January 31–February 4, 1999; Chicago, Ill. Abstract 384.
64. Acosta EP, Gulick R, Katzenstein D, et al. Pharmacokinetic (PK) evaluation of saquinavir soft gel capsules (SQV)/ritonavir (RTV) or SQV/nelfinavir (NFV) in combination with delavirdine (DLV) and/or adefovir dip-

ivoxil (ADV)—ACTG 359. From: 6th Conference on Retroviruses and Opportunistic Infections; January 31–February 4, 1999; Chicago, Ill. Abstract 365.
65. Staszewski S, Keiser P, Gathe J, et al. Comparison of antiviral response with abacavir/combivir to indinavir/combivir in therapy-naïve adults at 48 weeks. From: 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; September 26-29, 1999; San Francisco, Calif. Abstract 505.
66. Murphy RL, Katlama C, Johnson V, et al. The Atlantic study. From: 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; September 26-29, 1999; San Francisco, Calif. Abstract LB-22.
67. Hirsch MS, Steigbigel R, Staszewski S, et al. A randomized, controlled trial of indinavir, zidovudine, and lamivudine in adults with advanced human immunodeficiency virus type 1 infection and prior antiretroviral therapy. *J Infect Dis*. 1999;180:659-665.
68. Fischl M, Greenberg S, Clumeck N, et al. Ziagen (Abacavir, ABC, 1592) combined with 3TC & ZDV is highly effective and durable through 48 weeks in HIV-1 infected antiretroviral-therapy-naive subjects (CNAA3003). From: 6th Conference on Retroviruses and Opportunistic Infections; January 31–February 4, 1999; Chicago, Ill. Abstract 19.
69. Staszewski S, Morales-Ramirez J, Tashima TK, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. *N Engl J Med*. 1999;341:1865-1873.
70. Manion DJ, Labriola DF, Ruiz NM. Efficacy of efavirenz (SUSTIVA) containing regimens in patients with baseline plasma HIV-RNA viral loads exceeding 100,000 copies/mL. From: 6th Conference on Retroviruses and Opportunistic Infections; January 31–February 4, 1999; Chicago, Ill. Abstract 383.
71. Montaner JSG, Reiss P, Cooper D, et al. Randomized, double-blind trial comparing combinations of nevirapine, didanosine, and zidovudine for HIV-infected patients. *JAMA*. 1998;279:930-937.
72. Katlama C, Murphy R, Johnson V, et al. The Atlantic study. From: 6th Conference on Retroviruses and Opportunistic Infections; January 31–February 4, 1999; Chicago, Ill. Abstract 18.
73. Cheeseman SH, Hattox SE, McLaughlin MM, et al. Pharmacokinetics of nevirapine. *Antimicrob Agents Chemother*. 1993;37:178-182.
74. Sargent S, Green S, Para M, et al. Sustained plasma viral burden reductions and CD4 increases in HIV-1 infected patients with RESCRIPTOR (DLV) + RETROVIR (ZDV) + EPIVIR (3TC). From: 5th Conference on Retroviruses and Opportunistic Infections; February 1-5, 1998; Chicago, Ill. Abstract 699.
75. Gulick RM, Mellors JW, Havlir D, et al. Simultaneous vs sequential initiation of therapy with indinavir, zidovudine, and lamivudine for HIV-1 infection. *JAMA*. 1998;280:35-41.
76. Saag M, Krowles M, Chang Y, et al. Durable effect of VIRACEPT (nelfinavir mesylate, NFV) in triple combination therapy. From: 37th Interscience Conference on Antimicrobial Agents and Chemotherapy; September 28–October 1, 1997; Toronto, Ontario. Abstract I-101.
77. Cameron DW, Heath-Chiozzi M, Danner S, et al. Randomized placebo-controlled trial of ritonavir in advanced HIV-1 disease. *Lancet*. 1998;315:543-549.
78. Murphy RL, De Gruttola V, Gulick RM, et al. Treatment with amprenavir alone or amprenavir with zidovudine and lamivudine in adults with human immunodeficiency virus infection. AIDS Clinical Trials Group 347 Study Team. *J Infect Dis*. 1999;179:808-816.
79. Paterson D, Swindells S, Mohr J, et al. How much adherence is enough? A prospective study of adherence to protease inhibitor therapy using MEMSCaps. From: 6th Conference on Retroviruses and Opportunistic Infections; January 31–February 4, 1999; Chicago, Ill. Abstract 92.
80. Hecht FM. Measuring HIV treatment adherence in clinical practice. *AIDS Clin Care*. 1998;10:57-59.
81. Brambilla D, Reichelderfer PS, Bremer JW, et. al. The contribution of assay variation and biological variation to the total variability of plasma HIV-1 RNA measurements. *AIDS*. 1999;13:2269-2279.
82. Kempf D, Rode R, Xu Y, et al. Duration of viral suppression during protease inhibitor therapy for HIV-1 infection is predicted by plasma HIV-1 RNA at the nadir. *AIDS*. 1998;12:F9-F14.
83. Raboud JM, Montaner JS, Conway B, et al. Suppression of plasma viral load below 20 copies/mL is required to achieve a long-term response to therapy. *AIDS*. 1998;12:1619-1624.
84. Demeter L, Hughes M, Fischl M, et al. Predictors of virologic and clinical responses to indinavir (IDV) + ZDV + 3TC or ZDV + 3TC. From: 5th Conference on Retroviruses and Opportunistic Infections; February 1-5, 1998; Chicago, Ill. Abstract 509.
85. Garraffo R, Durant J, Clevenbergh P. Relevance of protease inhibitor plasma levels in patients treated with genotypic adapted therapy [abstract]. *Antiviral Therapy*. 1999;4(suppl 1):75.
86. Hirsch MS, Conway B, D'Aquila RT, et al. Antiretroviral drug resistance testing in HIV infection of adults. *JAMA*. 1998;279:1984-1991.
87. Clevenbergh P, Durant J, Halfon P, et al. Persisting long-term benefit of antiretroviral genotypic guided treatment for HIV-infected patients failing HAART. *Antiviral Ther*. 1999;4(suppl 1):42.
88. Baxter JD, Mayers DL, Wentworth DN, et al. Final results of CPCRA 046. [abstract]. *Antiviral Ther*. 1999;4(suppl 1):43.
89. Call S, Westfall A, Cloud G, et al. Predictive value of HIV phenotypic susceptibility testing in a clinical cohort. From: 39th Interscience Conference on Antimicrobial Agents and Chemotherapy; September 26-29, 1999; San Francisco, Calif. Abstract LB-17.
90. Schuurman R, Demeter L, Reichelderfer P, et al. Worldwide evaluation of DNA sequencing approaches for identification of drug resistance mutations in the human immunodeficiency virus type 1 reverse transcriptase. *J Clin Microbiol*. 1999;37:2291-2296.
91. Ledergerber B, Egger M, Opravil M, et al. Clinical progression and virological failure on highly active antiretroviral therapy in HIV-1 patients. *Lancet*. 1999;353:863-868.
92. Deeks S, Barbour J, Swanson M, et al. Sustained CD4 T cell response after virologic failure of protease inhibitor based regimens. From: 6th Conference on Retroviruses and Opportunistic Infections; January 31–February 4, 1999; Chicago, Ill. Abstract 494.
93. Kaufmann D, Pantaleo G, Sudre P, et al. $CD4^+$ cell count in HIV-1 infected individuals remaining viraemic with highly active antiretroviral therapy (HAART). *Lancet*. 1998;351:723-724.
94. Havlir DV, Hellmann NS, Petropoulos CJ, et al. Drug susceptibility in HIV infection after viral rebound in patients receiving indinavir-containing regimens. *JAMA*. 2000;283:229-234.
95. Holder DJ, Condra JH, Schleif WA, et al. Virologic failure during combination therapy with CRIXIVAN and RT inhibitors is often associated with expression of resistance-associated mutations in RT only. From: 6th Conference on Retroviruses and Opportunistic Infections; January 31–February 4, 1999; Chicago, Ill. Abstract 492.
96. Descamps D, Peytavin G, Calvez V, et al. Virologic failure, resistance and plasma drug measurements in induction maintenance therapy trial (ANRS 072, Trilège). From: 6th Conference on Retroviruses and Opportunistic Infections; January 31–February 4, 1999; Chicago, Ill. Abstract 493.
97. Deeks SG, Hecht FM, Swanson M, et al. HIV RNA and CD4 cell count response to protease inhibitor therapy in an urban AIDS clinic. *AIDS*. 1999;13:F35-F43.
98. Phillips P, Kwiatkowski MB, Copland M, et al. Mycobacterial lymphadenitis associated with the initiation of combination antiretroviral therapy. *J Acquir Immune Defic Syndr Hum Retrovirol*. 20;1999:122-128.
99. Hengel RL, Watts NB, Lennox JL. Benign symmetric lipomatosis associated with protease inhibitors. *Lancet*. 1997;350:1596.
100. Lo JC, Mulligan K, Tai VW, et al. "Buffalo hump" in men with HIV-1 infection. *Lancet*. 1998;351:867-870.
101. Sullivan AK, Nelson MR. Marked hyperlipidaemia on ritonavir therapy. *AIDS*. 1997;11:938-939.
102. Ruiz L, Bonjoch A, Paredes R, et al. A multicenter, randomized, open-label, comparative trial of the clinical benefit of switching the protease inhibitor (PI) by nevirapine (NVP) in HAART-experienced patients suffering lipodystrophy (LD). From: 6th Conference on Retroviruses and Opportunistic Infections; January 31–February 4, 1999; Chicago, Ill. Abstract LB14.
103. Neumann AU, Tubiana R, Calvez V. HIV-1 rebound during interruption of highly active antiretroviral therapy has no deleterious effect on reinitiated treatment. *AIDS*. 1999;13:677-683.
104. Tebas P, Patick AK, Kane EM, et al. Virologic responses to a ritonavir-saquinavir-containing regimen in patients who have previously failed nelfinavir. *AIDS*. 1999;13:F23-F28.
105. Ait-Khaled M, Stone C, Mesogiti D, et al. Genotype and phenotype of HIV-1 in ART experienced adults prior and following therapy with Ziagen (Abacavir, ABC) added to stable background therapy (ABC + SBG). From: 6th Conference on Retroviruses and Opportunistic Infections; January 31–February 4, 1999; Chicago, Ill. Abstract 114.
106. Miller MD, Anton KE, Mulato AS, et al. Human immunodeficiency virus type 1 expressing the lamivudine-associated M184V mutation in reverse transcriptase shows increased susceptibility to adefovir and decreased replication capability in vitro. *J Infect Dis*. 1999;179:92-100.
107. Race E, Ferchal F, Dam E, et al. Selection of HIV-1 variants with wide cross-resistance to reverse transcriptase inhibitors during low-level escape to first-line dual nucleoside therapy [abstract]. *Antiviral Ther*. 1999;4(suppl 1):80.
108. Ross L, Danehower S, Johnson M, et al. Stavudine-based combination and monotherapy selects for zidovudine resistance HIV-1 mutations in zidovudine-naive adults and in paediatric patients. *Antiviral Ther*. 1999;4(suppl 1):79.
109. Coakley E, Gillis J, Hammer S. Phenotypic and genotypic resistance patterns of HIV-1 isolates derived from individuals treated with didanosine and stavudine in combination. *AIDS*. In press.
110. Miller V, Gute P, Carlebach A, et al. Baseline resistance and virological response to mega-HAART salvage therapies. From: 6th Conference on Retroviruses and Opportunistic Infections; January 31–February 4, 1999; Chicago, Ill. Abstract 130.
111. Montaner JS, Harrigan R, Jahnke N, et al. Multidrug rescue therapy (MDRT) for HIV-infected individuals with prior virologic failure to multiple regimens [abstract]. *Antiviral Ther*. 1998;3(suppl 5):80.
112. Miller V, Rottman C, Hertogs K. Mega-HAART, resistance and drug holidays. *Antiviral Ther*. In press.
113. Centers for Disease Control and Prevention. Public Health Service guidelines for the management of health-care worker exposure to HIV and recommendations for postexposure prophylaxis. *MMWR Morb Mortal Wkly Rep*. 1998;47(RR-7):1-33.

Printed and Published in the United States of America