Issues in Antiretroviral Therapy in 1998

At the Los Angeles course in February, Paul A. Volberding, MD, discussed current strategies for the use of antiretroviral drugs for the treatment of HIV infection, as well as the rationale underlying these strategies. Dr Volberding emphasized that although dramatic changes in treatment strategies have not occurred in the last year, increased experience with combination antiretroviral therapy has yielded practical knowledge about virologic responses and drug failures, immunologic responses and nonresponses, and the consequences of medication adherence and nonadherence.

The overall goal of antiretroviral therapy remains largely unchanged in 1998 from that in 1997. Potent antiretroviral regimens are used to effect sustained maximal suppression of HIV replication. Such suppression is considered important to prevent the emergence of drug-resistant viral variants and to allow the recovery of immune function. While the goal of antiretroviral therapy has remained straightforward, the clinical management of HIV-infected patients has become more complex as an increasing number of drug combinations are evaluated and found potent. In addition, identifying practical strategies for attaining durable virologic responses and defining and managing treatment failure remain significant challenges.

General Issues

Accumulating data continue to support treatment strategies, such as the early initiation of potent antiretroviral therapy. It is critical to choose the drugs used in initial therapy carefully, and newer studies are broadening the available options (Table 1). Considerations for the selection of a particular regimen include potency, tolerability, convenience, potential side effects, and the available therapeutic options should the initial regimen fail. Potent antiretroviral regimens are defined as those that achieve sustained maximal viral suppression. However, there is no clear consensus on the relative potencies of the numerous available regimens, and long-term, comparative clinical trial data are needed.

As noted, tolerance and convenience of the drugs and drug regimens are two considerations that are essential for the long-term success of antiretroviral therapy. Because tolerability and convenience vary by drug as well as from patient to patient, the clinician's role has expanded to include assisting patients to identify daily living strategies that can best support long-term medication adherence. Preliminary data suggest that patients who understand the rationale for adherence and the consequences of nonadherence are more likely to remain committed to their prescribed regimen (ie, with regard to dosing schedules and food restrictions). The possible consequences of nonadherence include emergence of drug-resistant viral variants, including cross-resistant and multi-drug-resistant virus strains, as well as transmission of drug-resistant viruses. Already, several cases of patients newly infected with HIV that is resistant to multiple antiretroviral agents have been reported.

Table 1. Examples of Potent Antiretroviral Regimens in Clinical Use or Under Investigation

- **nRTI + nRTI + PI**
- **nRTI + nRTI + NNRTI**
- **nRTI + nRTI + PI + PI**
- **PI + PI**
- **NNRTI + PI**
- **nRTI + nRTI + nRTI**
- **nRTI + hydroxyurea + PI**

nRTI indicates nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Short-term as well as long-term adverse effects of the drugs must be considered in the choice of the initial regimen. There is a growing body of information about the long-term metabolic sequelae of antiretroviral therapy, particularly with the use of protease inhibitors. These include abnormal fat distribution, glucose intolerance, and hyperlipidemias. The natural history, frequency, and clinical impact of these changes are still being elucidated, and concern about these complications do affect treatment decisions.

Data published in the past year show that, contrary to initial hopes, eradication of HIV in patients with established HIV infection is unlikely with the currently available drugs even after 2 to 3 years of potent therapy. Thus, it is crucial to ensure that patients are fully prepared to commit to the possibly life-long and complex therapeutic regimens before therapy is initiated. In fact, the optimum time to begin treatment may be more determined by the patient's ability to commit to long-term medication than by an arbitrary CD4+ cell or plasma HIV RNA threshold. The surprising degree of immune recovery following antiretroviral therapy may allow for a period of safe deferral of treatment. During this interval, treatment options can be carefully weighed against better knowledge of the patient's motivation and lifestyle.

When selecting an initial antiretroviral regimen, it is important to anticipate incomplete suppression or eventual virologic failure. The initial treatment strategy should take into account the resistance profiles of the currently available drugs to leave one or more subsequent therapeutic

options available. Ongoing clinical trials are providing sobering information on cross-resistance, particularly among the protease inhibitors and nonnucleoside reverse transcriptase inhibitors (NNRTIs).

Recent Preliminary Findings on Antiretroviral Therapy

Data relating to the virologic and immunologic effects of potent antiretroviral therapy are accumulating, and can be used to guide the use of antiretroviral treatment. New data are particularly encouraging regarding the role of the NNRTIs as components of potent regimens.

Predicting Virologic Responses

Data from the ACTG 320 study, reported by Hammer and colleagues, indicate that the virologic response at weeks 4 or 8 to the triple-drug regimen indinavir/zidovudine (or stavudine)/lamivudine is predictive of the virologic response at 6 months. Among the patients who had not achieved plasma HIV RNA levels below the assay detection limit (500 copies/mL in this study) by week 4 or 8, only 31% had a virologic response at 6 months. Conversely, of those patients who had plasma HIV RNA levels below 500 copies/mL at both weeks 4 and 8, 85% had plasma HIV RNA levels below 500 copies/mL at 6 months.

Definitive recommendations cannot be made based on these limited data, but they may provide some direction. For example, Dr Volberding suggested that if a patient has low but still detectable (>500 copies/mL) levels of plasma HIV RNA 8 weeks after starting therapy, it may be reasonable to attempt to intensify the regimen by adding another drug, especially if that patient is tolerating the initial regimen. Some clinicians may be inclined to change the entire regimen in such a scenario. At present, either approach seems more appropriate than waiting until the patient's viral load rebounds toward baseline levels. It should be noted, however, that an addition of a drug to the regimen must be made before the plasma HIV RNA level begins to rebound, because the addition of a single drug in the setting of virologic failure would be considered the equivalent of sequential monotherapy.

The correlation between magnitude of plasma viral load reduction and the duration of virologic response was assessed in the INCAS trial (which evaluated zidovudine/didanosine/nevirapine) and in the AVANTI 3 trial (which evaluated zidovudine/lamivudine/nelfinavir). Patients in whom plasma HIV RNA levels were below 500 copies/mL, but not below the detection limit of more sensitive assays (ie, <20-50 copies/mL), had shorter durations of virologic response than patients who had plasma HIV RNA levels that were reduced to below the 20 to 50 copies/mL threshold. In the AVANTI 3 trial, no durable responses occurred in patients who had plasma HIV RNA levels below 500 but greater than 50 copies/mL. Together, these findings suggest that the more sensitive plasma HIV RNA assays have clinical value for assessing the response to antiretroviral therapy. However, with the more sensitive assays, it may take longer (16 weeks or more in some trials) to reach a nadir or virus level below the detection limit after initiating therapy, depending on the patient's pretreatment plasma viral load.

The CD4+ cell count remains an important independent predictor of prognosis in HIV infection and cannot be replaced in patient management. Recent data from the Merck 028 study underscore the point that CD4+ counts are a more direct predictor of clinical progression risk than plasma viral load. Investigators assessed the last known CD4+ count plotted against the last known viral RNA measurement among treated subjects and distinguished between those who did or did not experience an opportunistic illness or death. Patients who had clinical events had a wide range of plasma viral loads, but almost all had CD4+ counts below 300 cells/μL, and most of these were below 100 cells/μL.

Predicting Virologic Failures

Growing experience with potent antiretroviral combinations is beginning to reveal factors that are predictive of treatment failure. One of the strongest predictors of virologic failure is nonadherence, and the best marker of nonadherence is patient self-reporting of this when questioned. Virologic failures due to nonadherence (assuming the patient is taking at least a substantial portion of prescribed doses) are usually due to the selection of drug-resistant viral variants. Ample evidence now exists supporting the hypothesis that incomplete suppression of HIV replication, as predicted with frequent missed drug doses, creates an environment that favors the emergence of drug-resistant viral variants. Other factors identified as independent predictors of virologic failure in patients with established infection include very high pretreatment plasma viral loads (eg, >50,000 copies/mL), very low pretreatment CD4+ counts (eg, <100 cells/μL), and the addition of a single drug to an existing failing drug regimen.

The CD4+ cell count remains an important independent predictor of prognosis.

Virologic failure and virologic rebound signal the need for replacing several and possibly all of the drugs in a patient's existing antiretroviral regimen. The specific drugs to be added or replaced depend on the individual clinical situation, including the patient's previous treatment history, as well as past and current plasma viral load, CD4+ cell count, and clinical status. Other important considerations include what the patient can tolerate and whether the patient is chronically nonadherent. Drug resistance or susceptibility assays (genotype or phenotype) may well add information although the role of this information for treatment decisions remains an important research question.

Virology and Treatment Decisions

The potential role of viral genotype data in clinical management is receiving increased attention. The presence of some specific resistance mutations does not necessarily predict or correspond with treatment failure. Much more in vivo re-

sistance data, especially with regard to the protease inhibitors, are needed before it becomes possible to understand which mutations actually confer resistance, which are natural polymorphisms, and which are compensatory or insignificant mutations. The issues surrounding the interpretation and use of viral genotyping are complex and confusing (see Hirsch et al. *JAMA*. 1998).

Technologic development of viral phenotyping assays for clinical isolates, including automation of these assays, may make virologic phenotyping more integral to the design of antiretroviral therapy regimens in the future. Dr Volberding noted that one assay in development may be able to provide results in 8 to 10 days, compared with the current 4 to 8 week turnaround time for phenotyping test results.

It is difficult to compare different dual protease inhibitor regimens because of the differences in patient populations in the different trials.

Phenotype data may be more easily interpreted by the clinician than genotype data. As recently described by Mellors, a phenotypic assay was used to determine the probability that a clinical isolate known to be at least 10-fold less susceptible to one protease inhibitor will be at least 4-fold less susceptible to all other approved drugs in this class.

Dual Protease Inhibitor Therapy

In an attempt to identify more-potent antiretroviral regimens using currently available drugs, several dual protease inhibitor combinations are being investigated.

In most cases, dual protease inhibitor combinations achieve high potency by one protease inhibitor positively influencing the pharmacokinetics of the second protease inhibitor (Table 2). Ritonavir/saquinavir is the best-studied combination at this time. Ritonavir is a strong inhibitor of the cytochrome P450 system and it raises the plasma drug concentration of saquinavir by about 20-fold when the two drugs are combined, which significantly increases the potency of saquinavir. There are insufficient data to identify which dual protease inhibitor combinations are superior in potency, tolerability, and durability of response. Dr Volberding noted that it is difficult to compare different combinations based on current data because of differences in the study populations as well as in the regimens used. For example, ritonavir/saquinavir trials actually involve regimens of these two drugs plus NNRTIs. Furthermore, completed or ongoing clinical trials evaluating dual protease inhibitor therapy for individual patients often have drugs added or changes made to the regimens throughout the course of the studies.

One question at this time is whether it is best to combine protease inhibitors that have similar resistance mutation patterns or those that have dissimilar resistance mutation patterns. It could be argued that the combination of ritonavir/indinavir, 2 drugs with numerous overlapping mutations, may provide potency while preserving future salvage therapy options. The opposite argument, using 2 protease inhibitors with a low frequency of overlapping mutations, such as nelfinavir/indinavir, may provide more sustained viral suppression given a broader genetic resistance profile. Clearly, long-term and comparative data from large studies are needed to answer this question.

Management of Protease Inhibitor Failure

At present, the potential for success of salvage therapy after a protease inhibitor-containing therapy fails is not very encouraging, and few large trials comparing different salvage regimens have yet been completed. However, there are some data to suggest that dual protease inhibitor therapy as an element of salvage therapy may be acceptable, or at least better than continuing with a failing regimen or discontinuing all therapies. A small trial evaluated stavudine/lamivudine/ritonavir/saquinavir as salvage therapy for zidovudine/lamivudine/nelfinavir failure in 26 patients who had received nelfinavir for a mean duration of 55 weeks. After 6 months of the 4-drug regimen, 68% of patients had plasma HIV RNA levels below 500 copies/mL, and 40% had below 50 copies/mL. Although these are short-term results, they suggest that ritonavir/saquinavir may be a potentially viable salvage strategy for patients heavily pretreated with nelfinavir. Longer-term data and additional studies evaluating various salvage regimens for patients in whom

Table 2. Dual Protease Inhibitor Combinations Under Investigation

Dual Protease Inhibitor Regimen	Primary Pharmacokinetic Effect
Ritonavir/saquinavir	↑ saquinavir concentration (20-fold)
Ritonavir/indinavir	↑ indinavir concentration (5-fold)
Indinavir/nelfinavir	↑ nelfinavir concentration (1.8-fold)
Nelfinavir/saquinavir	↑ saquinavir concentration (5-fold)
Ritonavir/ABT-378*	↑ ABT-378* concentration (200-fold)

* Investigational protease inhibitor

different initial protease inhibitor therapies have failed are needed.

Twice Daily Regimens for Protease Inhibitors

Medication adherence is directly related to the convenience of the antiretroviral regimen. Twice-daily-dosing schedules are easier to follow and more convenient than thrice-daily-dosing schedules. As such, lower-frequency schedules are expected to facilitate adherence.

The thrice-daily-dosing schedules for 3 of the 4 currently approved protease inhibitors were determined based on pharmacokinetics, or specifically, the peak and trough plasma concentrations and time to peak concentrations of each drug. Preliminary data indicate that higher doses of indinavir or nelfinavir, each taken on a twice-daily-dosing schedule, may result in similar or higher proportions of patients with plasma viral loads that decrease to below assay detection limits, compared with those achieved by the standard dose on a three-times-daily schedule. An obvious question that arises is whether the more convenient dosing schedule plays a role in these improved responses. However, it is also not yet known whether the higher doses of these drugs will result in a higher risk (for some) of adverse effects.

Induction-Maintenance Regimens

The strategy of starting with an aggressive regimen (termed "induction") and following up with a less intense regimen (termed "maintenance") is attractive for several obvious reasons. However, initial trial data are not supportive at this time. In the ACTG 343 study, patients began a 3-drug regimen of zidovudine/lamivudine/indinavir; patients in whom plasma HIV RNA levels were below the assay detection limits at 6 months were asked to participate in a randomization in which they would either continue on their regimen, receive indinavir monotherapy, or receive zidovudine/lamivudine. Patients had plasma HIV RNA levels below the detection limit at 6 months and most elected to participate in the randomization. Patients who received indinavir monotherapy or zidovudine/lamivudine experienced rapid viral rebound. Another trial, conducted by Raffi and colleagues in France, showed similar results with a different 2-drug maintenance regimen. The ADAM study was recently reported in which maintenance including a dual protease also failed rapidly.

> *Twice-daily-dosing schedules are easier to follow and more convenient than thrice-daily-dosing schedules and are expected to facilitate adherence.*

When some of the extremely aggressive, 5- or 6-drug regimens are used as induction for established infection, it may still be possible to retreat to a potent 3-drug regimen. The underlying rationale for such a strategy is that patients may not tolerate these extremely aggressive regimens very well or for very long. A Dutch study of an aggressive regimen for patients with advanced HIV disease, reported at the 5th Retrovirus Conference in Chicago, cited 40% of patients withdrawing from the study because of intolerability of the medications.

Summary

As in 1997, the current strategies for antiretroviral therapy are based on preventing or delaying viral resistance to the drug, which is believed necessary to delay virologic rebound. Indeed, the "hit hard, hit early" maxim is rooted in the belief that maximal suppression of HIV for as long as possible creates the least favorable environment for drug-resistant viral variants to emerge and propagate. Initiation or intensification of antiretroviral therapy requires a scientifically sound strategy, one that takes into account the potential for cross-resistance among the reverse transcriptase inhibitors or among the protease inhibitors.

Maximal and sustained suppression of virus is the primary goal of treating HIV infection; however, it is important to consider future therapeutic options for patients in whom the virologic response wanes with the initial potent regimen. Accumulating data suggest that in some situations it is possible to provide effective alternative regimens for patients in whom potent protease inhibitor-containing regimens have failed. Increased experience with potent antiretroviral regimens and with the patients taking them has created an evolving knowledge base about the various combinations of drugs, including such critical information as predictors of virologic response or failure.

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Suggested Readings

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Deeks SG, Grant RM, Beatty G, Horton C, Detmer J, Eastman S. Activity of a ritonavir plus saquinavir-containing regimen in patients with virologic evidence of indinavir or ritonavir failure. *AIDS*. 1998;12:F97-F102.

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Suggested Readings (continued)

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Reijers MME, Weverling GJ, Ten Kate RW, Frissen PMJ, De Wolf F, Scmuitemaker M, Lange JMA. ADAM study: Induction-maintenance therapy in HIV-1 infection: Early results. Presented: 12th World AIDS Conference; June 28-July 3, 1998; Geneva, Switzerland.

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