Strategies for Continuing Antiretroviral Therapy

Strategies for continuing antiretroviral therapy were discussed at the New York courses by Michael S. Saag, MD, from the University of Alabama at Birmingham, and Daniel R. Kuritzkes, MD, from the University of Colorado Health Sciences Center in Denver.

Effective strategies for continuing the benefits of treatment currently rely on the appropriate use of the growing number of available antiretroviral drugs and on the availability of plasma HIV RNA assays to follow patient response to treatment, as noted by both Dr Saag and Dr Kuritzkes. Overall, the goal of antiretroviral therapy is to keep viral load as low as possible for as long as possible (see Table 1). The majority of patients will not remain on their initial antiretroviral treatment for extended periods of time. Plasma HIV RNA assays provide a means for following the effect of treatment on viral load and are becoming routinely used in clinical practice along with measuring CD4+ cell counts for evaluating the response to therapy and identifying failure of the initial regimen. Drs Saag and Kuritzkes both focused their talks on nucleoside drugs and combinations, and noted that for many patients, the additional use of a protease inhibitor for these subsequent regimens would be appropriate. (For a review of protease inhibitors, see the April 1996 issue of *Improving the Management of HIV Disease.*)

Treatment Failure

Antiretroviral failure can be defined as drug intolerance or toxic effects that warrant discontinuation of therapy or as loss of antiretroviral effect. The return of plasma HIV RNA levels toward pretreatment values (whether pretreatment or values at the time of last treatment alteration) is considered to be an indication of the loss of antiretroviral effect. Factors involved in the loss of antiretroviral effect include incomplete suppression of HIV, emergence of drug-resistant variants, emergence of syncytium-inducing variants, and progressive immunologic decline. Incomplete viral suppression has been characteristic of prior widely used antiretroviral regimens. With the employment of new drugs and combinations, viral load can often be reduced, at least over the short term, to undetectable (ie, below the detection limits of the assay used [usually 200 to 500 copies/mL]) or to nearly undetectable levels. However, residual low-level viremia may persist even when maximal drug activity is achieved. Such incomplete viral suppression may be associated with persistent reservoirs of virus within chronically-infected, virus-producing cells (eg, macrophages) by incomplete penetration of drug into tissue compartments, or by changes in intracellular metabolism, resulting in reduced active drug levels.

Therapy should be changed at the first sign of treatment failure, such as clinical progression (new or recurrent opportunistic infections, persistent or worsening symptoms, or wasting syndrome), continuous CD4+ cell count decline, or an increase in plasma HIV RNA levels toward (or within 0.3 to 0.5 log of) baseline. While clinical progression should be taken as an indication of treatment failure, use of viral markers allows changing "ineffective" treatment before the lack of efficacy results in a clinical event. There are still many patients who are being given zidovudine monotherapy, and there is now a wealth of data that indicate that this is not an optimal regimen. All patients on zidovudine monotherapy should be reevaluated as to whether their treatment needs to be changed.

Table 1. Guiding Principles of Antiretroviral Therapy.

- Maximum suppression of HIV replication should be the goal of therapy
- Suppression must be continuous to maximize the benefits of therapy
- Treatment regimens will need to change in response to emergence of drug resistance
- Antiretroviral therapy alone may not be sufficient for immune restoration, particularly in patients with advanced disease

Viral Load Thresholds in Treatment

Given the intraassay and biologic variance of the plasma HIV RNA assays defined in clinical studies, the minimum decrease in viral burden indicating an antiretroviral effect is 0.5-log (or 3-fold) decrease. With regard to optimum decrease in viral burden, the goal of both initial treatment and subsequent alterations in treatment should be a reduction of viral load to at least 5,000 to 10,000 HIV RNA copies/mL, if achievable. The confirmed return to (ie, from 2 measurements) of plasma HIV RNA levels to within 0.3 log to 0.5 log of the pretreatment value is indicative of treatment failure. The return of CD4+ cell counts or CD4+ percentage to the pretreatment count also suggests an alteration in therapy is needed.

Factors in Changing Treatment

Factors to be considered when changing treatment because of antiretroviral failure include (1) the current regimen; (2) type of failure—ie, whether failure due to toxic effects or to loss of antiretroviral effect; (3) previous therapy—ie, whether resistance patterns resulting from prior use of a drug may still persist; (4) stage of underlying disease; (5) concomitant medications, to avoid or minimize potential adverse drug interactions; (6) availability of/access to drugs; (7) cost of drugs; and (8) philosophy of the treating physician and the patient (ie, how aggressive does the physician or patient want to be). Desirable characteristics of the new regimens include (1) greater potency; (2) different mechanism of action; (3) absence of cross-resistance or the reversal of resistance (eg, in the case of lamivudine and zidovudine); and (4) minimal drug interactions.

Nucleoside Reverse Transcriptase Inhibitors in Continuing Therapy

The potent protease inhibitors may eventually be included in virtually all antiretroviral regimens. In this "new" era of treatment (ie, in which there are a range of potent drugs to choose from and in which therapy can be tailored using viral markers), nucleoside reverse transcriptase inhibitors will continue to have an important role alone or in combination with other drugs. Recent trials have demonstrated the efficacy of the nucleoside drugs in continuing therapy. In addition, when protease inhibitors are used alone the development of resistance ultimately limits their usefulness in this regard. Finally, it has been found that the proportion of patients rendered "aviremic" (ie, with viral loads that have fallen below assay detection limits) is maximized with combinations of protease inhibitors and nucleoside analogues.

Clinical Trials Including Antiretroviral-experienced Patients

In AIDS Clinical Trials Group (ACTG) Study 175, patients with CD4+ cell counts between 200/μL and 500/μL (median, 350/μL) and without AIDS were randomized to zidovudine alone, zidovudine plus didanosine, zidovudine plus zalcitabine, or didanosine alone. Study endpoints consisted of a 50% decrease in CD4+ cell count, AIDS-related opportunistic infection or cancer, death, and grades 3 or 4 toxic effects. The data on antiretroviral-naive patients were discussed in the previous issue of this publication (See *Improving the Management of HIV Disease*, 1996;4[1]:4–6). In the zidovudine-experienced population of the study, patients who continued on zidovudine monotherapy exhibited a loss of CD4+ cells from the start of study treatment, whereas those in the three remaining groups experienced an initial increase. Those who were given zidovudine/didanosine showed a particularly marked increase in CD4+ cell counts, with the mean level approaching the pretreatment level only by week 48. In the zidovudine-experienced population, patients who were given zidovudine/didanosine or didanosine monotherapy had significantly lower rates of progression to all three endpoints compared with those who were given zidovudine alone. The zidovudine/zalcitabine arm had a significantly lower rate only for progression to the CD4+ cell count/death aggregate endpoint.

The European/Australian Delta study was similar in design to ACTG 175 except that the patients studied had somewhat more advanced disease and no didanosine monotherapy arm was included in the trial. Patients with AIDS-related complex (ARC) or AIDS and CD4+ cell counts greater than 50/μL and patients with asymptomatic disease and CD4+ cell counts less than 350/μL were randomized to continued zidovudine monotherapy, zidovudine/didanosine or zidovudine/zalcitabine. In Delta 2, the portion of the study in zidovudine-experienced patients, 50% of patients were asymptomatic and 17% had AIDS; the median CD4+ cell count was 189/μL. In the final Delta 2 study analysis, clinical progression, defined as a new AIDS-defining event or death, occurred in 44% of zidovudine monotherapy recipients, 39% of zidovudine/didanosine recipients, and 43% of zidovudine/zalcitabine recipients. Death occurred in 27% of zidovudine alone recipients, 23% of zidovudine/didanosine recipients, and 26% of zidovudine/zalcitabine recipients. An interim analysis had indicated that there were no differences among the treatment groups with regard to progression in the zidovudine-experienced patients; however, final analysis indicated a significant reduction in the rate of clinical progression in patients who were given zidovudine/didanosine, but not in those given zidovudine/zalcitabine.

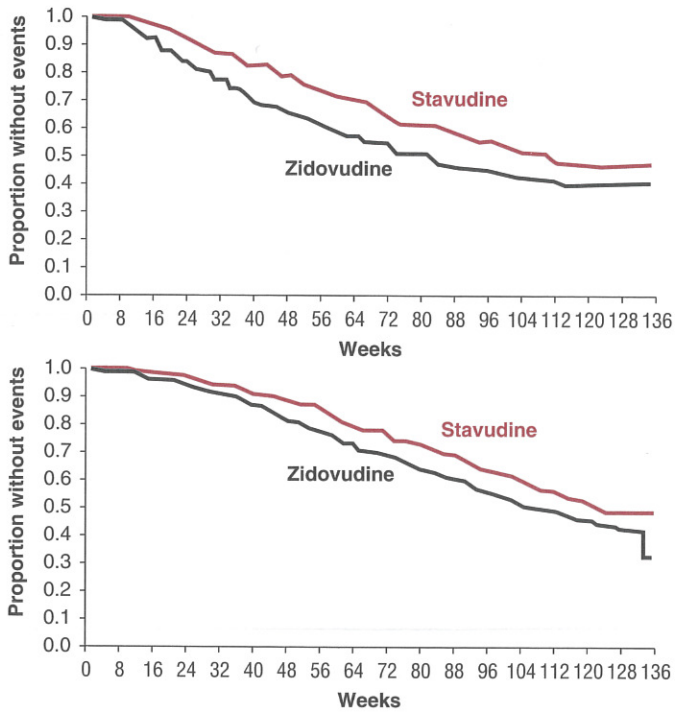

*Figure 1. Time to treatment failure **(top)** and time to clinical progression **(bottom)** in patients enrolled in Bristol-Myers Squibb (BMS) Study 019. Adapted from Bristol-Myers Squibb Co.* Stavudine (Zerit), Also Known as d4T: Final Results of the Study BMS-019 Phase III Comparative Trial. *1995.*

In the Community Programs for Clinical Research on AIDS (CPCRA) 007 NuCombo trial, patients with CD4+ cell counts less than 200/μL (median 92/μL), 75% of whom had received prior zidovudine therapy, were randomized (partially double-blind) to zidovudine, zidovudine/didanosine, or zidovudine/zalcitabine. Results showed superior CD4+ cell count changes in the zidovudine-experienced patients in the two combination therapy groups, but no significant differences in the rate of clinical progression or mortality. Given the advanced disease of patients in this trial and the substantial time spent on zidovudine prior to the study, zidovudine likely had little effect in the combination regimens, which were thus tantamount to didanosine or zalcitabine monotherapy. These three trials indicate a gradient of effect of nucleoside combinations in zidovudine-experienced patients: (1) a marked effect in patients with relatively early disease; (2) some effect, particularly on the part of zidovudine/didanosine in those patients with somewhat more advanced disease; and (3) little effect in those with even more advanced disease. These results argue for the earlier introduction of combination therapy. The effects of the protease inhibitors have been most notable in these latter patient groups.

Stavudine monotherapy is another regimen that has been studied in zidovudine-experienced patients. In Bristol-Myers

Table 2. Possible Nucleoside Regimens for Continuing Antiretroviral Therapy.*

Choices in zidovudine-intolerant patients

- Didanosine monotherapy
- Stavudine monotherapy
- Didanosine/stavudine?
- Didanosine/lamivudine?
- Stavudine/lamivudine?

Combination therapies

Useful combinations
- Zidovudine/didanosine
- Zidovudine/lamivudine
- Zidovudine/zalcitabine†
  (†in zidovudine-naive patients only)

Possible combinations
- Stavudine/didanosine
- Zidovudine/didanosine/nevirapine
- Zidovudine/delavirdine

Unknown combinations
- Zidovudine/stavudine
- Stavudine/lamivudine
- Lamivudine/didanosine

Combinations to avoid
- Stavudine/zalcitabine
- Didanosine/zalcitabine

*For many patients, nucleoside regimens will be used in combination with protease inhibitors.

Squibb (BMS) study 019, patients with CD4+ cell counts between 50/μL and 500/μL who had been given more than 6 months of prior zidovudine therapy were randomized to continued zidovudine or stavudine. The CD4+ cell counts in the stavudine group remained above the pretreatment level for more than 20 weeks, compared with less than 4 weeks in the zidovudine group; a persistent significant difference in the rate of treatment failure was observed in favor of stavudine (Figure 1[top]). A difference in the rate of clinical progression was noted also in favor of stavudine (Figure 1[bottom]). However, there was no difference between the two groups with regard to survival. Stavudine is associated with peripheral neuropathy; in this study, most of the cases were observed in the second year of treatment, with the incidence in stavudine patients becoming significantly greater than that in the zidovudine patients at this time. Although recent data on the combination of stavudine and didanosine (also associated with peripheral neuropathy) have yielded encouraging results with regard to limited neuropathy, these data have not included longer term follow-ups. Moreover, this combination regimen was studied in a relatively healthy population.

Another nucleoside combination that is generating much enthusiasm is zidovudine/lamivudine, in part because of the combination's potential benefit of reversing zidovudine resistance. In NUCA 3002, an evaluation of the lamivudine-zidovudine combination in patients with advanced disease, zidovudine-experienced patients with CD4+ cell counts between 100/μL and 300/μL were randomized to zidovudine plus either lamivudine 150 mg bid or lamivudine 300 mg bid or zidovudine plus zalcitabine. The peak median decreases in plasma HIV RNA levels were 0.7 log (approximately 5-fold) with the addition of zalcitabine and 1.5 log with either of the lamivudine dosages. Differences in plasma HIV RNA reduction disappeared as resistance to lamivudine emerged; with all three regimens, plasma HIV RNA levels remained below baseline for at least 48 weeks. It is of interest that whereas both lamivudine regimens resulted in marked increases in mean CD4+ cell counts, no increase was observed in the zidovudine/zalcitabine recipients. Results from ACTG 175, the Delta 2 study, and the NUCA trial all indicate that the addition of zalcitabine to zidovudine in zidovudine-experienced patients does not appear to produce the same benefit as addition of other drugs (eg, didanosine or lamivudine), and that this phenomenon may warrant closer examination.

The role of nonnucleoside reverse transcriptase inhibitors (NNRTIs) remains unclear. **(See Note, End of Text.)** Nevirapine is associated with a prompt and dramatic reduction in viral load that is rapidly reversed in up to 80% of recipients, in association with the onset of high-level resistance. However, a significant proportion (20% to 30%) of patients exhibit a persistent response despite the development of nevirapine resistance. A recent ACTG study (protocol 260) showed that delavirdine resistance resulted in loss of activity by 4 to 8 weeks even at very high doses. Other studies have shown that delavirdine resistance is somewhat delayed when the drug is used in combination with zidovudine, but not when combined with didanosine.

The NNRTIs will likely be used in combination with nucleoside analogues. Until drug interaction studies are completed, the use of these drugs in combination with protease inhibitors should be avoided. In ACTG 241, patients who had been on zidovudine or didanosine for 25 months and who had a median CD4+ cell count of 130/μL were given either zidovudine/didanosine or the triple combination of zidovudine, didanosine, and nevirapine. At week 48, the three-drug combination was associated with a 25% greater increase in CD4+ cell count and a 50% greater decrease in viral infectivity (on quantitative microculture) and in plasma HIV RNA levels than was the two-drug combination.

Other Potential Combinations

There has been significant concern about potential antagonism of zidovudine and stavudine given that these drugs compete for the same enzyme for intracellular phosphorylation. A recent in vitro study, however, has indicated that the two drugs are synergistic against zidovudine-susceptible virus; however, the combination was antagonistic when tested against zidovudine-resistant virus. This combination is currently being evaluated in two clinical trials.

Lamivudine and stavudine is an attractive, promising combination because it might avoid the gastrointestinal intolerance associated with didanosine and zidovudine and the hematologic toxic effects associated with zidovudine. In vitro studies have indicated synergy of the combination, and there is no known ad-

verse or favorable interaction of resistance mutations. An important issue is whether this combination provides the same durability of effect as does lamivudine/zidovudine. Lamivudine/ stavudine is currently being evaluated in an ACTG trial, and firmer data on how it compares with the lamivudine/zidovudine are expected before the end of the year.

Individualizing Therapy

The availability of the new assays for plasma HIV RNA permits truly individualized therapy. The choice of a replacement regimen will be guided by sequential viral load measurements, replacing reliance on group data from clinical trials. The clinical trial setting is artificial in that there are prescribed criteria for entry, treatment, and management that often do not coincide with how a patient would be managed in the clinical setting. Perhaps more important is that intent-to-treat analyses of efficacy, commonly employed in clinical trials, obscure individual treatment responses. A patient may demonstrate an antiviral effect (as measured by viral markers) for only 2 weeks of treatment with a regimen, and yet analysis at, for example, 2 years includes that patient as though he or she had been responding to the study regimen for the entire treatment duration. Group results thus include good responders and poor responders without differentiating between them. Use of the viral markers currently available provide an opportunity to tailor treatment to the individual patient.

Current Options

Table 2 shows proposed options for continuing antiretroviral therapy. The nucleoside analogue combinations that have the most clinical trial experience are zidovudine/didanosine, zidovudine/zalcitabine, and zidovudine/lamivudine. Ongoing studies will define the activities of lamivudine/didanosine, lamivudine/stavudine, and didanosine/stavudine.

NOTE: Preliminary data presented to the FDA in June suggest the suppression of plasma HIV RNA to levels below detection was achieved in the majority of previously untreated patients who received the combination of zidovudine/didanosine/nevirapine.

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Suggested Readings

Abrams DI, Goldman AI, Launer C, et al. A comparative trial of didanosine or zalcitabine after treatment with zidovudine in patients with human immunodeficiency virus infection. *N Engl J Med.* 1994;330:657–662.

Collier AC, Coombs RW, Schoenfeld DA, et al. Treatment of human immunodeficiency virus infection with saquinavir, zidovudine, and zalcitabine. *N Engl J Med.* 1996;334:1011–1017.

Danner SA, Carr A, Leonard JM, et al. A short-term study of the safety, pharmacokinetics, and efficacy of ritonavir, an inhibitor of HIV-1 protease. *N Engl J Med.* 1995;333:1528–1533.

Eron JJ, Benoit SL, Jemsek J, et al. Treatment with lamivudine, zidovudine, or both in HIV-positive patients with 200 to 500 CD4+ cells per cubic millimeter. *N Engl J Med.* 1995;333:1662–1669.

Fischl MA, Stanley K, Collier AC, et al. Combination and monotherapy with zidovudine and zalcitabine in patients with advanced disease. *Ann Intern Med.* 1995;122:24–32.

Havlir D, Cheeseman SH, McLaughlin M, et al. High-dose nevirapine: safety, pharmacokinetics, and antiviral effect in patients with human immunodeficiency virus infection. *J Infect Dis.* 1995;171:537–545.

Mellors JW, Rinaldo CR Jr, Gupta P, White RM, Todd JA, Kingsley LA. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. *Science.* 1996;272:1167-1170.

Montaner JSG, Schechter MT, Rachlis A, et al. Didanosine compared with continued zidovudine therapy for HIV-infected patients with 200 to 500 CD4 cells/mm^3. A double-blind, randomized, controlled trial. *Ann Intern Med.* 1995;123:561-571.

O'Brien WA, Hartigan PM, Martin D, et al. Changes in plasma HIV-1 RNA and CD4+ lymphocyte counts and the risk of progression to AIDS. *N Engl J Med.* 1996;334:426–431.

Pavia AT, Gathe J, BMS-019 Study Group Investigators, et al. Clinical efficacy of stavudine (d4T, Zerit) compared to zidovudine (ZDV, Retrovir) in ZDV-pretreated HIV positive patients. Presented at Thirty-fifth Interscience Conference on Antimicrobial Agents and Chemotherapy; September 17–20, 1995; San Francisco, Calif.

Yeni P, on behalf of the International Coordinating Committee. Preliminary results of the European/Australian Delta trial: Based on data up to 31st May 1995. Presented at Fifth European Conference on Clinical Aspects and Treatment of HIV Infection; September 1995; Copenhagen, Denmark.