Initiation of Antiretroviral Therapy

Initiation of antiretroviral therapy was discussed at the Los Angeles conference by Paul A. Volberding, MD, from the University of California San Francisco.

Recent studies have contributed to a growing consensus on when to initiate antiretroviral therapy, although many issues persist. Findings from the AIDS Clinical Trials Group (ACTG) protocol 175 and the Delta trials indicate that antiretroviral therapy should be initiated in asymptomatic patients with CD4+ cell counts less than 500/µL. Data from these and other studies also suggest that even earlier treatment may be warranted in patients with high plasma HIV RNA titers or with rapidly declining CD4+ cell counts. With the growing list of antiretroviral drugs available for use, it is less clear what constitutes optimal therapy. However, there is a healthy consensus that initial therapy should consist of combinations of drugs.

ACTG 175

In ACTG 175, 2467 patients with CD4+ cell counts of 200/µL to 500/µL were randomized to zidovudine, didanosine, zidovudine/didanosine, or zidovudine/zalcitabine. Overall, 82% of patients were asymptomatic, 40% had received no prior zidovudine therapy, and the median CD4+ cell count was 352/µL. Dr Volberding largely confined his discussion to outcome in antiretroviral-naive patients, ie, those in whom the study therapy constituted initial therapy. Based on analyses of progression to the combined endpoint of a 50% decline in CD4+ cell counts, an AIDS-defining condition, or death, and of death as a single endpoint, the combination treatments were superior to monotherapy for antiretroviral-naive patients, with zidovudine/zalcitabine appearing to be the most effective combination on both analyses. Although didanosine monotherapy performed surprisingly well with regard to study end points, there appeared to be a consistent advantage to combination treatment in treatment-naive patients that supports recommendation of its use as initial treatment.

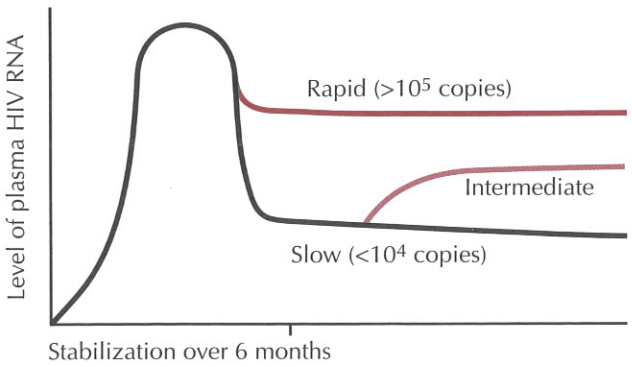

Figure 1. Simplified "dogma" of HIV titer set point. Set point is established within 6 months after primary infection, with level of replication determining rate of disease progression. Rapid progression occurs in patients with viral loads greater than 10^5 HIV RNA copies/mL, slow progression in those with levels less than 10^4 HIV RNA copies/mL.

The Delta trial was similar in design to ACTG 175 except that it did not include a didanosine monotherapy arm and had a study population with somewhat more advanced disease. The study also showed superiority of combination treatment over zidovudine in zidovudine-naive patients, as well as in the overall population. In this trial, zidovudine/didanosine proved to be the most effective combination regimen.

Some data from virology studies in the ACTG 175 population have recently become available. While the findings with regard to treatment outcome provide firm support for treatment of asymptomatic patients with CD4+ cell counts less than 500/µL, the results regarding the predictive value of plasma HIV RNA also provide support for making treatment decisions on the basis of risk of progression. Measurement of plasma HIV RNA showed decreases of 0.4 log with zidovudine monotherapy, 1 log with zidovudine/zalcitabine, and 1.5 log with zidovudine/didanosine. When the population was apportioned into quartiles based on baseline plasma HIV RNA levels, a dramatically increased risk of progression to an AIDS-defining condition or death was associated with higher plasma HIV RNA levels. Patients with plasma HIV RNA levels of less than 5000 copies/mL and those with 5000 copies/mL to 18,000 copies/mL (first and second quartiles) both had a 3% risk of progression; those with plasma HIV RNA levels of 18,000 copies/mL to 54,000 copies/mL had a 10% risk of progression, while those with levels greater than 54,000 copies/mL had a 32% risk of progression. It was found that baseline and 8-week plasma HIV RNA levels were the best overall predictors of risk of progression. Other factors associated with increased risk of progression were a decrease of 100 CD4+ cells/µL from baseline, which was associated with a 1.5-fold increased risk, and a 1-log increase in plasma HIV RNA levels from baseline, which was associated with a 4- to 6-fold increased risk of progression. Changes in CD4+ cell counts lost much of their predictive value over time, whereas plasma HIV RNA levels retained their predictive value.

There is a consistent advantage to combination therapy in treatment-naive patients.

According to Dr Volberding, the bottom line of the ACTG 175 findings is that antiretroviral treatment is clearly associated with a survival advantage and that treatment is effective in asymptomatic patients with CD4+ cell counts less than 500/µL. The findings in both ACTG 175 and the Delta trial also suggest that zidovudine/zalcitabine and zidovudine/didanosine as well as didanosine monotherapy are rational choices for initiating therapy. Finally, the virology findings, particularly when coupled with data from the Multicenter AIDS Cohort Study (MACS) showing an increased risk of disease progression with increased plasma HIV RNA levels (see below), suggest that high plasma HIV RNA levels should be considered an important determinant of risk of more rapid progression and a relative indication for treatment initiation.

MACS Study of Plasma HIV RNA as a Predictor of Progression

Several recent clinical studies have pointed to the plasma HIV RNA level as an accurate predictor of risk of progression. In a study in which patients from the MACS in Pittsburgh were followed for several years, those patients who progressed to AIDS exhibited steadily increasing plasma HIV RNA levels, whereas those who did not progress over the same time period had relatively stable viral loads. In a further analysis of this population, the risk of death was shown to dramatically increase with increasing plasma HIV RNA levels as measured by a sensitive branched-DNA assay (sensitivity limit, 500 copies/mL). When the patients were apportioned into quartiles based on the average of two baseline measurements of plasma HIV RNA, the risks of death were as follows: (1) less than 5100 copies/mL, 0%; (2) 5100 copies/mL to 12,800 copies/mL, 5%; (3) 12,800 copies/mL to 34,500 copies/mL, 33%; and (4) greater than 34,500 copies/mL, 65%. In addition to showing the importance of viral burden to disease progression and suggesting that treatment outside of the more conservative CD4+ cell count-defined threshold should be considered in cases in high viral load, these findings also point to the potential importance of viral dynamics in determining disease progression and possibly in helping guide treatment decisions. In particular, studies involving longitudinal follow-up of viral load or changes in viral load with therapeutic intervention have suggested that each HIV-infected person manifests a viral replication set point, ie, a level of viral replication that persists for a relatively prolonged period (Figure 1). This set point, which may be largely a function of the host immune response, appears to be determined in an HIV-infected person sometime within the first 6 months of infection, after resolution of the initial viremia characteristic of primary infection. Determining whether institution of potent antiretroviral therapy before the establishment of the set point may serve to effectively lower that set point in an individual otherwise destined to have more rapidly progressive disease is an issue that warrants investigation.

Other Potential Initial Regimens

Clinical trial data on a number of other potential initial regimens have become available recently.

Lamivudine/zidovudine. The lamivudine/zidovudine combination has been shown to have persistently lower plasma HIV RNA levels and to maintain CD4+ cell count increases. Figure 2 shows the effects of this combination on plasma HIV RNA levels over the first 48 weeks of treatment in NUCA 3001, one of the recent trials investigating zidovudine/lamivudine. A 76-week follow-up of this study population has shown this combination treatment is associated with (1) persistence of CD4+ cell count benefit; (2) maintenance of an approximately 1-log decrease in plasma HIV RNA levels from baseline; (3) plasma HIV RNA levels below the detection limit in 20% of patients and in 50% of those with low levels at baseline; and (4) a trend toward fewer minor opportunistic infections compared with monotherapy, with very few AIDS-defining conditions having occurred in the study population overall. The proportion of patients who experience decreases in viral load to below assay detection limits is important to consider in weighing the effectiveness of a regimen, since the magnitude and quality of the decrease in these patients are not accurately reflected in the numeric value of the decrease in viral load.

When used alone, lamivudine also showed persistent activity that appeared to be equivalent to zidovudine monotherapy, despite the fact that virtually all patients developed high-level resistance to this drug after a relatively short period of time. This persistent activity may actually depend on the development of the resistance mutation. Although Dr Volberding expressed doubt regarding whether this drug or any other single antiretroviral agent should be used alone in initial treatment, he noted that there may be a place for lamivudine monotherapy, given its low toxicity, in patients who are unable to tolerate other antiretroviral drugs.

Stavudine. In a recent placebo-controlled trial of stavudine as initial monotherapy in patients with CD4+ cell counts of

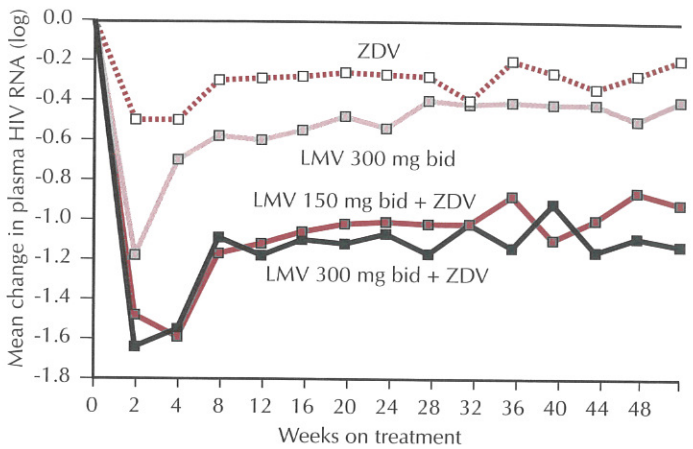

Figure 2. Log mean-change in plasma HIV RNA in patients in NUCA 3001 according to treatment with zidovudine (ZDV) monotherapy, lamivudine (LMV) monotherapy at 300 mg bid, lamivudine 150 mg bid plus zidovudine, or lamivudine 300 mg bid plus zidovudine for 48 weeks. Adapted from Eron JJ, et al. N Engl J Med. *1995.*

350/µL to 750/µL, full-dose stavudine treatment for 12 weeks was associated with a median 0.5- to 0.8-log decrease in plasma HIV RNA and a median increase in CD4+ count of 40 cells/µL. During an open-label half-dose continuation phase, the viral load and CD4+ cell count benefits were lost.

Didanosine/stavudine. In a recent trial, 76 patients with CD4+ cell counts of 200/µL to 500/µL were given various doses of didanosine/stavudine for 52 weeks. Plasma HIV RNA decreases of 1.2 to 1.4 log were observed, with 60% of patients exhibiting a decrease of at least 1 log and 15% to 30% exhibiting a decrease of at least 2 log. In the standard-dose combination group, CD4+ counts increased by 140 cells/µL. Almost no neurotoxicity was reported with this combination regimen.

Protease inhibitors. Dr Volberding did not discuss recent findings with regard to protease inhibitor treatment, since the topic was extensively treated by another speaker at the Los Angeles meeting [see "Protease Inhibitors" (Steven A. Miles, MD, and Kathleen E. Squires, MD) in this issue]. However, he noted that protease inhibitors exhibit remarkable potency, and that a combination regimen of protease inhibitors with one or two nucleoside analogues may prove to be the most potent antiretro-

viral treatment strategy in the near future. Such combinations are currently being investigated.

Summary

A conservative approach to initial antiretroviral therapy, ie, one based primarily on available clinical trial results, can be summarized as follows: With regard to general principles of initiation, treatment should be begun before symptom onset: if the patient has a CD4+ cell count greater than 500 cells/μL, the burden of proof is on the decision to treat; if the patient has a CD4+ cell count less than 500 cells/μL, the burden of proof is on the decision not to treat. Unique indications for treatment include post-exposure (occupational, sexual) treatment, treatment during pregnancy of infected women, and treatment during primary infection. There are now data that clearly demonstrate benefit of treatment in the first two indications and data that suggest benefit of treatment in the third. The importance of viral burden as a predictor of progression is increasingly being recognized. Thus, it seems likely that high viral load will eventually be taken as an indication for treatment regardless of CD4+ cell count.

A conservative approach to selecting the initial treatment regimen would be to choose among the combinations of zidovudine/didanosine, zidovudine/zalcitabine, or zidovudine/lamivudine. Dr Volberding noted that although didanosine monotherapy may be considered as a first-line option given its performance in ACTG 175, he would generally not recommend monotherapy for initial treatment with any currently available agent.

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For patients who become zidovudine-intolerant or who refuse zidovudine, the combinations of stavudine/didanosine or stavudine/lamivudine should be considered, as well as monotherapy with either didanosine or stavudine. The addition of one of the protease inhibitors (ritonavir, indinavir, or the newer formulation of saquinavir with increased bioavailability if and when it becomes available) to nucleoside analogue treatment may be considered in patients with a high risk of progression as indicated by low or declining CD4+ cell counts or high plasma HIV RNA titers.

With regard to trends in the near future, there may well be a continuing movement toward early aggressive initial therapy, the addition of protease inhibitors to such treatment, and the use of viral quantitation as a standard tool in the management of HIV-infected patients.

Paul A. Volberding is Professor of Medicine at the University of California San Francisco, and Director of the AIDS Program at San Francisco General Hospital.

Suggested Readings

Cameron B, Heath-Chiozz M, Kravcik S, et al. Prolongation of life and prevention of AIDS in advanced HIV immunodeficiency with ritonavir. Presented at Third Conference on Retroviruses and Opportunistic Infections; January 28–February 1, 1996; Washington, DC.

Centers for Disease Control and Prevention. Case-control study of HIV seroconversion in health-care workers after percutaneous exposure to HIV-infected blood. France, United Kingdom, and United States, January 1988-August 1994. *MMWR.* 1995; 44:929–933.

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.

Freimuth WW, Chuang-Stein CV, Greenwald CA, et al. Delavirdine (DLV) + didanosine (ddI) combination therapy has sustained surrogate marker response in advanced HIV-1 population. Presented at Third Conference on Retroviruses and Opportunistic Infections; January 28–February 1, 1996; Washington, DC.

Gazzard B on behalf of the International Coordinating Committee. Further results from European/Australian Delta trial. Presented at Third Conference on Retroviruses and Opportunistic Infections; January 28–February 1, 1996; Washington, DC.

Hammer S, Katzenstein D, Hughes M, Gundacker H, Hirsch M, Merigan T for the ACTG Study Team. Nucleoside monotherapy (MT) vs. combination therapy (CT) in HIV infected adults: a randomized, double-blind, placebo-controlled trial in persons with CD4 cell counts 200–500/mm³. Presented at Thirty fifth Interscience Conference on Antimicrobial Agents and Chemotherapy; September 17–20, 1995; San Francisco, CA.

Kinloch-de Loës S, Hirschel BJ, Hoen B, et al. A controlled trial of zidovudine in primary human immunodeficiency virus infection. *N Engl J Med.* 1995;333:408–413.

Pollard R, Peterson D, Hardy D, et al. Antiviral effect and safety of stavudine (d4T) and didanosine (ddI) combination therapy in HIV-infection subjects in an ongoing pilot randomized double-blinded trial. Presented at Third Conference on Retroviruses and Opportunistic Infections; January 28–February 1, 1996; Washington, DC.

Volberding PA, Grimes JM, Lagakos SW, et al. A comparison of immediate with deferred zidovudine therapy for asymptomatic HIV-infected adults with CD4+ cell counts of 500 or more per cubic millimeter. *N Engl J Med.* 1995;333:401–407.