Initiation of Antiretroviral Therapy

Initiation of antiretroviral therapy was discussed at the Los Angeles meeting by Paul A. Volberding, MD, from the University of California at San Francisco and San Francisco General Hospital, and at the Chicago meeting by John P. Phair, MD, from Northwestern University Medical School and Northwestern Memorial Hospital in Chicago.

As stated by both Dr Volberding and Dr Phair, existing data do not provide a single compelling answer to the question of when antiretroviral therapy is optimally begun. As noted by both speakers, the increasing evidence that HIV continues to replicate at high rates during the period of clinical latency supports the use of effective treatments very early in disease course; as noted by Dr Volberding, the improving understanding of HIV disease pathogenesis also indicates a need for reassessing the notion of 'early' disease, insofar as what has been considered early treatment in clinical trials – eg, therapy initiated at a CD4+ cell count of 500/μL – is actually occurring at a relatively late stage of infection. Despite the theoretical motivation for early intervention, the results of clinical trials have raised concerns regarding such a strategy using currently available treatment options. One major debate over the timing of initiation of existing treatments has been fueled by the reporting of apparently contradictory findings in asymptomatic patients in ACTG 019 and the Concorde study, which were reviewed by both Dr Volberding and Dr Phair.

Long term study of ACTG 019 patients

The initial ACTG 019 analysis, reported in 1990, showed that zidovudine was associated with a significant effect in delaying clinical progression of disease over approximately 13 months in asymptomatic patients with CD4+ cell counts <500/μL, with the optimal dosage being 500 mg/d; overall mortality was too low to hazard conclusions regarding any potential treatment effect. Subsequently, data available from an extended analysis of ACTG 019 patients, expected to be published in the fall of 1994, have indicated a durable benefit of early initiation of treatment. In this study extension, approximately 1000 patients who either initially received zidovudine 500 mg/d or switched to this regimen from the original placebo group or the zidovudine 1500 mg/d group were followed for an average of more than 2.5 years. It was found that patients initially receiving zidovudine had a significant delay in progression to AIDS or death compared with patients beginning treatment after approximately 13 months of no treatment on the placebo arm. No significant effect on mortality alone was observed. Although the effect on progression was observed for all initial zidovudine recipients combined, subgroup analysis showed that statistically significant benefit was confined to patients initially receiving the 500 mg/d dosage. Similarly, subgroup analysis showed that significant benefit of zidovudine treatment occurred only for the comparison of zidovudine patients and initial placebo patients beginning treatment with CD4+ cell counts >300/μL and that the benefit was confined to those zidovudine patients initially receiving 500 mg/d. Dr Volberding noted that results of the ACTG 019 substudy in 1600 asymptomatic patients with CD4+ cell counts >500/μL are likely to be available later this year.

Concorde

In the Concorde trial, results of which have been published since the time of the meetings, approximately 1800 asymptomatic patients with any CD4+ cell count received immediate zidovudine 1000 mg/d or the same treatment deferred until development of AIDS-related complex (ARC) or AIDS. Available data from an intent-to-treat analysis indicate that there has been no difference between immediate and delayed treatment groups with regard to progression to ARC or AIDS or mortality during approximately 3 years of follow-up, although average CD4+ cell count in the immediate treatment group remained approximately 30/μL higher than that in the delayed-treatment group.

A primary concern with the Concorde findings has been the change in the protocol made on the basis of the initial ACTG 019 findings whereby, approximately halfway through patient accrual, patients in the deferred treatment group were permitted to begin treatment at a CD4+ cell count of <500/μL. According to Dr Volberding, approximately one third of deferred treatment patients actually began treatment when they were asymptomatic, with these patients nevertheless not being considered to have begun therapy early in intent-to-treat analysis. According to Dr Phair, deferred group patients were receiving treatment for approximately 15% of the study duration and approximately 20% of the immediate-treatment group dropped out of the study, potentially confounding intent-to-treat analysis. Further, opportunistic infection prophylaxis, permitted in an amendment to the study, may have been more frequent in the deferred-treatment patients (given the lower CD4+ cell counts in the group), potentially confounding survival analysis. A retrospective analysis of a Concorde study patient group comparable to the patient population in ACTG 019 has shown benefits of early treatment comparable to those observed in ACTG 019 over a similar period.

Among the questions posed by Dr Volberding regarding the Concorde findings was whether analysis on other than an intent-to-treat basis would reveal benefit of early treatment. He also suggested that the data raise the questions of whether treatment was continued for too long – in the face of evidence that nucleoside analogues provide a time-limited benefit – and whether optimal treatment might involve using available agents in sequence or combination after an optimal period of monotherapy.

- ***ACTG 019 extension: benefit of zidovudine for ≥2.5 years in >300 CD4+ cells/μL subgroup***
- ***Concorde shows no benefit of early treatment after three years: methodologic problems confound interpretation?***
- ***Initiation of treatment: driven by virology, changes in lab markers, CD4+ threshold, symptoms?***
- ***Treatment strategies should reflect variability of patient course and treatment response***

Current options

With regard to the range of currently available treatment options, Dr Volberding identified zidovudine as the most active drug in initial monotherapy based on comparative studies with didanosine and zalcitabine in previously untreated patients; he pointed out, however, that as-yet unpublished data from ACTG 116A indicate that although zidovudine was superior to didanosine in delaying mortality in zidovudine-naive patients, the contrary was true in patients with 8 to 16 weeks of prior zidovudine.

The relative benefits of beginning treatment with combination therapy currently are being evaluated in ACTG 175, results of which will not be available for some

time; Dr Volberding suggested that some rationale for this approach may be provided by findings in ACTG 155, in which patients with baseline CD4+ cell counts of 150 to 300/μL, the highest stratum in the study, were found to have delayed disease progression with the combination of zidovudine and zalcitabine compared with either alone, although overall results showed no benefit of combination treatment.

With regard to when to begin antiretroviral therapy, Dr Volberding enumerated four options based on available evidence: (1) at any stage of HIV disease – eg, based on pathogenesis data and some data from European-Australian Collaborative Group protocol 020 (see below); (2) when laboratory studies indicate rapid deterioration regardless of CD4+ cell count – eg, based on declining cell count, increased HIV p24 antigen, or HIV titer; (3) at an arbitrary CD4+ cell count regardless of clinical state – eg, 500/μL, as supported by ACTG 019, or 200/μL, as supported by the Veterans Affairs Cooperative Study Group protocol 298; or (4) when clinical condition deteriorates regardless of laboratory values – eg, based on the current Concorde study data. He suggested that the decision should be one jointly made by the patient and physician on the basis of discussion of evidence supporting a given approach and with the acknowledgement that the courses of disease and responses to treatment in individual patients are likely to be highly variable.

Table 1. National Institute of Allergy and Infectious Diseases Consensus Conference HIV Therapy Guidelines

Patients Naive to Antiretroviral Therapy

CD4+ cell count >500/μL
- Continued observation (see text for potential exceptions)

CD4+ cell count 200-500/μL, asymptomatic
- Continued observation, OR
- Zidovudine monotherapy: 600 mg/d in three divided doses

CD4+ cell count 200-500/μL, symptomatic
- Zidovudine monotherapy

CD4+ cell count <200/μL, symptomatic or asymptomatic
- Zidovudine monotherapy

Patients Tolerating Initial Antiretroviral Therapy

CD4+ cell count >300/μL
- Continued zidovudine monotherapy

CD4+ cell count <300/μL
- Didanosine monotherapy, OR
- Continued zidovudine monotherapy

Patients Intolerant of Zidovudine

CD4+ cell count >500/μL, asymptomatic
- Discontinue antiretroviral therapy
- Continued observation

CD4+ cell count 50-500/μL
- Alternative monotherapy; the majority of the panel would select didanosine

Patients Experiencing Progression on Zidovudine

CD4+ cell count 50-500/μL
- Alternative monotherapy, OR
- Combination therapy

Patients With CD4+ Cell Count <50/μL

Intolerant of zidovudine
- Didanosine monotherapy, OR
- Zalcitabine monotherapy, OR
- Discontinue antiretroviral therapy

Experiencing progression on zidovudine
- Didanosine monotherapy, OR
- Zalcitabine monotherapy

Adapted from Sande et al, JAMA 1993;270:2583

As stated by Dr Volberding, the decision to initiate treatment early could be made with more confidence if rational strategies for long-term treatment were available and if there were promise of availability of additional effective agents; he cited the ability of quantitative PCR and branched-DNA methods to measure ongoing viral replication, and outlined a potential strategy for optimizing response to treatment based on use of such techniques. In this strategy, therapy could be started at a predetermined CD4+ cell count or HIV load and load monitored regularly, with treatment being altered after a specified time by adding a drug (or drugs) or switching drugs if no decline in viral load is observed; therapy would be continued so long as viral load remained suppressed, with alteration occurring when the viral concentration increased by a specified amount. With regard to newer potentially useful agents, he identified stavudine (d4T), 3TC, nevirapine, delavirdine, and several candidate protease inhibitors as agents about which more should be known within the year.

NIAID Guidelines

In addressing the issue of optimal use of currently available options on the basis of currently available data, Dr Phair presented the recently published recommendations of a National Institute of Allergy and Infectious Diseases State of the Art panel, of which he was a member; the recommendations are shown in Table 1.

The recommendation of zidovudine 600 mg/d in three divided doses as first-time treatment was supported by results of comparative trials with didanosine (ACTG 116A) and zalcitabine (ACTG 114); the recommendation of tid dosing was supported by clinical experience indicating enhanced compliance without obvious changes in efficacy or safety. Although the panel recommended monitoring in asymptomatic patients with CD4+ cell counts above 400/μL, it also indicated that exceptions might include individuals with laboratory changes suggesting disease progression. As pointed out by Dr Phair, the European-Australian Collaborative Group study results indicate a benefit in delaying CD4+ cell count decline and progression to clinical symptoms, but no effect on mortality, in patients with CD4+ cell counts above 400/μL; he noted that findings in the ACTG 019 substudy in patients with cell counts greater than 500/μL would be likely to provide further guidance with regard to earlier initiation of treatment.

Debate over whether treatment should be instituted in asymptomatic patients with lower cell counts (200 to 500/μL) included balancing concern over whether such treatment uses up a time-limited benefit of currently available agents and the belief that earlier treatment can serve to prolong the period of asymptomatic disease. With regard to the recommendation that zidovudine be continued or a switch to didanosine instituted at CD4+ cell counts less than 300/μL, data supporting the switch are primarily those from ACTG 116B/117. In this trial, didanosine 500 mg/d was found to have a significant effect in delaying AIDS-defining events and death compared with continued zidovudine in advanced-disease patients with a median of 13.5 months of prior zidovudine; Dr Phair stated that it remains unclear at what point zidovudine efficacy may begin to wane in comparison with didanosine. Although the majority of panelists indicated that didanosine would be preferable for alternative therapy in patients not tolerating zidovudine on the basis of greater experience with the agent, some suggested that zalcitabine might be preferable on the basis of relative ease of administration. Combination therapy was cited as an option in patients experiencing progression on zidovudine; Dr Phair stated that a better idea of the role of combination therapy awaits the results of ongoing trials and that some available data indicate that tolerance of combination treatment in patients with cell counts <100/μL is relatively poor.

Variability of disease course and treatment response

Dr Phair emphasized that proposed treatment strategies are complicated by the variability in course of disease and response to treatment. Observational study data presented by Dr Phair showed a wide

continued on page 15

Future Directions *continued from page 9*

tration by augmenting immune response with IL-4 to further increase antibody response or IL-2 to augment CTL activity); potential immunologic priming of the host with gene therapy to recognize protease mutations (with subsequent treatment with the mutation-inducing agent resulting in enhanced immunologic clearance of virus); focus on development of small-molecule agents (eg, DM323) that would be easier and cheaper to design and produce; and investigation of combination therapy – eg, with protease inhibitors and NNRTIs. Dr Miles noted that protease inhibitors currently are under development at more than 15 pharmaceutical companies.

Other promising agents

Other promising agents under development include nonimmunosuppressive cyclosporin analogues. As related by Dr Richman, recent studies have shown that the gag proteins of the HIV ribonucleic protein complex bind to host cell components and are active in transporting the complex to the host cell nucleus, with a similar phenomenon likely occurring in transport of virion components from the nucleus and cytoplasm to the budding membrane. The finding that cyclosporin can inhibit these processes has led to identification and development of nonimmunosuppressive analogues – eg, SDZ 811 – as potential antiretroviral agents. SDZ 811 has been found to bind to cyclophilin in the host cell and inhibit the HIV gag-cyclophilin interaction, inhibiting transport of reverse transcripts to the nucleus at micromolar concentrations. Further, it inhibits the infectivity of virions at later steps of replication at 10- to 100-fold lower concentrations. Marked inhibitory effects have been observed in vitro in CD4+ lymphocytes and in monocytes at achievable drug concentrations.

Another class of compounds that have been shown to have potent activity in vitro is the bicyclams. These agents prevent uncoating of the virus after cell entry; the exact mechanism of action of the agents remains unclear, although it is known that they do not bind to the virion. Dr Richman anticipated that some of the bicyclams may enter development within the year. Other types of agents that have engendered interest but that are not likely to enter advanced phase clinical trials in the near future include the antisense oligonucleotides, ribozymes, and integrase inhibitors. ■

Initiation *continued from page 5*

variety of patient courses and associated prognoses after the start of zidovudine treatment; stratification of best and worst responses based on a baseline CD4+ cell count of 300/μL and CD4+ cell count increase or decrease of at least 50/μL, serum neopterin level changes, and increase or decrease in physical symptoms over 1 year of treatment indicated a 17-fold difference between best-case and worst-case response in risk for mortality within the following year. CD4+ cell count data from patients who had experienced rapid cell count declines for 5 to 6 years of follow-up prior to the start of zidovudine treatment similarly indicate heterogeneity of cell count response in association with time to clinical progression to AIDS: some exhibited continued steep cell count decline and rapid progression to AIDS, some exhibited reduced rate of cell count decline and progressed to AIDS after 2 years, and some exhibited relative maintainence of cell counts and did not progress to AIDS during the observation period. Dr Phair emphasized the variability of course of disease by presenting a histogram of 6-month changes in CD4+ cell count among individuals in a MACS cohort followed by his group for 8 years. Although most patients have decreases in cell count, with the majority experiencing 6-month decreases of 30 to 40/μL, some 15% have exhibited increased cell counts over the course of infection (Figure 4); similar observations have been made in San Francisco cohorts and in an Australian transfusion cohort. According to Dr Phair, although there is some evidence that such patients exhibit reduced viral load, how they differ from other patients in their response to infection remains unexplained. ■

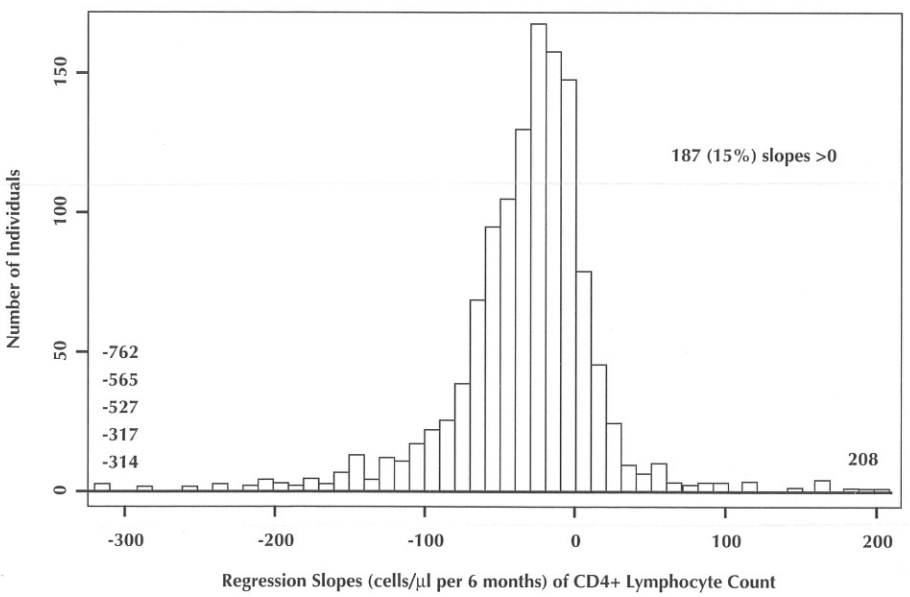

Figure 4. CD4+ cell count changes over 6-month intervals in patients with HIV infection followed for up to 8 years. Figure from Kirby et al (submitted for publication).