Current Report—HIV

Zidovudine for Asymptomatic HIV-Infected Patients: Answers and Questions

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The results of a key study examining whether treatment with zidovudine (AZT, Retrovir™) can delay or prevent the development of clinical AIDS have recently been published.[1] Data from this study support zidovudine use in HIV-infected persons with fewer than 500 CD4+ (T-helper) lymphocytes per cubic millimeter. Fewer subjects in the treated groups developed AIDS or severe AIDS-related conditions than subjects in the placebo group, leading the Food and Drug Administration (FDA) to approve zidovudine at a dosage of 500 mg daily for patients with fewer than 500 CD4+ cells/mm^3. Following FDA approval, a state-of-the-art conference conducted by the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health issued some recommendations for the clinical use of zidovudine in asymptomatic persons.[2]

These developments challenge the family physician to test at-risk patients for HIV infection and to provide early drug intervention when indicated. Some very important questions remain, however. The study had a relatively short follow-up (less than 1 year); therefore, long-term efficacy and toxicity remain uncertain. In addition, the optimal time to initiate zidovudine therapy remains to be established.

The ACTG 019 Zidovudine Study

This randomized, double blind, controlled study (AIDS Clinical Trials Group [ACTG] Protocol 019) of 1338 subjects had three arms: a placebo group (428 subjects), a group treated with 500 mg zidovudine daily (453 subjects), and a group treated with 1500 mg zidovudine daily (457 subjects). All subjects were asymptomatic and had CD4+ (T-helper) lymphocyte counts of fewer than 500 cells/mm^3. The mean duration of follow-up after intervention was 55 weeks (range 19–107). Endpoints were the development of either CDC-defined AIDS or severe AIDS-related conditions (ARC). Severe ARC was defined as the presence of two successive CD4+ cell counts below 200/mm^3 and at least two of the following signs or symptoms: oral hairy leukoplakia, recurrent oral candidiasis, weight loss of at least 4.5 kg (10 lb) or 10 percent of body weight within 6 months, multidermatomal herpes zoster, temperature greater than 38.5° C [101.3° F] for more than 15 days in a 30-day period, or diarrhea with more than three liquid stools per day for at least 30 days.

Analysis was based on an intention-to-treat approach, whereby results were reported for all subjects even when they did not remain in the study. Of the original 1338 subjects, 412 did not remain on protocol because they did not meet study criteria, dropped out of the study, or were lost to follow-up. Data about treatment (or nontreatment) received by these 412 subjects are not available. The intention-to-treat approach to analysis tends to underestimate differences among groups.[3 pp 185-6]

Toward the end of the ACTG 019 study period, inhaled pentamidine received FDA approval for prophylaxis against *Pneumocystis carinii* pneumonia (PCP). Therefore, subjects with fewer than 200 CD4+ cells/mm^3 were allowed to receive inhaled pentamidine during the last few months of the study. Whether earlier PCP prophylaxis would have affected the study outcomes cannot be determined.

The study was terminated early by the data safety and monitoring board when 40 subjects in the placebo group developed one of the study endpoints (including 33 who developed AIDS), compared with 17 subjects (11 with AIDS) assigned to receive 500 mg of zidovudine daily and 20 subjects (14 with AIDS) assigned to receive 1500 mg daily. The number of patients develop-

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ing endpoints was small, but differences between the placebo group and the treatment groups were statistically significant. The efficacy of the 500 mg and 1500 mg daily dosages were comparable. The 500 mg daily dosage was minimally toxic, but the 1500 mg daily dosage was associated with significant toxicity.

Although widely reported in the press as a study of persons with CD4+ lymphocyte counts in the 200–500 cells/mm^3 range, the study group actually included 162 subjects (12 percent) with fewer than 200 CD4+ cells/mm^3 at the beginning of the study. This group accounted for 39 percent of the patients who developed endpoints. In addition, the authors state that CD4+ cell counts were severely depressed (usually less than 200) at the time most endpoints occurred. The actual baseline CD4+ cell counts of the 36 subjects within the broad 200–500 range who did develop endpoints were not provided.

The NIAID Panel Recommendations

Practice guidelines have been developed by a panel of experts brought together by the NIAID, sponsors of the ACTG 019 study. Their recommendations are based on results of the ACTG 019 study and from a study showing beneficial effects of zidovudine treatment of symptomatic persons with fewer than 500 CD4+ cells/mm^3 (ACTG Protocol 016).[4] Their recommendations for clinical care include:

1. HIV risk assessment for all patients, with voluntary, confidential testing and pre- and post-test counseling for all persons believed (by themselves or by their physicians) to be at risk.
2. Monitoring CD4+ lymphocyte counts with a baseline CD4+ count at the time HIV infection is diagnosed and repeated every 6 months as long as counts remain greater than 600 cells/mm. More frequent monitoring (every 3–4 months) is recommended for patients with fewer than 600 cells/mm or at any time symptoms of HIV disease occur.
3. Zidovudine therapy at a total daily dosage of 500 mg for symptomatic and asymptomatic HIV-infected patients whose CD4+ counts are less than 500/mm. Recognizing the laboratory variability of CD4+ lymphocyte counts, the panel recommends that when counts are in the 400–600 range, two consecutive counts below 500 be obtained, at least 1 week apart, before initiation of therapy.
4. Follow-up discussions, examination, and laboratory monitoring (especially complete blood cell counts to detect anemia or granulocytopenia caused by zidovudine) at 1–3 month intervals depending upon clinical and laboratory findings.

Comment

The apparent efficacy of early intervention with zidovudine in asymptomatic HIV-infected persons, as well as the efficacy of prophylaxis against *Pneumocystis carinii* pneumonia,[5] present important responsibilities and opportunities for the family physician. Assessment of each patient's risk for HIV infection is now a necessary component of patient care. Testing should be offered to all at-risk patients. When antibody positivity is confirmed,[6] CD4 counts should be obtained and early drug intervention considered.

Precisely when to initiate antiviral therapy with zidovudine or other antiviral agents remains a clinical dilemma. The latent period of HIV infection is quite long, with recent data suggesting an 11-year interval between infection and clinical illness.[7] During that time, CD4+ lymphocytes decline at a slow rate until a period of more rapid lymphocyte destruction of about 85 CD4+ cells per year. It must be kept in mind, however, that CD4+ lymphocyte counts are highly variable and may be misleading. CD4+ counts less than 500/mm^3 can, in fact, be within the normal range for healthy controls. In addition, low CD4+ cell counts occur in other conditions, both in HIV-infected and in uninfected patients. Therefore, clinical decisions should not be made on the basis of a single CD4+ cell count.

In the meantime, zidovudine can be offered to HIV-infected patients with CD4+ cell counts as high as 500 cells/mm^3. The limitations of the ACTG 019 findings allow the patient and physician some latitude in clinical decision making. It has not been established that zidovudine *must* be given to all patients with fewer than 500 CD4+ lymphocytes/mm^3. Whether the benefits of zidovudine translate into improved long-term outcomes, especially for patients with higher CD4+ counts within the 200–500 cells/mm^3 range, remains to be determined. The Concorde 1 study

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in Great Britain and France and the Veteran's Administration study 298 in the United States are in their second year and should provide longer-term data.[8]

The economic impact of monitoring and treating can be considerable. Zidovudine is sold to most hospitals and pharmacies at a cost of $120 to $150 per 100 capsules. Treatment with 500 mg zidovudine daily can cost $250–$700 per month ($3000–$8400 yearly) after pharmacy charges are added. T-lymphocyte counts cost from $60–$180, depending upon the laboratory. Complete blood counts generally cost about $15–$20. If these blood tests are obtained on average three times yearly, the costs would be between $225–$600 per year. Most insurance companies and health maintenance organizations will cover the costs of medications and laboratory tests (after deductibles and co-payments, depending upon the coverage) unless coverage is denied on the grounds of a preexisting condition. However, the loss of confidentiality inherent in insurance claims is a significant factor for many patients. Federal and state subsidy programs for zidovudine are available for most persons who do not have insurance coverage. In addition, patients enrolled in clinical trials can often have laboratory tests performed free as part of the study. The expense of testing and treatment can be expected to be between $3225–$9000 per year.

Initiating treatment of the HIV-infected person with zidovudine is a major step in patient care. The significance of these promising short-term findings in this chronic disease must be re-examined over time. As more experience with early intervention for HIV disease accumulates and other trials are concluded, results will be reported in *JABFP*'s "Current Report – HIV."

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