Current Report — HIV

The Concorde Zidovudine Trial And Antiretroviral Strategies For Asymptomatic Patients

Ronald H. Goldschmidt, MD

With the release of disappointing results from the Concorde zidovudine (AZT, Retrovir) trial,[1] providers and patients are reconsidering the indications for and timing of antiretroviral treatment. A more flexible approach, similar to the approach outlined in the *Current Report — HIV* series,[2-4] is replacing previous, more absolute, guidelines. It is now acknowledged that the effects of zidovudine are limited and wane with time[5] and that initiating treatment early, rather than later, during the asymptomatic phase of human immunodeficiency virus (HIV) disease is not a requirement for HIV care.

The Concorde Trial

The Concorde Trial began in October 1988 as a joint effort of investigators in the United Kingdom, Ireland, and France. The results of this double-blind, placebo-controlled study have been released in abbreviated form as a letter to the editor and in presentations at the Ninth International Conference on AIDS in Berlin, 7-11 June 1993. A total of 1749 asymptomatic patients with a wide range of CD4+ lymphocyte counts were randomized into two study groups: 877 received 250 mg of zidovudine four times daily beginning at randomization (the immediate treatment group); 872 were to receive matching placebo until they became symptomatic (the deferred treatment group). One year after the trial began, the results from the similar AIDS Clinical Trials Group (ACTG) Protocol 019 study[6] in the United States were released. The ACTG 019 results had demonstrated delay in time of progression to symptomatic HIV disease, opportunistic infections, or death during the 1-year study period. In late 1989 modification of the Concorde protocol was permitted, and about one-third of patients in the deferred treatment group began zidovudine treatment. Comparisons of the two Concorde groups, nevertheless, remained possible, as subjects in the immediate treatment group spent 82 percent of total time of the study on zidovudine, whereas the deferred treatment group spent 14 percent of the time on zidovudine. Few participants (7 percent) were lost to follow-up for more than 6 months during the mean follow-up period of 3 years. Zidovudine was remarkably well tolerated, with fewer than 15 percent of patients requiring discontinuation because of drug toxicity (e.g., anemia, neutropenia, gastrointestinal side effects).

Although CD4+ lymphocyte counts remained more than 30 cells/μL higher in the immediate treatment group throughout the study period, no significant difference in clinical outcomes between groups was noted at 3 years. The 3-year survival rates for these patients was 92 percent in the immediate treatment group and 93 percent in the deferred treatment group. Progression to either the acquired immunodeficiency syndrome (AIDS) or death was 18 percent in both groups. The early clinical benefit of zidovudine in delaying progression to AIDS or severe AIDS-related complex was similar to that noted in previous studies in the United States. During the 3-year study period, however, benefits did not increase with time on drug. Rather, these benefits appeared to be similar regardless of the point during asymptomatic disease that drug therapy was initiated. The findings are consistent with another, smaller-scale, study with

Submitted, revised, 16 August 1993.

From the Family Practice Residency Program, San Francisco General Hospital, and the Department of Family and Community Medicine, University of California, San Francisco. Address reprint requests to Ronald H. Goldschmidt, MD, Family Practice Inpatient Service, San Francisco General Hospital, San Francisco, CA 94110.

Supported in part by the Western AIDS Education and Training Center, Grant No. 1-D35 PE 00118-01, with the Bureau of Health Professions, Health Resources and Services Administration, Department of Health and Human Services.

J Am Board Fam Pract: first published as 10.3122/jabfm.6.6.604 on 1 November 1993. Downloaded from http://www.jabfm.org/ on 6 November 2026 by guest. Protected by copyright.

a 2-year follow-up period.[7] There was speculation that viral resistance to zidovudine, which usually occurs within 1 year, might be responsible for the lack of cumulative benefit. The Concorde trial investigators concluded that their preferred approach is to withhold therapy until patients become symptomatic.

The Concorde trial is the most extensive long-term clinical study of antiretroviral therapy to date, although it is not without methodologic problems,[8,9] and further analysis of this study will occur when it is published in full. The study featured more patient years of treatment, better patient compliance, and a longer (3-year) study period than any study to date, permitting a better understanding of the value of antiretroviral drug efficacy and timing for intervention.

What can be concluded from the Concorde results? The lack of sustained and progressive benefit of zidovudine (and presumably other nucleosides) in delaying progression of HIV disease force a reconsideration of the approach previously advocated in the United States.[10] Although the drug was remarkably well tolerated among asymptomatic patients, there appeared to be no data to support initiating antiretroviral therapy earlier, rather than later, in the long (5- to 10-year) asymptomatic phase of HIV disease. A second key point from the Concorde study is that CD4+ lymphocyte counts are not reliable surrogate markers for predicting antiretroviral efficacy, especially in early asymptomatic disease.

Primary Care Concepts

It is worthwhile restating some essential primary care concepts highlighted in previous *Current Report — HIV* articles.[2,3] Patients, families, and physicians all balance many variables when deciding upon treatment approaches. Some patients and their families prefer aggressive approaches that include any treatment option that offers a possible benefit. They can choose antiretroviral therapy (alone or in combination) early in asymptomatic disease soon after the CD4+ count declines to fewer than 500 cells/μL. At the other end of the spectrum are patients who elect to defer antiretroviral therapy out of concern for drug toxicities or because they know of others who have done poorly while receiving them. Many patients are unwilling or unable to make these decisions and will rely upon their primary care provider to make the decision.

Physicians and other primary care providers also balance variables in making treatment decisions and recommendations. These variables include information from the medical literature; the advice of local, regional, or national experts; and their personal experiences. Some physicians prefer an aggressive and proactive approach, whereas others prefer to withhold potentially toxic medications until later in the course of HIV disease.

The most appropriate strategy is an individualized one that reflects these variables. Until more information is available, no single recommendation can be considered correct (or incorrect). The aggressive approach based on the rationale that early multidrug therapy might produce better results is appealing but unproved in clinical studies. Evidence continues to mount that early antiretroviral intervention is well tolerated and can retard early clinical and laboratory manifestations of HIV disease.[11] These differences, however, do not translate into survival benefits. Delaying the onset of disease progression in anticipation of new drug development is also an appealing component of the aggressive approach. The conservative approach is strengthened by the results of the Concorde trial.

Many of these concepts are the foundation of new recommendations to be formally announced by a group selected by the National Institute of Allergy and Infectious Diseases. In a reversal of their previous recommendations that promoted early antiretroviral treatment when CD4+ lymphocyte counts decreased to fewer than 500 cells/μL,[11] this group now emphasizes flexibility in making the difficult decision about when to initiate antiretroviral therapy.

Recommendations

Patients should be educated about the present uncertainty regarding the optimal time to initiate antiretroviral therapy. Their preferences regarding treatment strategies must be paramount in making treatment decisions. Because many years can elapse between the 500 cells/μL threshold and symptomatic HIV disease or AIDS, I believe it is prudent to initiate treatment either when CD4+ counts are at or near 200

J Am Board Fam Pract: first published as 10.3122/jabfm.6.6.604 on 1 November 1993. Downloaded from http://www.jabfm.org/ on 6 November 2026 by guest. Protected by copyright.

cells/μL or when patients become symptomatic. This approach can avoid drug toxicities and the early development of drug resistance. For patients desiring earlier intervention, however, antiretroviral therapy (usually with zidovudine as first choice at the standard 500 to 600 mg oral daily dosage) can be offered to patients with CD4+ lymphocyte counts as high as 500 cells/μL. Some authorities endorse this early antiretroviral treatment as their preferred approach.[12] Patients with asymptomatic HIV disease with CD4+ counts between 200 and 500 cells/μL who have been receiving and tolerating antiretroviral therapy can either continue treatment, add or change to other antiretroviral agents (especially if they have been taking zidovudine for more than 1 year), or discontinue antiretroviral agents until the above criteria are met. For those asymptomatic patients with relatively high CD4+ counts (350 to 500 cells/μL) who have been receiving antiretroviral treatment and do not have strong treatment preferences, I would recommend discontinuing antiretroviral agents.

For patients with progressive symptomatic HIV disease despite zidovudine therapy, many approaches can be justified. Well-tolerated antiretroviral therapy can be continued unchanged if disease progression is modest. When disease progression is marked (e.g., new opportunistic infections, 50 percent decline in CD4+ cell count), however, changing to an alternative antiretroviral agent (e.g., didanosine [ddI, Videx] or zalcitabine [ddC, HIVID]) or a combination of zidovudine plus didanosine or zalcitabine is warranted, especially when zidovudine use exceeds 1 year. Discontinuing antiretroviral therapy is appropriate when serious toxicity or drug–drug interactions with other, more essential drugs (e.g., trimethoprim–sulfamethoxazole, pyrimethamine, ganciclovir, foscarnet, and amphotericin B) are unavoidable.

Questions about the efficacy and timing of antiretroviral therapy have created a discomforting dilemma for patients and their providers. The hopes many patients and their providers have placed on antiretroviral treatment are seriously undermined. The psychological effects of this reality must be incorporated into primary patient care. A supportive understanding and realistic dialogue with the patient and family will remain the cornerstone of excellent care. For the physician, a focus on proper care of opportunistic infections and other complications of HIV disease[3] to improve the health of HIV patients remains a most important and achievable goal in HIV primary care.

References

1. Aboulker J, Swart AM. Preliminary analysis of the Concorde trial. Lancet 1993; 341:889-90 (letter).
2. Goldschmidt RH, Legg JJ, Brossier KA. Antiretroviral strategies. J Am Board Fam Pract 1993; 6:75-9.
3. Goldschmidt RH, Dong BJ. Treatment of AIDS and HIV-related conditions — 1993. J Am Board Fam Pract 1993; 6:297-316.
4. Goldschmidt RH. Zidovudine for asymptomatic HIV-infected patients: answers and questions. J Am Board Fam Pract 1990; 3:221-3.
5. Lagakos S, Pettinelli C, Stein D, Volberding PA. The Concorde trial. Lancet 1993; 341:1276 (letter).
6. Volberding PA, Lagakos SW, Koch MA, Pettinelli C, Myers MW, Booth DK, et al. Zidovudine in asymptomatic human immunodeficiency virus infection: a controlled trial in persons with fewer than 500 CD4-positive cells per cubic millimeter. N Engl J Med 1990; 322:941-9.
7. Hamilton JD, Hartigan PM, Simberkoff MS, Day PL, Diamond GR, Dickinson GM, et al. A controlled trial of early versus late treatment with zidovudine in symptomatic human immunodeficiency virus infection: results of the Veterans Affairs Cooperative Study. N Engl J Med 1992; 326:437-43.
8. Danner SA. The Concorde trial. Lancet 1993; 341:1276 (letter).
9. Saah AJ. Immediate versus deferred zidovudine. Lancet 1993; 341:1023 (letter).
10. Recommendations for zidovudine: early infection. JAMA 1990; 263:1606, 1609.
11. Cooper DA, Gatell JM, Kroon S, Clumeck N, Millard J, Goebel F-D, et al. Zidovudine in persons with asymptomatic HIV infection and CD4+ cell counts greater than 400 per cubic millimeter. N Engl J Med 1993; 329:297-303.
12. Bartlett JG. Zidovudine now or later? N Engl J Med 1993; 329:351-2.

J Am Board Fam Pract: first published as 10.3122/jabfm.6.6.604 on 1 November 1993. Downloaded from http://www.jabfm.org/ on 6 November 2026 by guest. Protected by copyright.