Other AIDS Drug Regimens Beat AZT Alone, Reduce Clinical Progression and Mortality

TWO LONG-AWAITED trials of drugs to treat HIV disease and AIDS are yielding results that may prompt a shift away from using AZT (formally known as zidovudine) monotherapy as a first-line treatment for the viral infection.

Speaking to a standing-room-only crowd at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) held in San Francisco, Calif, last month, researchers from Harvard Medical School, Boston Mass, and Stanford (Calif) University School of Medicine described surprising findings from AIDS Clinical Trial Group 175 (ACTG 175), a multicenter study of nearly 2500 participants.

The trial found that AZT, the oldest and most widely prescribed drug for the infection, is less effective in patients with intermediate disease than monotherapy with an alternative antiretroviral drug, didanosine (also called ddI), or than regimens that combine AZT with ddI or another nucleoside analog, zalcitabine (also called ddC).

“The finding that treatment in intermediate-stage HIV disease can reduce clinical progression and mortality is a significant one,” says Lawrence Dayton, MSPH, MD, chief of the HIV research branch in the AIDS division at the National Institute of Allergy and Infectious Diseases (NIAID). The NIAID-sponsored trial is the first to provide conclusive evidence that a drug or drug combination can improve survival or slow the progression of HIV disease to AIDS.

Support From ‘Delta’ Trial

The study’s findings received additional support a week or so later at the Fifth European Conference on Clinical Aspects of HIV Infection, held in Copenhagen, Denmark, where researchers reported preliminary results from a similar European/Australian trial. That study, the Delta trial, also found that the drug combinations (AZT with either ddI or ddC) resulted in a marked survival benefit in patients with HIV disease slightly more advanced than that of ACTG 175 participants.

Both ddI and ddC are widely used but are generally regarded as second-line agents for patients who cannot tolerate or are resistant to AZT. All three drugs are nucleoside analogs that act as inhibitors of the enzyme reverse transcriptase, used by HIV to replicate.

ACTG 175 enrolled 2467 HIV-infected participants with CD4+ cell counts of 0.20 to 0.50×10^6/L (200 to 500/µL) and no history of AIDS-related conditions other than minimal Kaposi’s sarcoma. About 43% of the patients had never taken AZT or any other antiretroviral drugs before enrollment in the trial.

Patients were randomized to receive AZT (600 mg/d) alone, ddI (400 mg/d) alone, the same doses of AZT and ddI in combination, or AZT (600 mg/d) combined with ddC (2.25 mg/d). Patients in the study who experienced a 50% decline in their CD4+ cell counts were randomly reassigned to combination therapy or to a different combination therapy if they already had been receiving a two-drug regimen.

No major difference in safety of the four regimens was found.

The treatments were first evaluated for their ability to prevent a 50% decline in the CD4+ cell count, development of an AIDS-defining condition, or death in patients followed up for a median time of 143 weeks. In addition, the four regimens were assessed for clinical end points (ability to prevent progression to AIDS or death) irrespective of CD4+ cell status.

Overall, ddI alone or AZT combined with ddI or ddC were each more likely than AZT monotherapy to prevent a 50% or greater drop in CD4+ cells, development of AIDS-defining conditions, or death, regardless of whether the patients had previously taken AZT. When assessed only for clinical end points—preventing progression to AIDS and or prolonging survival—ddI alone or in combination with AZT were both superior to AZT monotherapy.

Prior AZT Use

Because of the possibility that prior treatment with AZT could influence the effectiveness of various treatment strategies, the investigators also examined the results of the different treatments in patients who had previously taken AZT and in AZT-naive patients.

They found that the 1067 AZT-naive patients were helped most by the combination of AZT and ddC, which yielded a significant benefit in preventing progression to AIDS and prolonging survival.

There were also supportive trends with respect to clinical end points (preventing progression to AIDS or death) for combined AZT-ddI therapy and ddI monotherapy in the AZT-naive patients, noted Scott Hammer, MD, of Harvard Medical School, who described the study’s findings at the ICAAC meeting. However, only the benefits observed in the AZT-ddC combination reached statistical significance, he noted.

The 1400 patients previously treated with AZT benefited most from treatment with either ddI alone or combined with AZT. Both these regimens were superior to AZT monotherapy in prolonging survival. However, unlike the AZT-naive patients, those receiving the AZT-ddC combination did no better than patients taking AZT alone.

It’s not yet clear why AZT-ddC combination therapy provided a clinical benefit in AZT-naive patients and not those with prior AZT experience. However, this particular wrinkle in the ACTG 175 results agrees with the overall findings of another clinical trial, ACTG 155, which found no significant difference between the AZT-ddC combination and either AZT or ddC monotherapy in heavily AZT-treated patients with advanced disease.

“The first trial to look at viral end points in real time,” he noted.

The researchers found that viral load declined during the first 8 weeks in all of the treatment groups, but continued to do so only in individuals receiving ddI alone or, to an even greater degree, those receiving one of the two combination therapies.

Combination therapy with AZT and ddI or AZT and ddC or monotherapy with ddI are reasonable approaches based on these results, noted Hammer.

“A change in the approach to initial management of HIV disease may be signaled [by these findings], or at least should be debated,” he said.

Combinations Score Again

Preliminary results from the Delta trial indicate that patients who took AZT
combined with either ddI or ddC had a mortality rate that was 38% lower during a 2-year period than that of patients receiving AZT monotherapy.

The Delta trial studied more than 3000 HIV-infected patients, divided into two subgroups according to whether they had previously taken AZT or not. Patients within each group were then randomized to one of three treatment arms: AZT monotherapy, combination AZT-ddI, or combination AZT-ddC.

Among the 2131 AZT-naive patients, 17% receiving AZT monotherapy died during the trial, compared with 10% of those receiving combination AZT-ddI and 12% of patients given combination AZT-ddC. Similarly, those receiving AZT alone fared significantly worse in terms of disease progression or death than patients on either combination therapy.

The benefit was sufficiently clear-cut that the trial was terminated on ethical grounds.

However, unlike the AZT-experienced patients in ACTG 175, the Delta results showed no clear benefit of combination treatment for the 1063 patients who had previously taken AZT. Neither disease progression nor mortality rate was significantly different for any of the three treatment groups.

One possible reason that AZT-experienced patients did not fare better with combination treatment is that they had slightly more advanced disease at baseline (reflected by lower baseline CD4+ cell counts) than did their counterparts in ACTG 175.

“We’ve seen with other therapies that they often work less well as patients become sicker due to their HIV disease,” says Dayton.

This difference in response may be clarified by findings of a second NIAID-supported study known as the Community Programs in Clinical Research on AIDS (CPCRA) 007 study, which includes a sicker population of patients—those with CD4+ cell counts of 0.20×10⁹/L or lower. CPCRA 007 is expected to be completed within the next 6 months.

“If we begin to see a sort of dose-response pattern, in which these therapies have some effect in relatively healthy patients, less in slightly sicker individuals, and still less in much sicker patients, that would confirm the sense that it’s harder to treat people at later-stage infection with these drugs,” says Dayton.

**Practice Implications**

It’s likely that the new findings, if they hold up to more intense scrutiny, will result in changes in the recommendations of how physicians should treat HIV-infected patients.

“Obviously, we will have to wait until we see the data published in a peer-reviewed journal, because all we’ve seen so far are some very early glimpses at both the ACTG 175 and Delta data,” cautions Dayton. “Then I hope that sometime in 1996, NIAID will host a state-of-the-art conference to make recommendations to clinicians and patients on the role of combination therapies in the treatment of HIV infection.”

In the meantime, physicians who treat patients with HIV and AIDS should be aware of the new findings because they appear to provide some rationale for using approaches other than AZT monotherapy. “Doctors and patients should weigh this information in light of each individual patient’s situation and make decisions based on that,” says Dayton.

—by Joan Stephenson, PhD

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**Informed Consent Waiver for Emergency Research**

**THE REQUIREMENT** for informed consent from subjects participating in some types of clinical experimental studies is in the process of being waived. The Food and Drug Administration (FDA) is proposing ways to make it easier for drugs and devices to be tested under life-threatening situations where the patient is unable to give consent to participate in research.

The action is prompted by growing concern that the current rules, as they are interpreted, are “making high quality acute care research difficult or impossible to carry out at a time when the need for such research is increasingly recognized,” said the FDA in announcing the proposed rule.

The proposal is designed to amend the rule for drug and device testing in circumstances where the patient is unable to give informed consent. It provides that an independent physician and the institutional review board (IRB) granting approval of such research agree that the study addresses a life-threatening medical condition.

In addition the following criteria must be met:

- Available treatments are unproven or unsatisfactory;
- Research is needed to determine the best intervention;
- The research could not be conducted otherwise;
- Obtaining informed consent is not feasible; the intervention must be done immediately, precluding obtaining surrogate permission from the patient’s representative; and
- The risks and benefits of the experimental treatment are reasonable.

The need for clarifying the testing of drugs and devices under such circumstances arose from a decision in August 1993 by the Office for Protection from Research Risks (OPRR) at the National Institutes of Health (NIH) to stop such studies on the grounds that they were not in accordance with federal regulations regarding the protection of human subjects in research because prior informed consent had not been obtained.

Until then, many such studies had used “deferred consent.” Virtually by definition, eligible patients are unable to give prior consent. Under deferred consent, the patient or legally authorized representative was asked to participate in the study after initial entry. This, the OPRR ruled, did not constitute valid prospective informed consent.

This ruling by OPRR prompted an airing of the whole issue earlier this year at a joint meeting between the FDA and the NIH in January (JAMA. 1995;273:687-688) and prompted the development of a consensus statement from a coalition of researchers in acute resuscitation and critical care, including the Society for Academic Emergency Medicine and American Heart Association.

The coalition examined the issues involved and drafted a series of recommendations, widely discussed at the January meeting, that should be met when research was being planned under circumstances where the patient is unable to give prospective consent. The coalition’s statement has been published (JAMA. 1995;273:1283-1287).

Announcing publication of the new proposal, FDA Commissioner David A. Kessler, MD, said that when the rules are implemented they “will enable us to get the information we need to approve new and better therapies for use in emergency medicine.” Health and Human Services Secretary Donna Shalala, PhD, said the proposal had “broad support from industry, medical, and consumer groups.”

Certainly the proposal seems to have the support of the research communities involved. Michelle H. Biros, MD, research director of the Department of Emergency Medicine at Hennepin County Medical