AIDS THERAPIES

Early AZT Takes a Pounding in French-British 'Concorde' Trial

The anti-HIV drug AZT is one of the few weapons in the clinical struggle against AIDS, and, as such, clinicians rely on it heavily in spite of its obvious limits. For example, the drug can stave off death from AIDS only relatively briefly, because after about a year, on average, the rapidly multiplying virus develops resistance to the drug. Nonetheless, clinicians have hoped that administering AZT early in HIV infection to people who have not yet developed symptoms could help postpone the onset of fullblown AIDS. But new results from a large European trial indicate that those hopes may well be misplaced —and that the limits of AZT may be even more severe than was previously understood.

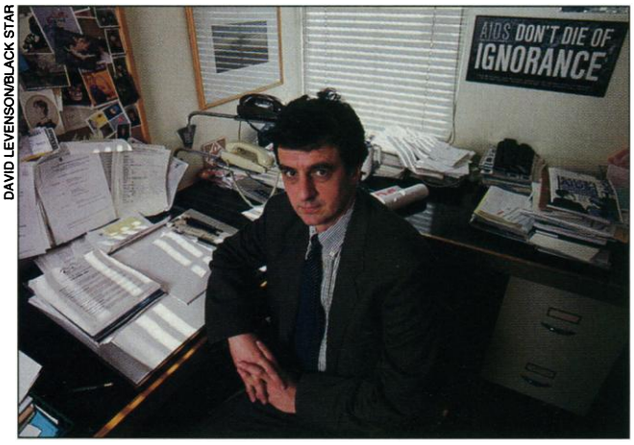
In the 2 April *Lancet*, researchers from the joint French-British "Concorde" study report that AZT offered no "significant benefit" in improving rates of survival or disease progression for 3 years in HIV-infected people who were free of AIDS symptoms at the trial's start. The results of the trial, sponsored by Britain's Medical Research Council (MRC) and France's National AIDS Research Agency, call into question U.S. guidelines that suggest treating asymptomatic HIV-infected patients as soon as their immune systems show evidence of damage. Because it appears to contradict current U.S. practice, the *Lancet* letter has become Topic A on both sides of the Atlantic for researchers, HIV-infected people, and the drug's manufacturer. Some lay media have also played the story to the hilt, the most egregious case being that of Britain's *Daily Express*, which trumpeted scientists' "admission" that a "'miracle' AIDS drug had flopped."

AIDS researchers are dismayed by that kind of hyperbole. Indeed, it was to short-circuit even more outrageous kinds of coverage resulting from leaks before the study was published that the investigators decided to publish a preliminary report in a letter to *Lancet*. "This is really just a press release to the scientific community," says Ian Weller, principal investigator for the British team who is a professor at London's University College and Middlesex School of Medicine. Weller calls Concorde "a very, very powerful study," but he cautions that it is "premature" for clinicians to change the way they prescribe AZT until data from the trial are more thoroughly analyzed and published in full.

But many AIDS clinicians already see the writing on the wall. If Concorde's findings hold up, says Deborah Cotton, an AIDS researcher at the Harvard School of Public Health who sits on the Food and Drug Administration (FDA) advisory board that recommended licensing of AZT for use in asymptomatic, infected people, it will change treatment. "In my own practice, this sways me toward waiting before recommending AZT," says Cotton.

The Concorde trial included 1749 participants from France, the United Kingdom, and Ireland. Participants were randomly divided into two groups irrespective of their number of CD4 cells (critical immune system cells that steadily decline in people infected with HIV). The "immediate" group received AZT, while people in the "deferred" group started with a placebo and switched to AZT only when they began experiencing AIDS symptoms. When the trial ended on 31 December 1992, 92% of the immediate group had survived. But so had 93% of the deferred group. The progression rate to disease or death was 29% for those who took AZT immediately and 32% for those who were deferred.

Those findings appear to conflict with the results that led FDA to approve AZT for HIV-infected people who are asymptomatic.



DAVID LEVENSON/BLACK STAR

Study guide. Concorde's British principal investigator, Ian Weller.

The most compelling data suggesting that AZT can benefit asymptomatic people came from a trial organized by the National Institute of Allergy and Infectious Disease's (NIAID) AIDS Clinical Trials Group (ACTG) called "Protocol 019." The 1338-person trial was stopped after 1 year when an interim analysis revealed that treated patients were more slowly progressing to AIDS. It led FDA to approve the use of AZT in asymptomatic people who had fewer than 500 CD4 cells (about half the normal amount). It also led Concorde researchers to offer AZT to people in that CD4 range who were receiving placeboes, one-third of whom did so during the latter part of the trial; this, argues AZT-manufacturer Burroughs Wellcome, caused "heavy contamination" of the data—a point Weller vigorously disputes.

Burroughs Wellcome may be trying to downplay the Concorde findings, but it's too late: The data are causing a welter of powerful reactions among AIDS activists and researchers. AIDS activist Mark Harrington sees the Concorde trial as a real setback, since early treatment with AZT drew many people into the health-care system who otherwise would have stayed clear. "It's a terrible result," says Harrington. "It undermines the foundation for early AIDS care."

Part of the uproar has to do with NIAID. NIAID director Anthony Fauci, who stresses that there can't be "an official line until we have a chance to go over the data," says his initial response to the *Lancet* paper is that "it confirms on a short-term basis that there is a benefit to AZT." Fauci was referring to the fact that, although in the 3-year data there was no difference between treated and untreated groups in survival or disease progression, when the data are evaluated after only 1 year, the investigators did see a delay of disease, a finding that they noted was "not inconsistent" with the results of four similar trials in "early" HIV-infection conducted in the United States. Fauci adds that with the availability of the anti-HIV drugs ddI and ddC, the trend now is away from treatment with a single agent anyway. "I don't look at this as a cataclysmic change," says Fauci.

AIDS activists and even officials from Britain's MRC were critical of NIAID officials for downplaying the possibility that early administration of AZT may not be a good idea. Mark Harrington slams NIAID officials for going into "damage-control mentality" and focusing on the Concorde trial's design. Alan Stone, head of the MRC's AIDS Secretariat, also was disappointed that NIAID officials spent so much time listing questions the study raised rather than acknowledging the potential import of the trial. "When they do see the results, I'm sure they'll say they were being overcritical and overcautious," says Stone.

The controversy should come to a head soon. In the next few weeks, new data from another large AZT trial in asymptomatics conducted in Australia and Europe is expected to be published. Then, in late June, NIAID plans to hold a "state-of-the-art" meeting, where a panel will review all of the available data from trials with AZT and make suggestions for treatment strategies.

–Jon Cohen