AIDS RESEARCH

AIDS Researchers, Activists Fight Crisis in Clinical Trials

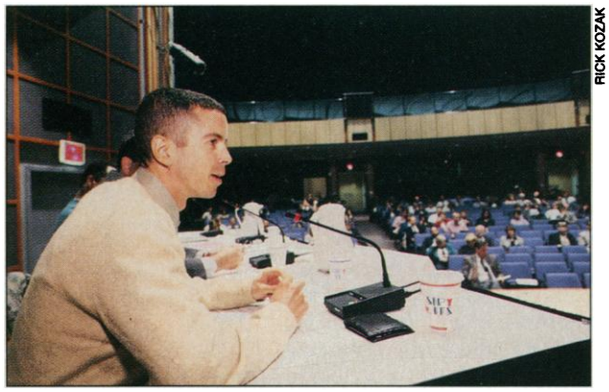
The short history of AIDS research has been punctuated with frequent, explosive altercations between AIDS activists and drug regulators over how to bring effective, safe anti-HIV drugs to patients as quickly as possible. Earlier this month, however, the battlefield experienced an unusual calm as the feuding parties got together to discuss how to solve an emerging crisis in AIDS drug development.

At a workshop on "Current Issues in AIDS Clinical Trials: Clinical Endpoint Confirmation Studies," which was held from 6 to 8 September at the National Institutes of Health (NIH) in Bethesda, Maryland, Food and Drug Administration (FDA) officials, drug company representatives, academic AIDS researchers, and AIDS activists agreed that radical new strategies are needed to keep patients in clinical trials for long enough to be able to sort the good drugs from the bad or useless. Testing drugs in early HIV disease is "unwieldy ... difficult, if not impossible," said AIDS physician-researcher Michael Saag of the University of Alabama, Birmingham. The problem: With only marginally effective anti-HIV drugs available by prescription, but myriad experimental drugs available through other channels, HIV-infected patients cheat to get into clinical trial protocols, fail to follow the trial protocols, and drop out in record numbers.

"AIDS activists brag about how they cheat to get into a clinical trial. That is incredibly unethical," said David Barr of the Gay Men's Health Crisis in New York City. "We have to educate people about the value of AIDS research for ourselves and for those who follow."

But education wasn't the only remedy that participants at the meeting, which was run jointly by the FDA and the National Task Force on AIDS Drug Development, came up with. Another key recommendation is to ease the conditions of the trials by allowing patients to take additional drugs after, or in combination with, the test and placebo drugs. But the meeting failed to reach consensus on an old controversy that has resurfaced in part due to the difficulty of keeping patients in trials: the use of changes in "surrogate markers," in this case, the amount of virus in a patient's blood, as a quick gauge of treatment efficacy.

Results reported earlier this week at the 35th Interscience Conference on Anti-Microbial Agents and Chemotherapy in San Francisco illustrate just how difficult conducting AIDS trials can be. Scott Hammer of Harvard Medical School in Boston presented the results of protocol 175 of the AIDS Clinical Trials Group. That trial compared the effects of AZT, the oldest of the approved AIDS drugs, with related drugs called ddI and ddC, either alone or in combination with AZT, in patients who had taken AZT previously and in those who had not. The results were encouraging in one regard, Hammer says.



RICK KOZAK

Ambassador-activist. Peter Staley of the Treatment Action Group counsels researchers to concentrate on finding out which anti-HIV drugs improve survival rates.

Patients in midstage disease who had previously taken AZT and continued to do so had a death rate of 10%, but when the AZT was replaced with ddI or ddI was added to the AZT, the death rate fell to 5% to 6%. That increase in survival is seen by many as a breakthrough. But Hammer says, "We were fortunate to be able to detect the difference." The main problem was that by the time the trial ended, 53% of the 2467 patients in the trial had discontinued the study treatment.

This is a recurrent problem in AIDS trials, says Whaijen Soo, vice president of virology at Hoffmann-La Roche, which manufactures ddC and the protease inhibitor Saquinavir. "We're running in circles," complains Soo, who is also the spokesperson for the InterCompany Collaboration, a loose confederation of 16 companies working on anti-HIV therapies. "Our current statistical methodologies cannot accommodate the rate of [patient] withdrawal."

The high dropout rate isn't the only problem bedeviling such trials, say other AIDS experts. They also have to contend with subjects who lie to meet recruitment criteria or use drugs not specified by the protocol while enrolled in the trial. At the root of these problems, say AIDS experts, is the combination of the patients' desperation and the wide variety of experimental therapies available.

With their lives at stake and few proven therapies to choose from, HIV patients are willing to gamble on experimental therapies that they can get by enrolling in clinical trials. And many other therapies are available outside the trials, through such sources as FDA's accelerated review program, which approves drugs for life-threatening diseases on the basis of preliminary data; drug company's expanded access programs that provide experimental drugs to patients who have exhausted all other options; and the underground "buyers' markets." As a result, once enrolled in a trial, many patients fail to comply with the trial protocol. Or they drop out—sometimes after only a few weeks—to enlist in another trial, or simply to design their own drug regimens. This makes it difficult to detect a difference in survival between patients on different test therapies, or to tell whether any differences that do occur—good or bad—are due to the therapy under test or some other drug, says statistician Victor DeGruttola of the Harvard School of Public Health in Boston.

In a breakout session focusing on how to solve these compliance problems, AIDS activists and researchers agreed on a new strategy designed to encourage participants to stick with clinical trials. Their recommendations included allowing patients to enroll in more than one clinical trial at a time; individualizing therapy so that in clinical trials testing a sequence of drugs, patients switch from one to the next according to how rapidly their disease is progressing, rather than according to some arbitrary time table; and abolishing rudimentary control treatments—usually AZT alone—in favor of "standard of care" controls. In those studies, patients in the test arm would receive standard care plus the test drug, ensuring that all patients have the option to pursue what they see as the best available therapy.

"Getting acceptable compliance depends on finding the conditions that are acceptable to patients and physicians," DeGruttola told the workshop. According to the chief of NIH's HIV research branch, Lawrence Deyton, more flexible protocols do not undermine the scientific basis of a clinical trial, because the best test of a drug is to show it works against the real-world backdrop of multiple therapies, both mainstream and alternative. But it does mean that clinical trials must be strictly randomized and enroll large

numbers of patients—several thousand, at least—if the subtle differences in survival are going to be detectable, he says.

Even if more flexible protocols do help keep subjects in clinical trials, some experts believe that it will no longer be possible to run large trials on every drug combination in all stages of HIV disease for long enough to get data on changes in death rate or symptoms, the gold standards for clinical trial efficacy. And that is resurrecting the issue of surrogate markers for judging the efficacy of a treatment. Each camp's arguments mirror those used a few years ago when the use of CD4 counts, which assess the status of the principal immune cell destroyed in AIDS, as a surrogate marker came under scrutiny. That practice was curtailed after a barrage of criticism from statisticians and clinical trialists (*Science*, 10 June 1994, p. 1538), who argued that surrogate markers are deceptive, not least because they can miss the toxic side effects that outweigh any beneficial effects of a drug.

But in the current AIDS research environment, surrogate markers, especially viral load, are regaining popularity. Alabama's Saag is one of the proponents of the surrogate marker approach. He points out that changes in the amount of virus in a patient's blood are a far more direct measure of a drug's activity than CD4 counts. Considering the urgency of the situation, he says, "if a drug regimen persistently lowers the viral burden, it should be enough to convince us of a drug's efficacy without having to go to more grotesque clinical endpoints."

But others fear that AIDS researchers may be jumping the gun on the use of surrogate markers. They counter that even though viral load is a good prognostic tool—patients with a high virus count usually decline very quickly—so far there's been no definitive study showing that a drug that decreases viral load improves survival or any other clinical symptom of HIV disease. "We need five or six good clinical trials ... to be able to say that viral load is a viable surrogate marker," said biostatistician Laurence Freedman of the National Cancer Institute.

Some AIDS research experts at the meeting took an even firmer stance against surrogate markers. They argued that it's not possible to validate a surrogate marker for drug efficacy, because a marker that correlates with survival under one drug regimen may not with a second regimen because of different toxicities. "You can have a home-run surrogate marker drug that kills more people than the disease," said AIDS activist Peter Staley, founding director of the Treatment Action Group in New York City. To illustrate his point, Staley referred to the recent brouhaha over the calcium blocker nifedipine. On the basis of nifedipine's ability to lower high blood pressure—a surrogate marker for stroke and heart disease—it is prescribed to millions of Americans. But a meta-analysis of 16 clinical trials reported in the 1 September issue of *Circulation* suggests that patients with heart disease who take the highest recommended dose of the drug die at three times the rate of patients who do not.

"If you want to know the clinical benefits [of a drug], you have to look at clinical endpoints," said David Feigel, head of the FDA's anti-retroviral drug division. "There's no free lunch to this." And that's a sentiment with which Staley clearly agrees: "As AIDS activists, we've always realized that there is a crisis in [drug] access, but there is also increasingly a crisis in information." And without clinical endpoint studies, he said, "we will never know whether we are inadvertently doing more harm than good around anti-retroviral therapy."

–Rachel Nowak

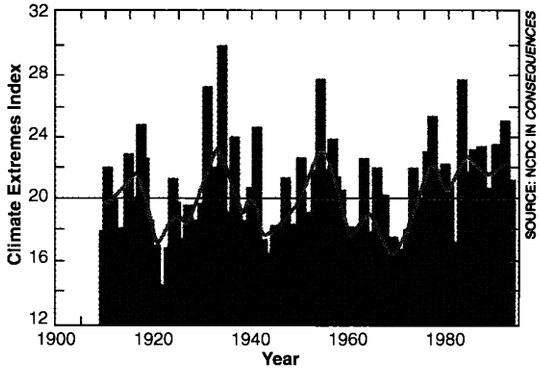
GLOBAL CHANGE

Scientists See Greenhouse, Semiofficially

The greenhouse warming is now official—at least that was the unofficial word last week. The global warming of this century "is unlikely to be entirely due to natural causes," in the words of a draft report from the United Nations–sponsored Intergovernmental Panel on Climate Change (IPCC), which represents the consensus view of the international scientific community. That judgment, however, came not in an official news release but via the Internet and the *New York Times*.

The IPCC report, the panel's first full report in 5 years, will not be officially approved until later this year. But in a well-intentioned effort by U.S. researchers to expedite review of the draft, part of it—a selective synthesis of the full report—was posted on the World Wide Web, where it was available to anybody who cared to read it. "We weren't the ones who published it," says Bruce Callander of the IPCC Working Group I technical support unit in Bracknell, England. "This is not an IPCC-approved statement. At the moment, the document could change." But the essence of the statement is likely to survive into the final report, say panel members, and it offers a window on the latest thinking on climate change—and on the meaning of publication in the electronic age.

The source of the leak was the home page of the U.S. Global Change Research Program (USGCRP), where the draft of the IPCC synthesis report had been placed, according to Michael MacCracken, executive director of USGCRP in Washington, D.C. The idea was to make the synthesis, which had been transmitted to the U.S. government for comment, more accessible to the U.S. scientists who would help supply that critique. The electronic document was festooned with warnings that it was for U.S. government review only and not for publication or distribution, but a *Times* reporter read the document. The *Times* considered its appearance on the Web to be tantamount to publication, says Richard Moss of the IPCC technical support unit in Washington, and went with the story.



Fever line. A composite index of weather extremes has been high since the mid-1970s.

Unofficial though it may be, the IPCC statement on detection of greenhouse warming marks a milestone in awareness that human activity is changing the climate. Since the last full IPCC report in 1990, researchers trying to model what greenhouse warming should look like have gained a better understanding of the climate system, including how pollutant aerosols have been cooling some regions (*Science*, 16 June, p. 1567). As a result, the models and the temperature record are now "much more similar than they are different," says Thomas Karl of the National Climatic Data Center in Asheville, North Carolina, who is an author of part of the Working Group I report. Karl and other researchers have also traced an increase in weather extremes since the mid-1970s that seems to bear the signature of the greenhouse effect (*Science*, 21 April, p. 363).

The evidence suggests that the observed warming "is unlikely to be caused by natural variability," says Karl, who cautions that he is speaking for himself, not the IPCC. "There's a 90 to 95% chance that we're not being fooled." For 99% confidence, he says, we'll have to wait at least another 5 years.

–Richard A. Kerr