AIDS

Ethics of AZT Studies in Poorer Countries Attacked

Tuskegee. Nazi experiments. The needless deaths of babies. The rhetoric certainly heated up at a congressional hearing on bioethics held on 8 May when the topic turned to U.S. government–funded studies in developing countries aimed at preventing the transmission of HIV from mothers to infants. After listening to criticisms of the studies by the Washington, D.C.–based Public Citizen's Health Research Group, Representative Christopher Shays (R–CN), chair of the Subcommittee on Human Resources, opined: "It does blow my mind."

Public Citizen, a consumer-advocacy organization, has been waging a high-profile campaign in recent weeks to modify the trials, arguing that it is no less than mind blowing that they include as control subjects pregnant women who are given no treatment to prevent maternal transmission of HIV. But at the hearing, AIDS researchers and their sponsors vigorously defended the trials, which are under way in Africa, Thailand, and the Caribbean, testifying that they may answer critical questions for HIV-infected women in those countries. Several people called to testify also expressed dismay at the inflammatory rhetoric and the aura of an emerging crisis fostered by Public Citizen, noting that the studies were thoroughly debated before they were launched. As Harold Varmus, head of the National Institutes of Health (NIH), said to the subcommittee, "The issues that were raised by Public Citizen and brought to your attention are not new ones."

Public Citizen's Health Research Group first weighed in on the trials at a press conference 3 weeks ago. The organization's head, Sidney Wolfe, branded nine U.S.-funded studies as "Tuskegee Part Two," a reference to the infamous syphilis trials in which African-American men were denied effective treatment so researchers could observe the progression of the disease. Wolfe claimed that more than 1000 children in foreign countries whose mothers took part in the trials would needlessly be born with HIV infections.

The trials themselves grew out of a critical discovery more than 3 years ago. In February 1994, a large study of HIV-infected pregnant women in the United States and France, known as ACTG 076, found that an intensive course of treatment with the anti-HIV drug AZT could prevent maternal transmission of HIV nearly 70% of the time. Researchers quickly realized that the results would have little relevance in most developing countries, where the incidence of AIDS is rising the fastest. The reason is that most HIV-infected women in those countries cannot afford the treatment, which entails taking AZT during pregnancy, receiving an intravenous drip of the drug throughout labor, and feeding the infant AZT syrup for 6 weeks after birth.

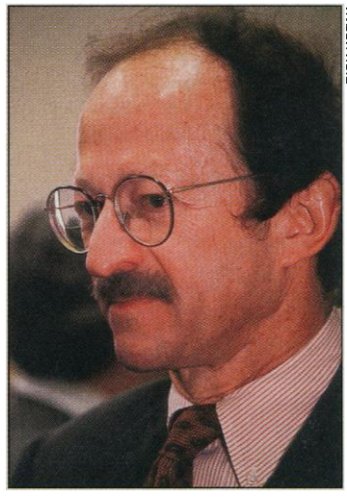
This realization got many investigators interested in testing cheaper prevention strategies, such as shorter drug regimens, vitamin supplements, or HIV-antibody injections (*Science*, 4 August 1995, p. 624). At the time, researchers debated whether it would be ethical to incorporate into the studies a control group that would receive only a placebo.

According to a widely held ethical precept, people who volunteer to take part in clinical trials should be given, at the very least, the standard of care in their country. Proponents of placebo-controlled trials argued that if the standard of care was no treatment at all, the use of placebos would be ethically justified. At a World Health Organization meeting in June 1994, AIDS researchers from around the world agreed, recommending that "[p]lacebo-controlled trials offer the best option for a rapid and scientifically valid assessment" of alternatives to ACTG 076.

Wolfe and his co-worker, AIDS researcher Peter Lurie of the University of California, San Francisco, disagree vehemently. In a 22 April letter to Health and Human Services (HHS) Secretary Donna Shalala, they called such trials "blatantly unethical" and called for an investigation by HHS's inspector-general into how the trials received approval. "We are confident that you would not wish the reputation of your department to be stained with the blood of foreign infants," they concluded.

In his testimony at the hearing, Lurie pointed to two trials in Thailand that he said illustrate the "inconsistencies and the lack of coordination" in this area: NIH is funding one trial that compares short treatments of AZT to a regimen similar to ACTG 076; the Centers for Disease Control and Prevention (CDC) in Atlanta is supporting a trial that compares similar short treatments to a placebo control. "How can that be?" asked Lurie. "The minute people go overseas, it's like they change their research ethics at the customs desk."

Anne Willoughby, who heads the pediatric and adolescent AIDS branch at the National Institute of Child Health and Human Development, contends that the two studies—although not by design—actually "fit together." Willoughby notes that the smaller and simpler CDC trial, which should end next year, addresses safety questions that the just-beginning, NIH-funded one does not. "In AIDS, we often think one study solves everything, and it doesn't," says Willoughby. CDC director David Satcher also told the subcommittee that the trials Wolfe and Lurie are attacking were approved by independent review boards both in the United States and in the host country. He further stressed that he regards "respect" for the host country's desires as an essential ethical principle.



RICK KOZAK

In the hot seat. At the hearing, NIH's Harold Varmus fielded questions about studies aimed at preventing maternal transmission of HIV.

NIH's Varmus offered the subcommittee letters he has received from foreign and U.S. researchers blasting Public Citizen's arguments. One came from Edward Mbidde, chair of Uganda's AIDS Research Committee, who wrote that he read Public Citizen's arguments with "dismay and disbelief." He described their attack as "patronizing" and said it reeked of "ethical imperialism." Mbidde outlined a scenario in which a control group of women receiving the full ACTG 076 treatment would fare better than a group given an experimental treatment that could be widely used in his country. "Obviously, we would say those [experimental] treatments are inferior and therefore not recommended," wrote Mbidde. But what if the treatments, when compared to no treatment at all, reduced transmission significantly? asked Mbidde. "The reaction and recommendations would be different!"

Shays concluded the hearing by saying there "will definitely be follow-up"—possibly in the form of another hearing.

–Jon Cohen