Did Liability Block AIDS Trial?

Abbott claims that legal risks led it to delay a planned trial of an AIDS drug for infected pregnant women, but researchers involved in the project are outraged–and skeptical about the company's motivation

At the eleventh hour, Abbott Laboratories has blocked human trials of a promising immune preparation that might prevent the spread of the AIDS virus from infected pregnant women to their infants. In a heated 6 July conference call with more than 30 organizers of what was to be a landmark experiment sponsored by the National Institutes of Health (NIH), Abbott officials announced that testing its HIV hyperimmune globulin (HIVIG) in these women would make the company too vulnerable to lawsuits, and so they had decided to put off the trial. The company also refused to allow NIH to use $150,000 worth of Abbott HIVIG already on hand.

Researchers who have spent more than 2 years organizing the trial are outraged that the trial will not begin this month as planned. Although NIH is shopping for a new manufacturer of HIVIG (a leading contender is the New York Blood Center, which has made HIVIG for chimpanzee experiments), the researchers complain that an Abbott pull-out will delay the study for at least a year. And a delay could cost lives. In the United States, HIV is transmitted from an infected mother to her infant about 30% of the time. At least 6000 HIV-infected women give birth in the United States each year, and therefore a minimum of 1800 children become infected in a year's time. Many more in the developing world become infected. "Potentially," says the University of Rochester's John Lambert, one of the study's two principal investigators, "this means that many thousands of infants will be infected with HIV while a new HIVIG product is made."

AIDS activists quickly attacked the Illinois-based pharmaceutical company for interrupting plans for the trial of HIVIG, a mix of concentrated antibodies from healthy HIV-infected people. The AIDS Coalition to Unleash Power (ACT UP) last week led protests at the Pacific Stock Exchange in San Francisco, briefly stopping trading one day when three members sneaked onto the floor and unfurled anti-Abbott banners. The protesters are urging investors to sell Abbott stock and encouraging consumers to boycott the company's popular infant formula, Similac. And activists have vowed to make sure Abbott representatives attending the Eighth International AIDS Conference in Amsterdam next week will not be "well received." ACT UP says it also is planning large demonstrations in several U.S. cities.

In spite of the uproar, top NIH officials agree with Abbott that liability is a significant issue in AIDS vaccine and therapy research. A recent investigation by *Science* (10 April, p. 168) revealed that fear of lawsuits has led several HIV vaccine developers to delay or even abandon promising projects. The *Science* article stimulated discussions at the 17 April meeting of NIH's AIDS Program Advisory Committee, where National Institute of Allergy and Infectious Diseases (NIAID) director Anthony Fauci was asked whether liability was a "smoke screen" for HIV vaccine developers. Fauci replied that liability "is very real," he was "very concerned about it," and the issues "are something that we have to address."

Abbott refused requests to interview company attorneys or researchers. But the company did offer a statement and provided responses to some questions. The statement read, in part: "Abbott is continuing to work towards execution of NIH contract for the HIVIG study. Throughout the discussions, Abbott has sought assurances that NIH will waive Abbott's liability for the use of HIVIG in clinical studies....Abbott continues to expect that this waiver for product liability will be granted. Abbott will begin to supply the product for clinical trials once the waiver is granted."

"I don't have problems that they want indemnification," says Elaine Sloand, a hematologist at the National Heart, Lung, and Blood Institute (NHLBI) who helped put the study together. "The quarrel I have with them is not saying that at the beginning. If you don't want to do it, say you don't want to do it." To Sloand, and other researchers involved in the trial, Abbott officials knew all about liability concerns when the negotiations over the project began more than 2 years ago—and little has changed since then.

NIH officials add that they do not have the authority to waive completely the company's liability. Assuming the liability risk, they say, would require a specific appropriation for the purpose by Congress—leading NHLBI's Sloand to say, incredulously: "They're asking us for an Act of Congress." And several researchers noted in interviews that no pharmaceutical company has ever been given complete indemnification for an experimental preparation.

Although emotions are heated about HIVIG now, at the beginning feelings were more amicable and optimistic. Part of the hope that HIVIG might work stems from the successful use of a similar method in preventing newborns from becoming infected with hepatitis B. Though less is known about HIV infection than about hepatitis B, researchers think a mixture of concentrated antibodies from healthy, infected people might "mop up" the pregnant mother's virus, reducing her viral "load" and decreasing the

HIVIG TRIAL: NIH-APPROVED SITES AND INVESTIGATORS

Bronx Lebanon Hospital Bronx, New York	Andrew Wiznia	Medical University of South Carolina	Ronald Turner
San Juan City Hospital San Juan, Puerto Rico	Eleanor Jimenez	University of California, San Francisco	Diane Wara
Ramon Ruiz Arnau University Hospital Bayamon, Puerto Rico	David Garcia Trias Rafael Diaz	University of California, San Diego	Steven Spector
Baylor University Texas Children's Hospital	William Shearer	Children's Hospital at Albany Medical Center	Nancy Wade
University of Texas Medical School	Keith Hoots	University of Rochester Medical Center	John Lambert
Duke University Medical School	Ross McKenney Jr.	New York Medical College	Asha Gupta
Mt. Sinai Hospital New York, New York	Henry Sacks	Columbia Presbyterian Medical Center	Anne Gershon
		New Jersey Children's Hospital Newark, New Jersey	Ed Connor

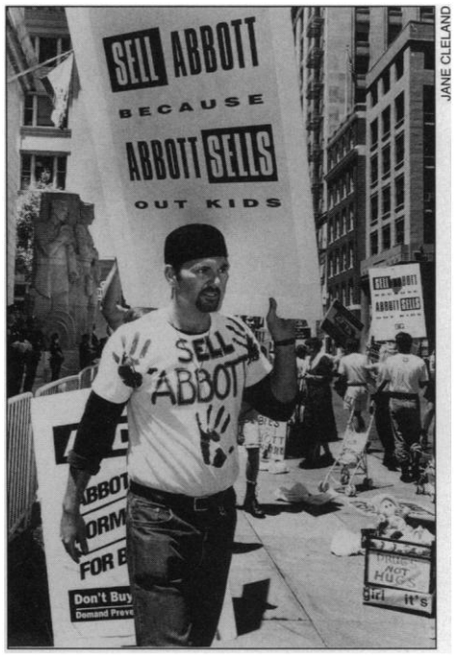
risk of her passing the virus to her fetus. Because transmission can also occur during delivery, infants in the trial would receive HIVIG infusions soon after birth.

The hope that HIVIG will work in this way has been increased by studies in chimpanzees and monkeys suggesting that, in those animals, HIVIG can clear HIV from the bloodstream (although the virus remains sequestered in cells). In addition, recent data comparing DNA sequences of HIV genes in mother-infant pairs suggest that children may become infected when their mother's immune systems are overwhelmed by the rapidly mutating virus, which produces many strains, including specific "escape mutants" (*Science*, 28 February, p. 1069 and p. 1134). Researchers suspect HIVIG might be able to keep escape mutants in check and thereby decrease the risk of transmission.

The notion that anti-HIV antibodies might work in this way probably occurred to many investigators more or less simultaneously, researchers say. Among them were scientists at Abbott. Indeed, one of the ironies of the recent controversy is that Abbott initiated the idea of an NIH-sponsored trial of HIVIG. In 1989 E. Richard Stiehm of the University of California, Los Angeles (UCLA), the other principal investigator, came to NIH and explained that Abbott had an AIDS product it would like to test in pregnant women. NIH was receptive, and planning for the study began, with the aim of eventually enrolling 400 pregnant, HIV-infected women at up to 35 sites; NIH has so far approved 15 sites (see table). A delicate collaboration between three branches of the NIH—NHLBI, NIAID, and the National Institute of Child Health and Human Development (NICHD)—had to be arranged. And the Food and Drug Administration (FDA) was persuaded to give its blessing.

During these protracted negotiations, the issue of liability was not raised until 6 months ago, according to Lynne Mofenson, chief study designer at the NICHD. By that point, Mofenson says, an Abbott representative had sat in on several monthly protocol meetings, NIH had made a site visit to Abbott, and the FDA had approved the study. Furthermore, says Mofenson, when Abbott raised the liability concern, NIH was responsive: They changed the informed consent form to reduce the company's liability risk. After that, "I didn't know, nor did our lawyers think, that there was a remaining liability problem," Mofenson says.

But liability concerns hadn't gone away—from Abbott's point of view. At the end of June, the company's upper management balked at signing the final contract laying out the details of the huge clinical trial. *Science* has obtained a confidential NIH memo dated 1 July that outlines the sequence of events. "Despite completion of apparent



JANE CLELAND

Sign of the times. San Francisco protest against Abbott's decision to delay HIVIG trial.

final contract negotiations between authorized legal and contract representatives from Abbott and NIH," the memo reads, "and despite earlier affirmation...of clearance at the 'highest levels' of Abbott, we were notified Monday that the Abbott chairman of the board (Mr. Burnham) has refused to sign off on the contract as negotiated due to renewed concerns regarding liability."

A sense of what those renewed concerns are comes from Abbott's statement, in which the company argues that the liability issue has been raised because "the risk exists, though small, for potentially enhanced transmission to an infant of an HIV-infected mother by infusing HIVIG...into the mother and infant." This statement refers to the possibility that HIVIG could theoretically contain HIV antibodies that might make it easier for the virus to infect infants. That may seem paradoxical, since the job of antibodies is to wipe out viruses and other invaders. Yet so-called enhancing antibodies have been seen in laboratory experiments, though there is scant data on their presence in living human beings.

Several trial organizers insist the medical risk in a clinical test is small. Principal investigator Stiehm notes that Abbott has already safety tested HIVIG in 13 infected people and found no enhancement by antibodies or other adverse effects. Stiehm adds that the trial design calls for the project to begin with a small number of well-informed women and to be halted immediately if adverse effects appear.

But those provisions didn't mollify Abbott. During the 6 July conference call, an Abbott representative suggested that Congress could tag on an indemnification statement removing liability from Abbott to the annual NIH appropriations bill. To which an NIH researcher replied, "Don't be absurd," according to several participants in the conference call.

Stiehm and several other researchers say they are skeptical of Abbott's announced motivation for delaying the trial. They don't think liability is a sufficient threat to cause the company to put the trial off. They told *Science* they think the real reason is the fact that the product is expensive to produce and that the market—pregnant women infected with AIDS—is small. A small market and high production costs lead to a very expensive product: The NIH rate is $10,000 per mother-infant pair. And they point to the criticism Burroughs Wellcome took when it initially priced the anti-AIDS drug AZT in that range. Though the expense of the trial itself was covered, researchers speculate that Abbott worried about HIVIG working well in clinical trials—and as a result the company would be pressured into marketing a money loser.

Abbott denied that it was motivated by concerns about profitability. In fact, the company said, Abbott "has no intent to commercialize HIVIG. Abbott has committed to work with NIH in clinical studies and to work diligently to find a company able to produce and commercialize the product if it is found to be clinically beneficial. In order to accomplish transfer of knowledge and technology, it is Abbott's belief that product liability concerns...will need to be resolved."

Whatever its motivations, Stiehm believes Abbott will regret pulling the plug on this study. "We geared up a lot of sites, there are a lot of pregnant women involved, and [Abbott] has accelerated this," says Stiehm. "If Abbott doesn't go forward, its name will be held in great disrepute in both the scientific and the pediatric community."

There are some signs that that is true, at least among those involved in the planned trial. Diane Wara of the University of California, San Francisco, who heads the pediatric core committee of the AIDS Clinical Trials Group at NIAID, said, "I think it's totally irresponsible for a company to work along with investigators and NIH and seem to support development of a trial as important as this and then withdraw its support at the last minute."

Wara may have stronger opinions than most researchers on the subject, but the HIVIG controversy isn't likely to go away unless a compromise can be achieved. As *Science* went to press, a meeting was planned between lawyers for Abbott and NIH. AIDS activists also have been discussing the delay with Abbott attorneys and attempting to negotiate a meeting with company executives. But if no compromise is reached, Abbott could be in for a long, hot summer.

–Jon Cohen

Jon Cohen is a free-lance writer based in Washington, D.C.