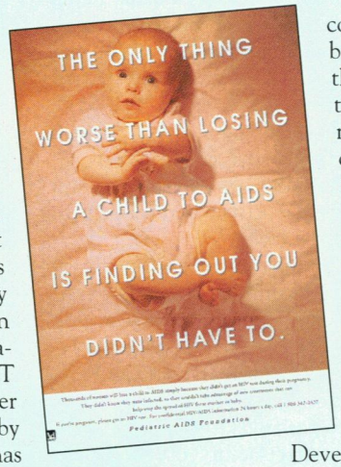
Bringing AZT to Poor Countries

This drug can reduce HIV transmission from mothers to infants—but dramatic new means must be found in order for developing countries to make use of it

In the next few weeks, magazines and newspapers in the United States will begin running advertisements that show a baby lying on a quilt with these words superimposed over the image: "The only thing worse than losing a child to AIDS is finding out you didn't have to." The ad is part of a campaign launched by the Pediatric AIDS Foundation in response to last year's dramatic finding that the drug AZT can reduce the risk of a mother transmitting HIV to her baby by almost 70%. That finding has been heralded by AIDS researchers as their first real breakthrough in a decade-long effort to find chinks in HIV's armor.



But many have also been upset that, as the new ad warns, thousands of HIV-infected pregnant women are not heeding the August 1994 recommendation of the U.S. Public Health Service (PHS) that they take advantage of this good news. That call was reinforced just last month when the PHS suggested that all pregnant women voluntarily receive HIV testing, as there is now an effective means of preventing HIV from being transmitted to their infants.

The tragedy of babies unnecessarily becoming infected with HIV is a troubling development that the ad campaign and PHS's pronouncements may help. But another, even starker problem has been highlighted by this AIDS research victory: It means next to nothing to most of the world's HIV-infected pregnant women, the ones who live in developing countries. There are several reasons why this trial, known by its protocol number, 076, isn't very relevant to these women. The main obstacle is that poorer countries can't afford either AZT or the sophisticated clinics used in 076. In addition, 076 calls for repeatedly dosing the mother with AZT during her pregnancy, and many women in developing countries don't visit medical clinics until they are in labor—if then. What's more, these women often don't know they are infected with HIV.

Protocol 076 is also out of synch with developing countries because it requires mothers to use infant formula to avoid the possibility of transmitting HIV through breast milk. Not only do most women in poor countries breast-feed, they've been encouraged to do so by the World Health Organization (WHO) and UNICEF, regardless of HIV status, because breast milk reduces infant morbidity and mortality. In sum, "there are many problems with the transition of the 076 regimen to the developing world," says pediatric infectious disease specialist Lynne Mofenson of the National Institute of Child Health and Human Development (NICHD), a cosponsor of the trial.

Yet, in spite of these drawbacks, researchers focusing on the poor regions of the world are not by any means ignoring the trial's conclusions. On the contrary, a variety of studies now in the planning stages aim to translate 076's success into a preventive strategy that makes sense in the developing world. And other researchers are investigating low-budget strategies to prevent perinatal transmission that do not involve any anti-HIV drugs (see box). In developing these trials, researchers have had to confront a difficult ethical question: Is it acceptable to test new treatments in developing countries against placebos, rather than against a treatment known to work—the 076 protocol?

Even if some of these strategies prove successful in clinical trials, the researchers' work will have just begun, because much of the work of public health in those countries lies in actually delivering drugs to the far-flung, desperately poor population. "Our job as scientists will not stop on the day we have scientific results," says epidemiologist François Dabis of the University of Bordeaux II, who is heading two trials in Africa that will use a simplified version of 076, "especially if we have efficacy."

Remarkable result

When Protocol 076 was launched in April 1991 by the AIDS Clinical Trials Group of the National Institute of Allergy and Infectious Diseases, its design called for enrolling 748 HIV-infected pregnant women in the United States and France. But the data were so strong that that number was never reached. In February 1994, researchers halted the placebo-controlled trial because an interim analysis revealed that AZT had a powerful effect in reducing mother-to-child transmission of HIV. Patients being given placebos immediately were offered AZT.

Previous work had shown that from 15% to 40% of babies born to HIV-infected women become infected with the virus. In 076, 409 women gave birth to live infants. They were divided into a placebo group and

UPCOMING TRIALS IN DEVELOPING COUNTRIES

Investigator/Organization	Protocol+	Size and Location
François Dabis University of Bordeaux II	Placebo vs. AZT, 2x/day, 38th wk to 1 wk postdelivery	150 women in both Ivory Coast and Burkina Faso
CDC	Placebo vs. AZT, 2x/day, 36th wk to delivery	1500 women in both Ivory Coast and Thailand (not breast-feeding)
Marc Lallemant Harvard	*076 vs. AZT 5x/day, 4 arms: • mother 26th wk to delivery + baby through 6 wks • mother 26th wk to delivery + baby through <1wk • mother 38th wk to delivery + baby through 6 wks • mother 38th wk to delivery + baby through <1 wk	1500 women in Northern Thailand (not breast-feeding)
WHO	Placebo vs. AZT/3TC 2x/day, 3 arms: • mother 38th wk to 1 wk postdelivery + baby through 1 wk • mother labor to 1 wk postdelivery + baby through 1 wk • mother only at labor and delivery	1900 women total, in Tanzania, South Africa, and Uganda

+ All studies give an extra dose of AZT at labor. * Preliminary study design.

a treatment group, in which the mothers took AZT five times a day for an average of 11 weeks prior to giving birth. When the treated women went into labor, they were given AZT intravenously. Their newborns then received AZT syrup four times a day for 6 weeks. The interim analysis showed that in the placebo group, 40 babies, or 25.5%, were born infected with HIV. In the treated group, only 13, or 8.3%, of the babies became infected.

Striking as that result was, it left open one of the biggest mysteries in mother-infant transmission: When does it happen? The answer to that question has profound implications for women in developing countries. If transmission is as likely to occur at 20 weeks gestation as it is during birth, a successful drug intervention will have to start early, end late, and include both mother and baby. That thinking is what led to 076's "shotgun" approach, which strove to knock down HIV wherever and whenever it might infect the baby.

But other data are leading researchers to conclude that most transmission occurs in the narrow window shortly before or during labor. "More and more people are coming around to a late transmission time," says NICHD's Mofenson. The combination of this change in researchers' thinking and the difficulty of applying 076 in its original form in developing countries has led many research groups around the world to begin asking just how little AZT a mother—or perhaps only the baby—must be given in order to prevent transmission.

Turning down the volume

Reflecting this recent thinking, the half-dozen 076 spin-off trials now getting under way or being planned in developing countries concentrate on what might be called bow-and-arrow approaches. These trials generally use lower doses of drug than did 076 itself, and they call for shorter treatment schedules, focusing on the period around birth.

The first of these studies is set to begin in the next few months in the West African countries of Burkina Faso and the Ivory Coast. Working with local researchers, French investigators led by the University of Bordeaux's Dabis and gynecologist Laurent Mandelbrot of Cochin Hospital in Paris have designed two separate trials, each involving 150 women. Dabis stresses that these initial studies are not designed to assess efficacy. Rather, the researchers want to make sure the drug is safe and acceptable in these populations. "We're all concerned about giving [AZT] in African women," says Dabis. One of the main worries is that AZT causes anemia, which is already prevalent in these populations. He adds that they do not know whether women in these countries will even agree to take AZT.

The protocol calls for half the women to begin taking AZT twice a day in the 38th week of pregnancy. At entry into the delivery room, they will be asked to take two extra pills, to mimic the IV dose of the drug used in 076. The mothers—nearly all of whom plan to breast-feed—will continue taking AZT for 1 week after delivery in an attempt to prevent transmission through colostrum, the concentrated first milk that comes through a mother's breasts.

The other group of women will take a placebo. In some settings, this would be a controversial decision, as the control is usually the best available treatment—in this case, the 076 regimen. But in these countries, AZT is scarce, and the trial's designers considered it naive to use 076 as a point of reference. "Nobody was in favor—and most importantly, that includes the nationals—of using 076 as a gold standard because it's totally unrealistic," says Dabis. A WHO panel last year also recommended using a placebo rather than 076 in developing-world trials because the differences between treated and control groups will be more pronounced, which will reveal more quickly whether the intervention works. The researchers expect these "tolerance" trials to last 9 months.

Even as Dabis's studies get under way, a full-fledged efficacy study in the Ivory Coast sponsored by the U.S. Centers for Disease Control and Prevention (CDC) is also in the works. Although CDC researchers have safety concerns about AZT and plan to monitor the trial closely for side effects, CDC epidemiologist Phillip Nieburg explains that he thinks an efficacy trial can safely be done now. "Data from 076 don't suggest any major adverse effects, and we're planning to use a much shorter course [of AZT]," says Nieburg. The placebo-controlled trial, which should start by the end of the year, will enroll about 1500 women, who will take AZT twice a day from the 36th week of pregnancy, supplemented by additional doses when they go into labor. Unlike the Dabis trial, the mothers will not take AZT after delivery.

Nieburg notes that this trial will take longer to reach conclusions than 076 did: In

Exploring Alternatives to AZT

Many studies are now under way to test whether relatively small doses of AZT can prevent transmission of HIV from mother to infant (see main text). But even small doses of AZT are expensive by the standards of the developing world, so researchers are also wondering whether transmission can be blocked without any anti-HIV drugs whatsoever. These alternatives are being explored because "no one wants to point everything in one direction," says epidemiologist Neal Halsey of Johns Hopkins University.

Halsey and colleagues are about to start a trial in Haiti that attempts to block perinatal transmission by giving newborns an intravenous preparation of HIV antibodies known as HIV immunoglobulin, or HIVIG. HIVIG is derived from the blood of healthy, HIV-infected donors. Researchers hope this "passive immunization" will thwart HIV in the baby before the virus can establish an infection. Halsey notes that this approach, which he plans to test in nearly 600 infants over the next 4 years, protects chimps from HIV, and immunoglobulins are routinely used to protect infants from hepatitis B infection. In October, virologist Brooks Jackson of Case Western Reserve University in Cleveland and co-workers plan to start an HIVIG trial in Uganda that treats both mother and baby.

An even simpler approach under study is to wash the vagina or the cervix with disinfectants immediately before birth, an attempt to reduce the amount of infectious HIV the baby might come in contact with while traveling through the birth canal. Epidemiologist Robert Biggar of the National Cancer Institute has already tried this approach, using chlorhexidine as a disinfectant in a controlled study of 2000 HIV-infected women in Malawi. Data should be released this fall. François Dabis of the University of Bordeaux II and co-workers plan to launch a similar study this fall in Burkina Faso and the Ivory Coast using benzalkonium chloride.

Johns Hopkins ophthalmologist Richard Semba has a simple idea of his own that may stop perinatal transmission: vitamin A supplements. Semba and co-workers plan to start trials in Malawi in the next few weeks to test this approach, which is based on their observation that HIV-infected mothers deficient in vitamin A are more likely to transmit the virus to their infants (*Science*, 15 July 1994, p. 315).

These alternative approaches may well be a long shot compared to AZT. But if countries can't afford AZT and these alternatives provide even marginal protection, they may be the best shot mothers in some developing countries have to prevent their children from becoming infected with HIV.

–J.C.

a breast-feeding population, it's more difficult to determine efficacy because researchers have to follow the infants for more than a year to make sure that they have not become infected through their mother's milk. To assess the effect of breast-feeding, the CDC plans to stage a similar trial next spring in Thailand, where HIV-infected women routinely use infant formula.

Northern Thailand could also be the site for a hotly debated efficacy study that has been proposed by epidemiologist Marc Lallemant and co-workers at the Harvard School of Public Health, but not yet funded. This trial has stirred controversy because it calls for using the 076 protocol, rather than a placebo, as a control. Lallemant, who is collaborating with 30 Thai physicians under the aegis of Thai officials, defends using 076 as a control because AZT is available to some Thais. He also contends that the trial, which will test four different strategies with 1500 women, will arrive at a more meaningful conclusion. "The real question is, Is [the shorter regimen] going to work less well or as well as 076," Lallemant says. He submitted a grant proposal for this study to the National Institutes of Health last year and hopes to hear a decision in the next few weeks.

And that doesn't exhaust the list of mother-infant AZT trials now on the drawing board. An ambitious mother-infant intervention, involving 1900 women near or in labor, is being planned at the WHO's Global Programme on AIDS. In that trial, scientists hope to cut the dose of drug and simultaneously increase its potency by exploiting a recent finding that AZT is much better at reducing the amount of HIV in a person if it is combined with the experimental anti-HIV drug 3TC. WHO is planning AZT/3TC tests in Uganda, Tanzania, and South Africa. "If the trial is conducted well, we hope to have scientific answers in 3 or 4 years," says Joseph Saba of WHO's Global Programme on AIDS.

Backs to the future?

It doesn't take a crystal ball to see that even if positive results come from some of the clutch of AZT trials now gaining momentum, women in developing countries will still have great difficulty getting drugs to stop HIV from reaching their babies. As a review article on perinatal HIV transmission in the May issue of the journal *AIDS* notes, some countries spend $2 a year per capita on health care—roughly the retail price of two AZT capsules in the United States.

Saba says WHO scientists have spoken to representatives of Glaxo Wellcome, maker of AZT and 3TC, about providing those drugs to pregnant women in developing countries if the planned trials pan out. "We don't need to tell them, 'You need to make [the drugs] more affordable,' " says Saba, who notes that the company is donating the drugs for the WHO trials. "The idea is to work with them." Harvard's Lallemant believes this problem could solve itself when researchers show that shorter regimens work. "The only way for us to lobby for change is 'Let's do it, show it works, and put people in front of their responsibility,' " says Lallemant.

Andrew Revell, project manager for AZT at Wellcome, says providing anti-HIV drugs to developing countries is a familiar quandary for the company that is put in "sharper focus" by 076. "This is a terribly difficult issue," says Revell. "This really does require special thinking, [but] I very much doubt that it will be Glaxo Wellcome giving away unlimited amounts of AZT."

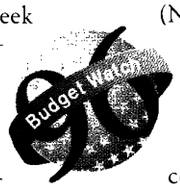
Given that reality, if researchers, government officials, public health advocates, and Glaxo Wellcome don't reach consensus soon, in a few years developing countries may find themselves in a situation that mirrors the problem in the poster that will soon appear in magazines in the rich countries: Watching babies die of AIDS and knowing they didn't have to.

–Jon Cohen

ENERGY RESEARCH

Senate Targets Fusion, Backs NIF

"It's a dismantlement budget," said one senior Department of Energy (DOE) official about the latest bad news fusion researchers are getting from Capitol Hill. The Senate Appropriations Committee last week approved a budget for the fusion program even lower than the drastically reduced level the House approved earlier in July. In its DOE appropriations bill, the panel slashed fusion funding to $225 million—$4 million less than the House level and far below the $373 million the department is spending in 1995. That's also less than the $320 million that a White House advisory panel recently recommended as the bare minimum to keep a viable program.



The constricted fusion budget approved by the Senate panel would allow continued work on the International Thermonuclear Experimental Reactor (ITER), an international effort to build a huge tokamak. But it would halt plans for a U.S. experiment that had been planned as a steppingstone to ITER, the Tokamak Physics Experiment at Princeton Laboratory. "The promise of fusion energy can only be realized through international collaboration," the bill's report states.

Amid that gloomy news for fusion researchers there was one bright spot: The Senate bill, which also includes funding for other DOE science projects, allots money to start work on the National Ignition Facility (NIF), a $2 billion laser project at Lawrence Livermore National Laboratory in California designed to trigger miniature fusion explosions in pellets of hydrogen isotopes. The House rejected NIF last month as too costly, but the Senate bill would provide the entire $37.4 million down payment the Clinton Administration requested for the project.

The football stadium–sized facility, which would help ensure the future of the Livermore lab, would provide an alternative to full-scale tests for the nuclear weapons program. At the same time, it could be used for experiments in inertial confinement fusion, an alternative route to fusion energy. Until now, the focus of the U.S. fusion effort has been on magnetic confinement of hot plasmas in tokamaks.

In nonfusion business, the committee called for DOE to conduct a competition for the site of a new neutron source facility. DOE and House lawmakers want the proposed facility to be built at the Oak Ridge National Laboratory in Tennessee, but the Senate panel says Argonne, Brookhaven, and Los Alamos National Laboratories should be added to the list of candidate sites. The DOE bill provides $8 million to study the new facility, which would be a more modest version of the Advanced Neutron Source the Administration abandoned earlier this year as too expensive (*Science*, 17 February, p. 952).

And in spite of the harsh news for fusion, the Senate committee did find money to provide both Democrats and Republicans with pork projects. The panel set aside $500,000, for example, for an education initiative in Louisiana, to be supported by Livermore and New Mexico's Sandia National Laboratory. Louisiana is home to Senator Bennett Johnston (D), the former chair of the subcommittee and now its ranking member. And Oregon, home state of Senate Appropriations Committee Chair Mark Hatfield (R), would receive $8.5 million from DOE's energy research budget for development of a high-speed computer network for the Oregon Health Science University.

The Senate is expected to debate the DOE bill this week, before Congress begins its August recess. A committee of representatives and senators will sit down in September to iron out a single version to send to President Bill Clinton.

–Andrew Lawler