The Mother of All HIV Challenges

Several studies have shown that cheap, simple treatments can reduce mother-to-child transmission. Applying these advances is another matter

Rachel I. begins to cry, her gaunt frame shaking as she tries to contain her grief. Rachel, 31, is sitting in a social worker's office at a clinic in Abidjan, Côte d'Ivoire, recalling how her life has been torn apart by AIDS.

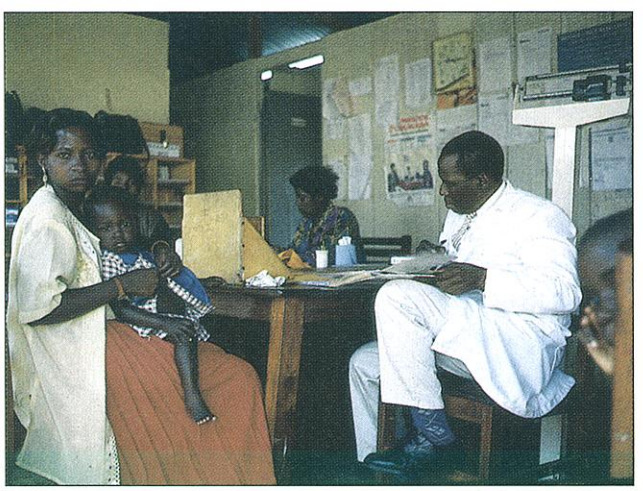
A few years ago, Rachel, who asked that her last name not be used, lost her first child, a 20-month-old boy. She soon became pregnant again and felt sick herself, so, at her husband's insistence, she finally went to see a doctor. The visit stunned her: She was infected with HIV. When she told her husband, who she believes infected her, he exploded with rage. Fearing for her safety, Rachel moved in with her mother.

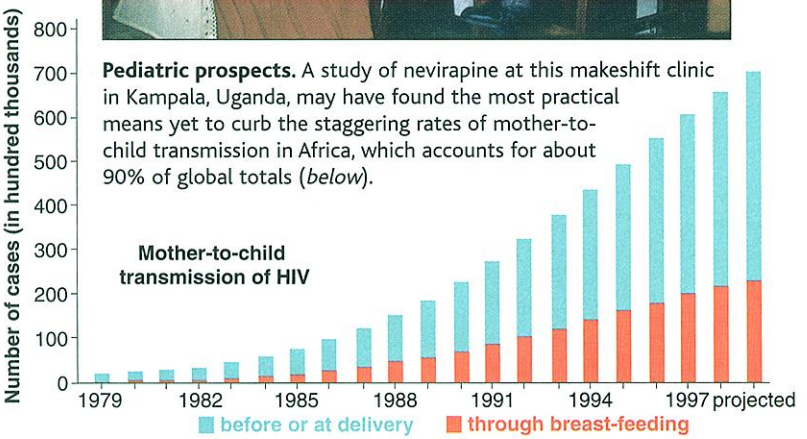
Through her doctor, Rachel learned of an experimental treatment that might help protect her second baby. Researchers in Europe and the United States had discovered that giving the anti-HIV drug AZT to infected women during pregnancy sharply reduces the chance that the virus will be transmitted to her child. A French-sponsored trial called DITRAME in Côte d'Ivoire and Burkina Faso, headed by François Dabis and Phillippe Van de Perre, was testing whether a simpler—and cheaper—version of the therapy would work in Africa, where between 25% and 35% of babies born to HIV-infected women become infected themselves. Rachel enrolled in the trial and soon heard the first piece of good news she had received in a long time: Her second child, a girl, had been born uninfected.

But tragedy quickly struck again. Like the vast majority of women in Côte d'Ivoire, Rachel breast-fed her daughter. Six months later, she learned that she, too, had become infected, presumably through breast milk. "I haven't been well informed," says Rachel. With help from France's Fund for International Solidarity, Rachel began to treat her baby with the anti-HIV drugs ddI, d4T, and 3TC. But it was too late, says Rachel. Her daughter died at 27 months of age.

Rachel's story epitomizes the dilemma throughout sub-Saharan Africa, where nearly 90% of the half-million babies infected by their mothers each year are born. AIDS researchers are finding cheaper and simpler ways to slow the spread of HIV from mother to child, and more pregnant women, even in the poorest countries, have access to anti-HIV drugs and formula—thanks to the largesse of donors, discounts from industry, new trade laws, and the tenacity of individual clinicians (see profile on p. 2163). But even these advances are barely making a dent in the grim statistics, because just as researchers offer ways to clear one enormous hurdle—drug availability—they run smack into other ones, ranging from social stigmas that discourage testing to disinterest on the part of cash-strapped health authorities to a deeply ingrained culture of breast-feeding—often supported by government policy for otherwise sound health reasons.

"With mother-to-child transmission, many scientific questions have been answered," says DITRAME trial researcher Phillipe Msellati, sitting in an Abidjan café one evening this March. "But now we have to implement things, and the question is, 'How do you do it in reality?' "





Pediatric prospects. A study of nevirapine at this makeshift clinic in Kampala, Uganda, may have found the most practical means yet to curb the staggering rates of mother-to-child transmission in Africa, which accounts for about 90% of global totals (*below*).

SOURCE: UNAIDS

Status quo

On Old Mulago Hill in Kampala, Uganda, prehistoric-looking marabou storks stroll on the lawn behind a mustard-colored shack and a canvas tent that helped change AIDS research history.

This shack and tent served as the main clinic and waiting room for a study that involved more than 600 pregnant, HIV-infected women and was run jointly by researchers who work across the street at Makerere University and their collaborators from Johns Hopkins University in Baltimore, Maryland. Half of the women received AZT throughout labor and delivery, and their infants received two doses of the drug each day for the first week of life. In the other group, women in labor swallowed one pill of nevirapine, an anti-HIV drug that the body processes more slowly, and the newborns received one dose of the same medication during the first 3 days after birth. Nearly every woman breast-fed.

In July 1999, an independent group of experts monitoring the trial abruptly ended it because of a startling difference between the babies in the two groups. When they were between 14 and 16 weeks old, 25.1% of the infants in the AZT group had become infected, while only 13.1% in the nevirapine arm were HIV positive. "It blew us all away," says Laura Guay, a Johns Hopkins pediatrician who has lived in Kampala off and on since 1988 and helped run the study.

Guay has since been blown away by a less encouraging statistic: Not a single African country yet offers this $4 regimen of nevirapine to HIV-infected pregnant women, nearly 4 years after the drug came on the U.S. market. And only Uganda, Kenya, and South Africa have licensed it for sale. "It makes no sense to me," says Guay, sitting in her office, located in a new building (built with Johns Hopkins funds) up the

hill from the clinic. "In my talks with several government representatives from countries around here, they raise a lot of questions: 'We don't know about long-term toxicities, we don't know about drug resistance, so we're not going to do anything.' It's incredible." By contrast, she says, when 076 came out, wealthy countries worldwide implemented it within weeks.

Guay's shorthand mention of "076" refers to a study that provided the first convincing data indicating that anti-HIV drugs could reduce mother-to-child transmission of HIV. A drug regimen tested in the study—which was sponsored by the U.S. National Institutes of Health, as was the nevirapine study—cut the transmission rate by nearly 70%. But it had next to no relevance to poor countries, as the treatment cost about $800 and required an intravenous drip of AZT during labor. Further complicating matters, most women took the drug for 11 weeks before birth and none breast-fed. Poor African women, in contrast, often don't seek medical help until they go into labor, and most breast-feed.

In the 5 years between the headlines that celebrated the 076 results and those from the nevirapine study, several cheaper, simpler versions of 076 had proven themselves. Trials in Thailand, Uganda, South Africa, Tanzania, and Côte d'Ivoire, including the DITRAME study that Rachel I. joined, all showed that a short course of AZT or a combination of AZT and 3TC in the last month of pregnancy could lower the risk of transmission by up to 50%. Nevirapine promises similar or better results—with a much cheaper and simpler regimen.

The breast-feeding dilemma

A big question mark hangs over all of these studies: the risk of long-term breast-feeding. The PETRA trial—the largest mother-to-child transmission study to date, with 1792 enrolled—has reported data from only 6 weeks after birth; many African mothers breast-feed for the first few years of life. When continued breast-feeding is factored in, "the data will not be all that rosy," predicts Fred Mhalu, a leading AIDS researcher at Tanzania's Muhimbili University, one of the PETRA sites.

There's little question that breast-feeding greatly increases the risk of transmission. A 6-year study, conducted in Nairobi and published on 1 March in *The Journal of the American Medical Association*, compared infected mothers who used infant formula—provided by the study—to those who breast-fed (*Science*, 11 February, p. 942). Of the babies born uninfected, the study showed that formula-fed children had 16% fewer HIV infections at 2 years of age than the ones who exclusively breast-fed (for 17 months, on av-

Preventing Infections With Today's Tools

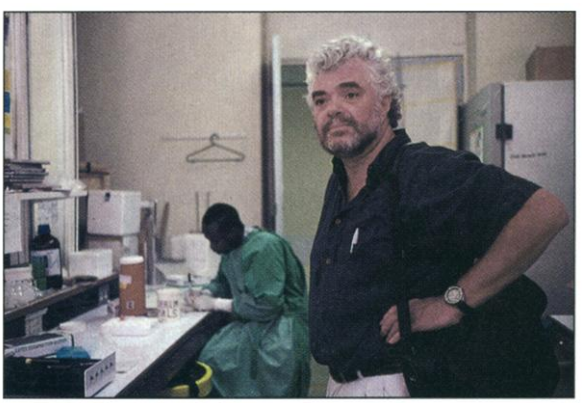
With no vaccine in sight powerful enough to halt the spread of HIV, Africa is left with one strategy to combat the epidemic: prevention. But the record of most countries on this front is dismal. The University of Manitoba's Frank Plummer, who oversees a large research collaboration in Nairobi, Kenya, says his group has identified a half-dozen effective interventions—from bottle feeding to targeting heavily infected groups to male circumcision—to lower HIV transmission rates, but "the scale at which they're implemented is tiny."

PROFILE

"We know how to prevent this infection by targeting behaviors and individuals who are at risk," says Plummer, a specialist in sexually transmitted diseases (STDs) whose team's pioneering studies have focused on sex workers, long-distance truck drivers, adolescents, and babies of infected mothers. "It's been shown to work in Thailand and by our group here. ... [The measures] need to be implemented as quickly as possible."

The collaboration's work with Nairobi prostitutes indicates the powerful multiplier effect of interventions aimed at "core groups" that infect many people. A study of more than 1000 sex workers published in the April 1991 issue of the journal *AIDS* by Plummer, the University of Nairobi's Elizabeth Ngugi and Jeckoniah Ndinya-Achola, and co-workers estimates that their interventions—such as peer-group education, HIV testing and counseling (with distribution of condoms), and treatment of STDs—prevented between 6000 and 10,000 new HIV infections per year among customers and their contacts. The researchers calculated that it only costs between $8 and $12 to prevent each infection. "We need to work with vulnerable groups like sex workers in a very humane way so we can reach people in that population whom they're infecting," says Ngugi, the main liaison with these women. "They are husbands. They are sons. Their sons have wives. High school kids tell me they go for 'breakfast' to sex workers."

The Kenyan group also has produced evidence that male circumcision may lower the risk of HIV infection. In 1994, Stephen Moses, Allan Ronald, Plummer, and co-workers published a sweeping review of 30 epidemiologic studies showing a strong correlation between high rates of HIV infection in Africa and populations that don't practice male circumcision. "If I had my way, there would be circumcision offered to all adult men in AIDS-endemic areas, plus newborn circumcision," says Plummer, who nevertheless recognizes the tricky medical and cultural issues.



Application denied. Frank Plummer sees several underused strategies to thwart the spread of HIV.

Although the Kenyan group and several others have shown a strong correlation between having an STD and the risk of being infected with HIV, two large studies in Africa have come to different conclusions on whether widespread STD treatments would cut HIV transmission rates. One study published in 1995 followed 8500 people in Mwanza, Tanzania, half of whom took part in an intensified STD care and treatment program, while the others received the standard care in the region. At the end of 2 years, there were 40% fewer HIV infections among the treatment group. Then last year, researchers working in Rakai, Uganda, surprisingly reported that their trial, which was nearly twice as large, found no connection between STD treatment and HIV infection rates.

AIDS researchers are passionately debating whether differences in overall HIV prevalences between the two cities—4% in Mwanza and 16% in Rakai—or differences in STD treatment strategies could explain the contradictory results. But in any case, researchers emphasize that it makes sense to treat STDs. As a commentary in *The Lancet*—which published both reports—noted when the Rakai paper appeared, "anything short of an immediate response and a sustained commitment to STD prevention and control programmes is unthinkable."

Although Plummer can point to successes in Kenya applying his group's research results, he says that for the most part, prevention efforts have few powerful advocates. "Prevention isn't at the top of the research agenda," says Plummer. He then quotes Allan Ronald, the Canadian who started the Nairobi collaboration: "One hundred years from now, they'll say, 'They certainly underestimated this and put far too little into it far too late.' " **–J.C.**

An Ambassador of Research

NAIROBI, KENYA—Elizabeth Ngugi sits on a well-worn mattress surrounded by prostitutes in a downtown brothel. "We feel great love for this woman," says one of the dozen prostitutes who have jammed onto the three beds in the room to meet with Ngugi (pronounced en-goog-ee), a dignified woman who declines to give her age but who clearly has seen it all. "I know I would never be alive today without her."

PROFILE

Indeed, without Ngugi, the collaborative AIDS research program based at the University of Nairobi may not have survived either. Ngugi, who joined the collaboration as a nurse in 1984 and went on to earn a Ph.D. in social work at the University of Washington, Seattle, plays a role that is crucial for many AIDS projects throughout Africa—but one that seldom receives credit in scientific circles. Like an ambassador of research, Ngugi connects ostracized communities that have little education and even less money to an international team of AIDS scientists that would like to follow them over time, learning the most intimate details about their sexual practices, their jobs and families, and, of course, their diseases. "With any infectious disease, you have to go where the prevalence is the highest in order to make a difference," says Ngugi. "To make a difference with malaria, you have to go where the mosquito is breeding."

Sisterhood is powerful. Elizabeth Ngugi (center) helps women help themselves at a Nairobi brothel.

The University of Manitoba's Frank Plummer, the de facto head of the collaboration, says the path-breaking studies this group has done with these sex workers would have been impossible without Ngugi's help. "She's a public health phenomenon," says Plummer. "She understands the country. She understands the values. And she's always reinforced that you can't just study things—you have to do something about it."

In exchange for participating in studies, these women receive checkups by top-notch doctors, as well as free condoms, treatments for sexually transmitted diseases (STDs), and Ngugi's news from the front about the latest weapons to combat HIV. Today, Ngugi speaks with the women about the female condom, a vaginal pouch that protects against HIV transmission but has a reputation, deserved or not, of being bulky and cumbersome. The women, holding six conversations at once, quiet down when Ngugi takes the hand of a woman wearing a colorful scarf on her head. "Let her tell her story," says Ngugi. "It's beautiful."

Prostitutes often receive offers of extra money if they do not require a man to wear a condom (a sure sign, these women say, that the man is infected). The woman wearing the scarf explains how she used a female condom that Ngugi gave her to turn the tables on a customer. "Men never know you have anything in there," the woman explains. "A few days ago, a man came and wanted to have sex, and he had never used a condom at all. I said, 'Wait, are you willing to pay more money?' " So the man paid extra, not realizing that *she* had on a condom. Ngugi and the other women have a good laugh. "Let's not get rid of the male condom, but let's empower women and give them something to negotiate safe sex [with]," Ngugi declares.

Ngugi says the work she and her colleagues do "has paid off in bigger ways than we can measure." But in one area—reducing the disease burden on the prostitutes she works with—there's at least an indirect measure of her success: "People say if we want to study STDs," Ngugi notes, "we have to go where you're not." **–J.C.**

erage). "We showed that in an urban setting with potable water, poor HIV-infected women with very limited education can use formula, and their children clearly have a much better outcome," says Joan Kreiss of the University of Washington, Seattle, who conducted the study with the University of Nairobi's Ruth Nduati and co-workers.

The simple implication is that clinicians should discourage HIV-positive mothers from breast-feeding. But, as the University of Nairobi's Dorothy Mbori-Ngacha acknowledges, what sounds simple is, in reality, "a very challenging intervention" in an African setting. Many governments and international aid organizations have long promoted breast-feeding. Not only does formula cost more than many people earn, but many have no access to clean water, increasing the risk that formula itself can cause life-threatening diarrheal disease. The Nairobi study indicated that formula can be used safely in some situations, but "safe water is a big deal," says Mbori-Ngacha. "Without it, formula becomes something you don't even want to discuss."

Even if clean water is available, there are fundamental barriers to bottle-feeding. "If you don't breast-feed your baby, you're announcing that you're HIV positive," says the University of Manitoba's Frank Plummer, who has lived in Nairobi for the past 16 years. "If you're on a bus and your baby starts crying, people will start yelling at you to breast-feed the baby." Indeed, given nevirapine's potential for cutting transmission rates, "to us, the major risk factor now is the stigma of not breast-feeding," says Hopkins's Guay.

Social barriers

In the end, the social stigma of being HIV positive presents the most intractable problem health workers face in trying to prevent infected African women from transmitting the virus to their babies. Many women, fearing the angry reaction Rachel's husband displayed, don't even tell their partners their HIV status—even though many are infected because of their partner's infidelity. Such fears discourage many women from even being tested. "It's one of the areas we've neglected till now: sociobehavioral research," says Thierry Roels, an official at Projet RETRO-CI. "We assumed if we found something, people would take it."

The RETRO-CI study indicates that such an assumption is not well founded. In February 1998, researchers at RETRO-CI offered pregnant women in Abidjan free HIV tests and counseling. They offered those who tested positive free AZT at 36 weeks of gestation through delivery. More than 9600 pregnant women visited the clinic during this study, 72% of whom agreed to be tested. Thirteen percent tested positive. But of those, only 46% returned to learn the test results. And at 36 weeks of gestation, the researchers could find only 70% of the infected group. Most of these 117 women took AZT, but they represented a mere 12.6% of those who tested positive in the study. "One of the problems is [that] between screening and enrollment in the study, there's a long period," explains Sibailly Toussaint, who heads the mother-child division of RETRO-CI.

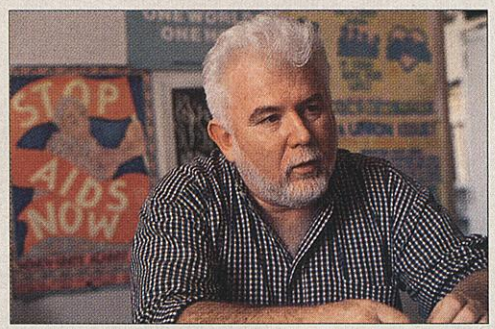
With this in mind, the RETRO-CI team developed a rapid test that determines HIV status in hours rather than weeks. This enabled the researchers to test women and enroll them for treatment on the same day. Of the nearly 4000 pregnant women offered the test, 68% took it and 10.9% were positive.

McIntyre and Gray Have a Will and a Way

SOWETO, SOUTH AFRICA—In an expansive waiting room for pregnant women at the Chris Hani Baragwanath Hospital here, one sign shows a drawing of a pistol inside a red circle with a slash through it. An embossed placard next to a check-in desk reads, "PATIENTS WILL ROUTINELY BE CHECKED FOR AIDS." A flyer taped to another wall by the Perinatal HIV Research Unit states in bold red type, "NO HIV POSITIVE WOMAN SHOULD GIVE BIRTH WITHOUT ANTIRETROVIRAL TREATMENT."

These three signs, each radical in its own way, capture the complicated world where pediatrician Glenda Gray and obstetrician James McIntyre aggressively try to help HIV-infected pregnant women stop the virus from infecting their babies. The international symbol for "no guns" hints at the level of mayhem just outside the razor-wire–topped walls that protect Chris Hani from the infamous shantytown of Soweto. The notice that patients will routinely be checked for AIDS—something that has never been done to whites—is a relic, a reminder of how badly the apartheid regime violated blacks, who make up nearly all of the patients here. And the sign about antiretroviral treatment is not simply a rallying cry but, rather, an amazing offer in a country whose government has declined to provide anti-HIV drugs to infected pregnant women (see p. 2168).

PROFILE



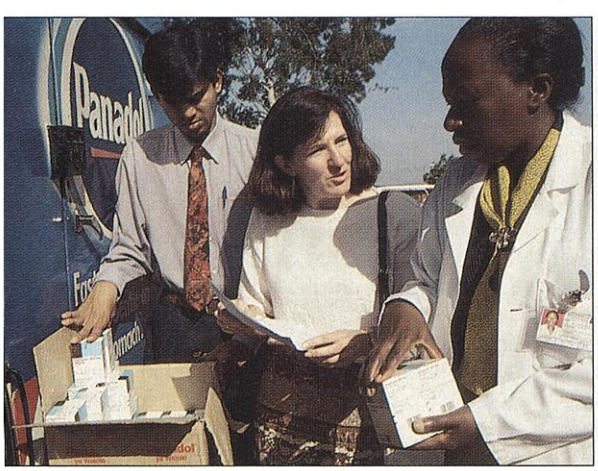
Guerilla health care. James McIntyre and Glenda Gray offer anti-HIV drugs to all pregnant, infected women at this Soweto hospital.

At Chris Hani, which suffers the dubious distinction of having more beds (3300) than any other hospital in the world, HIV infects more than 20% of the 17,000 pregnant women who give birth here each year. Gray and McIntyre constantly scout for appropriate clinical trials, new programs launched by nonprofit organizations such as the United Nations Children's Fund and the Pediatric AIDS Foundation, and anyone with deep pockets, which explains how they've managed to stockpile enough anti-HIV drugs to offer free treatment to infected pregnant women. According to McIntyre, 90% of the women they see accept the offer of free HIV testing and counseling, and virtually everyone who tests positive requests treatment. And when informed about the risk of transmitting the virus via breast milk, more than 90% of these women purchase formula that the clinic sells at a discount, says McIntyre.

Gray emphasizes that researchers can make a huge difference simply by applying pressure on drug companies and donors. She notes that UNAIDS even supplied them with AZT and 3TC long after the completion of a clinical trial so they could continue to treat women who had been helped by the drugs. And Gray is livid about her government's lack of a treatment policy. If a white government behaved that way, says Gray, "there would be a revolution." Costa Gazi, health secretary of the Pan African Congress, who has harshly criticized the ruling African National Congress's AIDS policies, says the country owes a "massive debt" to Gray and McIntyre.

Walking through the waiting room, McIntyre pauses to look at the apartheid-era warning that everyone will be tested for AIDS. "We really should take that down," he says. And he worries that they may run out of anti-HIV drugs one day and have to take down the sign they have taped to the wall, too. **–J.C.**

More than 75% of the women stuck around to learn their results—a big improvement. But half never showed up for treatment. In the end, only 37 of 294 infected women—again, 12.6%—took AZT.



C'est arrive! Philippa Musoke (right) and Laura Guay inventory a long-awaited nevirapine delivery in Kampala.

Toussaint remains optimistic, though, that a simple regimen of one dose of nevirapine to mother and child might vastly improve these numbers. "Imagine using the rapid test and we give them the pill and tell them to take it when they go into labor," says Toussaint. "We think we could reduce transmission significantly."

D-Day

Toussaint's optimism may soon be put to the test. On 20 March, Guay and Makerere University's Philippa Musoke, another principal researcher in the nevirapine study, excitedly watched a small truck pull into their parking lot on Old Mulago Hill. Inside was the first delivery of nevirapine sent to Africa as part of a project that will offer infected, pregnant women the drug free of charge, without even enrolling them in a study.

Similar nevirapine deliveries—part of an $800,000 effort funded by the Pediatric AIDS Foundation—soon will arrive in Rwanda, Kenya, South Africa, and Cameroon. Pharmaceutical companies have cut prices. Special projects launched by the U.S. and French governments will attempt to reach and treat pregnant women throughout Africa.

Clinician Eric Mercier oversees an ambitious $4 million project funded by the United Nations Children's Fund, with AZT donated by Glaxo Wellcome, that also delivers drugs and formula to eight African countries. Mercier says the world must provide treatments as quickly as possible or pregnant women will take worthless medications. "There are plenty of fake drugs around the world, and women don't want to infect their children," says Mercier. "They'll take anything." In the same breath, Mercier urges patience, too. "We're in a world where people want to see immediate change and results. It's important to start now: People will use it, [and] others will see it and come into it. But it takes time." **–JON COHEN**