There is no evidence that those who made the oral polio vaccine used chimp cells, however, and they have forcefully denied the assertion. The CIMRF collaborators also, to a person, reject the polio vaccine theory. "The two events have no connection," says Simon. "It is as stupid as to say, 'Since Africans drank Coca-Cola for 50 years, they have AIDS.' "

Hooper has had some strong scientific supporters, most notably the late Oxford evolutionary biologist William Hamilton. In January, Hamilton took a team to eastern Congo, hunting for SIVcpz samples from *schweinfurthii* and *Pan paniscus*. Hamilton, who collected samples of chimp feces to test for the virus, died a month later from malaria he contracted during the trip. The samples are now being analyzed. Hooper also has identified many labs that have old African samples of blood or tissues, and he has lobbied them to test the samples for HIV. His earlier efforts paid off when Aaron Diamond's David Ho tested a 1959 blood sample from a Congolese man and found HIV-1 sequences, now the oldest confirmed HIV-1 sequences on record.

Ratcheting up the debate, Bette Korber and colleagues at Los Alamos National Laboratory in New Mexico reported in the 9 June issue of *Science* (p. 1789) that their computer analysis of various HIV-1 isolates dates the origin of the M group to between 1915 and 1941—long before the polio vaccine tests took place. "Our results don't disprove that hypothesis but make it unlikely," says Korber. In September, the U.K.'s Royal Society plans to host a meeting where Korber and other leading AIDS researchers—and Hooper—can debate their ideas about HIV's origins.

Telfer and colleagues hope soon to begin a systematic collection of chimp feces in Gabon. Telfer will also continue to sample as many primates as he can find: On this day, he not only bleeds the pet monkey, he also takes tissue from yet another dead *cephus*. "We need to know how HIV-1 and HIV-2 occurred," says Telfer. "We need to understand not just the ultimate causes but [also] the proximal causes to start thinking about an HIV-3 epidemic." **–JON COHEN**

NEWS

Africa Boosts AIDS Vaccine R&D

Efforts have recently heated up in several countries to tailor-make preparations that many believe offer the best hope yet for stopping HIV cold

HLABISA, KWAZULU-NATAL PROVINCE—This lush region of gentle hills dotted with round mud huts that sits on the edge of the Hluhluwe Game Reserve doesn't look like an epicenter of South Africa's AIDS epidemic. But this poor rural area has one of the worst outbreaks of HIV in the world. The figures are staggering: Almost 40% of the pregnant women—a so-called "sentinel population" widely used to track the epidemic—in Hlabisa are infected with HIV. A decade ago, almost none tested positive.

In the sad calculus of AIDS, this makes Hlabisa an ideal place to test HIV vaccines—the best hope Africa has of truly containing this disease. And that was the reason Seth Berkley, head of the International AIDS Vaccine Initiative (IAVI), paid a visit here in late March.

Testing 1, 2, 3. Seth Berkley (left) of the International AIDS Vaccine Initiative meets with community educators who are teaching people in Hlabisa, South Africa, about upcoming AIDS vaccine trials.

Concerned that industry has shown little interest in developing an AIDS vaccine for poor countries, the nonprofit IAVI has launched innovative "product development teams" in South Africa, Kenya, and Uganda. Here, IAVI has teamed leading South African AIDS researchers with a North Carolina biotech company; together they hope to tailor an AIDS vaccine by next year for trials in Hlabisa (pronounced shla-bee-sa) and elsewhere in the country. As part of the project, to which IAVI has committed $4.5 million over 3 years, researchers work closely with participating communities.

Today, eight "community educators," whose job it is to lay the groundwork needed to conduct an ethical trial, pack into a trailer that serves as the headquarters of the Hlabisa Research Clinic to meet this boyish and gangly physician from New York. Ethics—something often ignored in the checkered history of medical research in Africa—demand that people who volunteer for the trial do so freely, fully understand whatever risks exist, and receive encouragement and advice about how to avoid becoming infected. These community educators, college-age men and women from the area, go from hut to hut to teach people about vaccines and AIDS, distribute condoms, and answer questions.

Berkley begins by asking the educators, "What's the community saying?"

"They feel positive here," says a university student, who wears a stylish beret. "They think they're going to help stop the epidemic."

"Do they ask any questions that stump you?" Berkley queries.

The educators squirm a bit. Berkley asks the question again.

"The one is, 'When are we going to have a vaccine that works?' " a woman answers.

"That's a good question," Berkley replies. The educators laugh. Berkley, who well understands the scientific and ethical challenges ahead, does not offer an answer.

Off safari

Human trials of AIDS vaccines began in Africa. The first test was conducted in Kinshasa in 1986 by Daniel Zagury of France's Pierre and Marie Curie University and his colleagues in Zaire. Ultimately, the trial went nowhere and was widely criticized for being run without the international community's knowledge, involving children, and using unapproved materials in the vaccine. No evidence ever surfaced that Zagury's trials injured anyone or violated Zairian or French regulations, and they did establish that a person could safely develop immune responses against pieces of HIV, which all vaccines contain. But the trials—which triggered media investigations and an official probe by the U.S. National Institutes of Health (NIH), which exonerated Zagury—also put AIDS vaccine researchers on notice that the ethics of the trials they stage, especially in poor countries, would receive intense scrutiny.

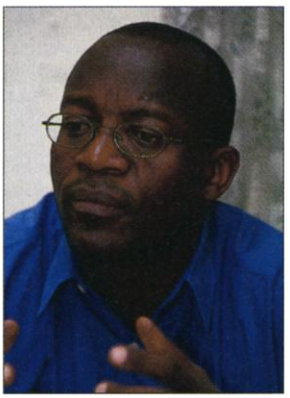
No other vaccines were tested in Africa until last year, when Uganda started a small trial to assess the safety of an Aventis Pasteur

A Native Son Comes Home to Help

PROFILE

NAIROBI, KENYA—In December 1996, when Omu Anzala returned to Kenya after completing his Ph.D. work in Canada on HIV's interactions with the immune system, his older brother was part of the family contingent that welcomed him home. "Just looking at him at the airport told me that all was not well," remembers Anzala. "They never told me." Four months later, his brother, then 37, died from AIDS.

Anzala, now a University of Nairobi researcher who runs the Kenyan end of one of the most advanced AIDS vaccine projects in Africa, takes a long look at the tabletop in his sparsely decorated office. "With all this knowledge I'd learned, I couldn't do anything," says Anzala. "I tried to get all the antiretrovirals, but it was late. It told me why I am even studying this. So AIDS is close to me. Very, very close. That really makes me push for vaccines, because that's where we'll save the majority of Kenyans and the majority of people."



Test shot. Omu Anzala pins his hopes on a vaccine.

Since 1987, Anzala has worked with a collaborative AIDS research project started by researchers from his university and the University of Manitoba. "If there's anyone who has benefited from this collaboration, that would be me," he says. The collaboration helped him earn his Ph.D. in Canada, which in turn led to postdoctoral work at Oxford University with one of the world's leading HIV immunologists, Andrew McMichael. Now the International AIDS Vaccine Initiative has funded Anzala, McMichael, and two European companies to fashion an AIDS vaccine based on a strain of HIV circulating in Kenya.

Kelly MacDonald, a veteran of the collaboration who studied with Anzala in Canada and now directs the University of Toronto's HIV research program, says Anzala represents "the new breed of African scientists" who are trained abroad but working at home with real opportunities. "There's a shortage of people like Anzala in Kenya and elsewhere in Africa," says MacDonald.

Anzala emphasizes that he has had to chart his own course. He says, for example, that he was encouraged to study epidemiology rather than virology for his Ph.D. "The Canadians told me that's what Africa needs," says Anzala. "No. We've been counting numbers for a long time. You want me to keep counting numbers? For how long?" Anzala replied. He also had to convince his Oxford collaborators that the Nairobi lab, if properly equipped, could do sophisticated analyses of blood samples for the vaccine trial. "They wanted us to ship things," says Anzala. "The whole issue has been, 'Oh you don't have support, you can't order reagents.' " He eventually prevailed. "We can do much more than be a collection point for other labs," asserts Anzala.

If all goes well, trials of the Kenyan vaccine—which is designed to boost the body's so-called killer T cell defenses—will begin in Nairobi by December. Anzala stresses how badly his country needs this weapon. "The answer to HIV and AIDS infection in Kenya is not going to be condoms and education," he says. "We've been telling people that for 15 years. What is happening? We're still seeing more infections. What we really need is the same thing that prevents measles and has almost eradicated polio." **–J.C.**

product, which had already been widely tested in developed countries (see table). Not only have most companies shrugged at the African market, but government agencies such as NIH have opted to conduct initial tests in developed countries, for ethical and practical reasons. "When in doubt with a brand-new candidate vaccine, you'll cause the least stress if you try the vaccine out in Bethesda, Maryland," says Yale University's Robert Levine, a bioethicist who has helped craft two sets of guidelines covering AIDS vaccine tests.

The first of these guidelines, a 1993 document prepared by the Geneva-based Council for International Organizations of Medical Sciences (CIOMS), said initial studies of a vaccine "should be conducted only in developed communities of the country of the sponsor." Levine says the guidelines aimed both to prevent "safari research"—in which researchers bag data in Africa to support licensing of products back home—and to protect more vulnerable populations from early safety studies that could take place anywhere. This year, Levine helped craft new guidelines by UNAIDS, the Joint United Nations Programme on HIV/AIDS, that relax this edict, concluding that developing countries can dive in first if they so choose. "Attacks on [the old guideline] came from low-income countries," says Levine. "They asked, 'Why is it that you treat us so paternalistically?' "

The new guidelines reinforce the CIOMS principle of "equitable distribution," which says communities that participate in trials should have access to the vaccine if it proves effective. IAVI follows that principle by insisting that the vaccines it bankrolls sell for a "very reasonable price," which the nonprofit hopes to regulate. First, IAVI requires companies it works with to reveal production costs and then allows them to make a negotiated profit (10%, in one case). If IAVI deems the company's production costs too high, it can hire a third-party manufacturer.

"IAVI's access to patents and in some cases the manufacturing know-how will certainly be helpful," says Peggy Johnston, who heads the AIDS vaccine program for NIH's National Institute of Allergy and Infectious Diseases (NIAID)—and who previously worked as IAVI's scientific director. But Johnston cautions that even these stipulations do not ensure community access, as it may ultimately involve a tangle of patent rights, with other manufacturers seeking licensing fees.

Success with anti-HIV drugs forced the drafters of the UNAIDS guidelines to confront another contentious issue: No vaccine works 100% of the time, so should sponsors provide the "best proven therapy" in the world to participants who become infected during the trial, or simply "the highest level of care attainable in the host country"? After fierce debate—including fire fights in *The New England Journal of Medicine* and the U.S. Congress—UNAIDS decided that each country should answer this question for itself (*Science*, 3 July 1998, p. 22).

Natural immunity

Finding the recipe for a vaccine that works remains, of course, the biggest obstacle facing researchers. Nothing tested in humans to date shows great promise, but even a mediocre vaccine could help. A 1992 NIAID statistical analysis made this point dramatically, showing that over the course of a decade, a 60% effective vaccine introduced today would prevent nearly twice as many infections as one with 90% efficacy introduced 5 years from now.

African studies, particularly in the IAVI-sponsored Kenyan project that Omu Anzala works with (see profile above), are turning up critical leads that might help make vaccines work better. Agnes Monifa is providing one such lead.

Monifa lives outside Nairobi in Pumwani, a shantytown of wattle and mud homes with corrugated tin roofs that also has a clinic, run by the collaboration, for sex workers. Monifa, who is 48 years old, says she started in the sex business in 1973. She was one of the first women to use the clinic's services, which freely treats the women's sexually transmitted diseases (STDs) and other health problems. Since 1985, doctors at the clinic have been filling test tubes with samples of Monifa's blood—some of the most interesting blood that AIDS vaccine researchers have ever studied.

Monifa is one of a group of Kenya prostitutes who, despite repeatedly being exposed to HIV, show no evidence of an infection. Inside the dark space of her one-room

shack, Monifa, a mother of five, describes the details of her life through an interpreter. On a good day, she'll have 10 customers who will pay 50 shillings—65 cents—each. Monifa insists that men wear condoms, she says, but the evidence suggests otherwise: The clinic has provided her with so many treatments for STDs that, she says, "if I had to buy my medicine, I'd be dead by now." Several close friends, she says, have died from AIDS. To explain her own fate, she turns to religion. "God loves me," she says. Surprise fills Monifa's weathered face when she learns that her blood might help researchers find a vaccine. "I didn't know that," she says. "I'm ready to help people."

In the early days of AIDS vaccine research, most studies focused on antibodies, the Y-shaped proteins that glue themselves to invaders and prevent them from establishing an infection. Monifa has no HIV antibodies in her blood. But the Kenyan team has shown that many "resistant" women who visit the Pumwani clinic have white blood cells trained to kill HIV after it has entered a cell. In part because of this work, several vaccine developers have put an increasing emphasis on stimulating production of these killer cells.

Yet this research also has uncovered less encouraging results. Recently, 10 of the 80 or so "resistant" women in this study became infected—after taking a break from sex work (*Science*, 11 February, p. 942). This odd finding challenges the robustness of "natural immunity," the phenomenon of immunologic memory that protects people from being infected twice by the same bug. Peter Kiama, a Pumwani clinician, contends that memory sometimes is fickle, requiring repeated stimulation from HIV to maintain immunity.

Fears have surfaced, too, that immunity to one strain of HIV might not protect against another. Logically, the simplest vaccine would train an immune system to defeat the strain of virus circulating in a given community. So IAVI and others insist that designers of vaccines, all of which contain modified forms of HIV, rely on subtypes circulating in the region where they intend to test the preparation. The small Uganda trial launched last year, however, did not follow this dictum, testing a vaccine based on subtype B—the most common subtype in the United States and Europe, but rare in Africa. David Serwadda of Kampala's Makerere University says this decision didn't sit well with some Ugandan researchers. They passed these concerns along to their collaborators. "We said, 'You've got a better negotiating position if you put in a [subtype] that matters to us,' " says Serwadda. Although the Ugandans agreed to participate in that small trial, Aventis Pasteur now is customizing an AIDS vaccine from an HIV subtype circulating in Uganda.

NIAID's Johnston, whose institution sponsored the Uganda trial, stresses that scientists still don't know the significance of the different subtypes. "If someone does know," she says, "they have a crystal ball clearer than mine."

The University of Munich's Michael Hoelscher is trying to make the crystal ball a little clearer. He has organized a large, multinational team to study 600 bar workers in Tanzania, where subtypes A, C, and D "cocirculate." Hoelscher says unraveling the success—or failure—of immune responses at stopping a second HIV infection may clarify their relationship to subtypes. "Nobody knows anything about dual infections," says Hoelscher. "It's a totally new field."

Vaccine lead. Agnes Monifa has been repeatedly exposed to HIV but remains uninfected. Researchers are studying why.

Vaccine dreams

Halfway into the meeting of the community educators in Hlabisa, two nurses who work at the local hospital walk into the trailer, taking seats next to Berkley. "If we had a vaccine that worked and was safe, would people take it?" Berkley asks the nurses, Catholic sisters who wear military-style shirts with epaulets. "People would flock to it," says one sister.

"We're all praying for it," adds the second sister. "Our children are dying. Our friends are dying. People 18 years old are lying in hospital beds that in the old days we had filled with grannies who had tuberculosis and cardiac failure. The vaccine would be wonderful. [The situation] is very difficult for young people. This is the time when they should be falling in love, and they say, 'Now that we've come to that stage, you want us to do what you did not do.' "

Berkley thanks everyone for coming to meet with him and for helping to organize an AIDS vaccine trial in this remote corner of Earth. "This is not just a problem for KwaZulu-Natal," says Berkley. "This is not just a problem in Hlabisa or South Africa. It's a problem for the world." **–JON COHEN**

AFRICAN AIDS VACCINE R&D

Location	Main collaborators	Sponsors	Vaccine	Comments
Kampala, Uganda	Makerere Univ., Case Western Reserve Univ.	NIAID	Aventis Pasteur Canarypox	Ongoing Phase I
Nairobi, Kenya	Univ. of Nairobi, Oxford Univ., IDT, Cobra Pharmaceuticals	IAVI	Modified Vaccinia Ankara and DNA	December start
Hlabisa, South Africa	Univ. of Natal, AlphaVax, Univ. of Cape Town	IAVI, NIAID, U.S. Army	Venezuelan equine encephalitis	Next year?
Kampala, Uganda	Johns Hopkins Univ., Makerere Univ.	NIAID	Canarypox and gp120	For breast-fed infants
Uganda	Institute of Human Virology, Ministry of Health	IAVI	*Salmonella* and DNA	Team announced in May
Rakai, Uganda		U.S. Army, NIAID	Canarypox Clade A	Under consideration
South Africa	Univ. of Cape Town, Univ. of Stellenbosch, Nat'l Inst. Virol.	SAAVI	BCG, Modified Vaccinia Ankara, DNA, and fungal vectors	Preclinical
Tanzania	Muhimbili Univ., Swedish Inst. for Infect. Disease Control	Swedish Int'l. Dev. & Coop. Agency		Cohort prep
Addis Ababa, Ethiopia	Ethio-Netherlands AIDS Research Project	Neth. Ministry for Dev. & Coop.		Cohort prep
Côte d'Ivoire	French cooperation	ANRS		Cohort prep

SOURCES: NIAID, UNAIDS, SAAVI