Searching for the Epidemic's Origins

Many theories purport to explain how HIV got a foothold in humans, but few researchers have gone into the field to look for answers

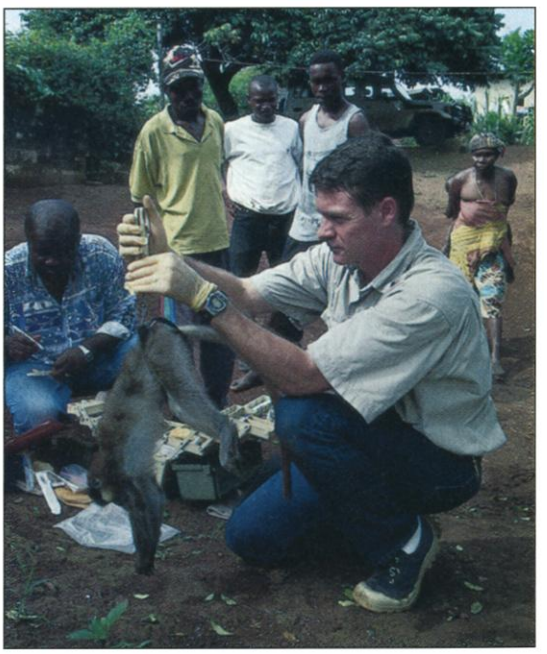
EASTERN GABON—Driving through the jungle on a brick-red mud road, Paul Telfer suddenly stops his Land Cruiser. "I saw a *cephus*," he says. Telfer backs up 100 meters and, sure enough, a dead monkey lies atop a metal drum, a dead brush-tail porcupine by its side.

In this remote part of western equatorial Africa, bushmeat makes up a large component of the diet. Hunters walk about with shotguns and machetes and display their bounty to the few cars that pass by in hope of making a sale. Telfer does not want to buy the monkey, though. He is looking for viruses. A primatologist from California, Telfer does fieldwork for the only team in the world that hunts for new simian immunodeficiency viruses (SIVs), HIV's cousins. He and his collaborators have found SIVs in chimpanzees, sooty mangabeys, mandrills, red cap monkeys, and two dozen other species. "Our goal is to understand the evolution of these viruses and attempt to understand what caused the AIDS epidemic and [what] the risks of future epidemics [are]," says Telfer.

Theories about the origin of AIDS all suffer from a dearth of data, and watching Telfer work explains why: It is labor-intensive and often tedious work. Today, Telfer is making a 4-hour round trip from his home base at the International Center for Medical Research of Franceville (CIMRF) to the village of Okondja solely to draw blood from a pet *Cercopithecus cephus* he found on an earlier expedition. If he can sample some dead animals along the way, so much the better.

Telfer, a Ph.D. student who works for virologist Preston Marx of Tulane Regional Primate Research Center in Covington, Louisiana, has spent much of the past 9 years cruising around Sierra Leone and Gabon searching for SIVs; few scientists have his knowledge or skills. Working with his Gabonese translator and assistant, Issa Bedjabaga, Telfer immediately displays a critical talent: the ability to convince someone selling a dead monkey to let him take samples for free. (He refuses to pay because he does not want to encourage the bushmeat trade.)

A woman comes out from her shack and gives Telfer and Bedjabaga her OK. After donning plastic gloves, Telfer plucks a few hairs, from which he later will extract DNA to confirm the species. He then weighs the animal and takes many measurements, with Bedjabaga recording the data in a notebook. When Telfer cuts off a bloody piece of the monkey's tongue, many men who have come out from nearby shacks begin talking excitedly. Telfer, who now is drenched in sweat, would like to remove the animal's spleen—a rich source of the white blood cells that SIV infects—but Bedjabaga, sensing that the men think Telfer is damaging their goods, hurriedly says goodbye to the villagers.



Origin hunter. Paul Telfer takes samples from a monkey that may harbor unknown simian immunodeficiency viruses, while Issa Bedjabaga takes notes.

Telfer has no idea whether this species carries SIV or whether he can isolate it from a bloody tongue sample, but he is thrilled. "That's priceless data, priceless data," he says, driving away. "You can never pass up an opportunity, because you never know what you're going to find. We may end up finding an important link."

For more than a decade, researchers have recognized the close genetic links between SIV from sooty mangabeys (SIVsm) and HIV-2, a type of the virus that is mostly confined to west African countries. Pioneering work by Marx, Telfer, and co-workers at the Aaron Diamond AIDS Research Center in New York City (Marx's other affiliation) further matched SIVsm found in wild animals to HIV-2 infections from the same area.

To date, there are scant data that closely link HIV-1, the predominant human AIDS virus, to SIVs found in primates. The closest connection comes from viruses, called SIVcpz, isolated from a mere six chimpanzees. France's François Simon, who works at CIMRF and collaborates with Telfer and Marx, co-authored a paper published in the January *Journal of Virology* that strongly ties HIV-1 found in humans in Cameroon to SIVcpz isolated from two chimpanzees. But these isolates are most closely related to the least common of the three known HIV-1 groups, a group known as N; they do not, then, explain the origin of the AIDS epidemic, which consists mostly of M (or main) group viruses.

Studies from the lab of another CIMRF collaborator, Beatrice Hahn of the University of Alabama, Birmingham, last year placed three of the other four chimp isolates somewhere among groups M, N, and O. Most interestingly, the researchers discovered that these three viruses came from one of four chimpanzee subspecies, *Pan troglodytes troglodytes.* The remaining isolate—which is different from the others—came from the *schweinfurthii* subspecies. Because chimps do not typically cross rivers, the subspecies have unique ranges, which led the researchers to conclude that HIV-1 initially jumped from chimps to humans in a restricted area of west equatorial Africa that includes Gabon. Most AIDS researchers suspect that the virus crossed the species barrier through the butchering of primates.

All of these details became a topic of hot debate last fall upon the publication of *The River*, a thick book by former BBC correspondent Edward Hooper, who traces the origin of AIDS back to trials in the late 1950s of an oral polio vaccine in Congo, Rwanda, and Burundi. Hooper confirms many early cases of AIDS in that region and posits that the polio researchers, who had a chimpanzee colony in Congo of the *schweinfurthii* subspecies and *Pan paniscus* (a separate species known as bonobo) common in that area, used cells from the animals to make the vaccine. According to the theory, some of these animals had SIVcpz infections with viruses more closely related to the M family than anything yet found. Their infected cells, Hooper argues, contaminated the vaccine. "I find it remarkable that there's a dearth of M present [in humans] in any *troglodytes* countries earlier than the 1980s," says Hooper.

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