Staging Ethical AIDS Trials in Africa

As ever more clinical studies are launched in Africa, the obstacles to establishing hard-and-fast ethical rules leave the realm of the theoretical

NAIROBI, KENYA, AND HARARE, ZIMBABWE—A few years ago, a major AIDS clinical trial in a nearby African country was compromised because of a serious ethical lapse, says Richard Marlink, director of the Harvard AIDS Institute. Marlink, who will only reveal a few details of the trial, says the trouble started when an African consultant to the study, which was funded by the U.S. government, attempted to boost his own academic and financial standing by using some of the subjects enrolled in the trial to launch a second HIV investigation. Not only was this sideline study unapproved by any in-country official body, says Marlink, the patients did not give their consent to participate in the trial, and, more outrageous still, they had to pay the researcher.

African express. Craig Cohen *(left)* hopes to find faster answers from studies in Kenya.

While this episode symbolizes the ethical problems that can riddle trials in a country that lacks a strong tradition of clinical research, it also carries a more hopeful lesson: This particular African country had recently established an ethical review board; when notified of the situation, it promptly ousted the researcher from the trial, says Marlink.

In much of Africa, which the World Health Organization (WHO) estimates is home to 9 million of the world's 15 million HIV-infected people, the international ethical principles of human subject research are just taking root. Indeed, 5 years ago, researchers conducting AIDS clinical trials in Africa had scant guidelines on how to set up review committees—commonly known as institutional review boards (IRBs)—and other ethical precepts (*Science*, 12 October 1990, p. 199). But since then, worries about potential abuses have led several organizations to spell out principles specifically for AIDS researchers.

Marlink's disturbing tale illustrates that those efforts are having an effect. Yet the guidelines are far too often ignored, claim many AIDS researchers. "AIDS has changed how people view ethical research in developing countries," says the Harvard AIDS Institute's Marc Lallemant, an AIDS pediatrician who has worked in several African countries. "But there's a real need for more training and more thinking about what are universal ethics."

A recent visit by *Science* with AIDS researchers in Cameroon, Kenya, and Zimbabwe, and interviews with dozens of others working in Africa, found few who were willing to discuss specific ethical infractions openly. Nonetheless, most lamented privately that despite a decade of experience in the field, HIV-related studies frequently violate internationally accepted norms. And the misgivings of these researchers are supported by a survey of experts on HIV-related research in developing countries—the majority of whom had worked in Africa—completed last year for the Office for Protection from Research Risks (OPRR) of the U.S. Department of Health and Human Services.

In the 130-page OPRR report, two fundamental safeguards for ethical human research stood out as "major problems": establishing IRBs and obtaining meaningful informed consent from trial volunteers. "Implementation [of international guidelines] is terrible," says Lawrence Gostin, a lawyer and ethicist at Georgetown University in Washington, D.C., who co-authored the OPRR study. "It's obvious that not everyone is rigorously following individual consent [procedures]." Peter Piot, head of the new United Nations Program on HIV/AIDS (which will take over the WHO's Global Programme on AIDS by year's end), is also uneasy about IRBs in African countries. "The major issue is having independent [ethical review] committees in every country that does AIDS research and training people to understand the [ethical] guidelines," says Piot, who has conducted extensive research himself in Zaire. "That's where much work has to be done."

Despite these widespread sentiments, fixing the problems is a daunting task. "We have to help each country develop [ethical guidelines] and then make sure that there are mechanisms in place to have them respected," says Piot. But, he cautions, it's a long process. "There isn't a magic formula."

A SAMPLING OF COLLABORATIVE AIDS STUDIES IN AFRICA

Collaborating Organizations	Protocol	Location
Institute of Tropical Medicine, Antwerp; University of Yaounde; and Gabon's Programme National de Lutte contre le SIDA	Antigenic, genetic, and biological variation of HIV-1	Cameroon and Gabon
Family Health International and Muhimbili University	Effect of HIV testing and counseling vs. traditional health education on HIV transmission	Tanzania
University of Bordeaux II, the University of Côte d'Ivoire, and Centre Muraz in Bobo Dioulawso	Ascertain safety and acceptability of short-course AZT treatment to prevent HIV transmission between mother and infant	Côte d'Ivoire and Burkina Faso
National Cancer Institute, Johns Hopkins Univ., and Malawi's Ministry of Health	Vaginal washing vs. normal delivery on maternal-infant transmission	Malawi
Family Health International and Cameroon Ministry of Public Health	Effect of nonoxynol-9 film and condoms vs. placebo film and condoms on HIV transmission rates	Cameroon
Case Western Reserve University, Karolinska Institute, and University of Makerere	HIV immunoglobulin immunization safety and effect on viral load in pregnant women	Uganda
Johns Hopkins University and Malawi's Ministry of Health	Vitamin A supplements vs. placebo on maternal-infant transmission of HIV	Malawi
Stanford University and University of Zimbabwe	Peer education and condom distribution in factories vs. existing education	Zimbabwe
Harvard AIDS Institute and Cheick Anta Diop University	Natural history of HIV-1 and HIV-2	Senegal

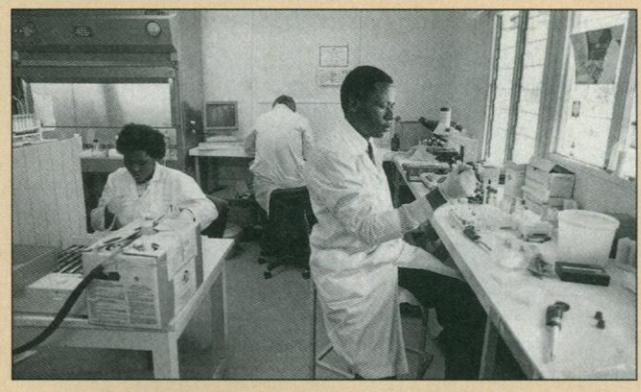
A Model Collaboration Built to Last

NAIROBI, KENYA—When Joan Kreiss lobbied her thesis adviser, Francis Plummer, in the mid-1980s to study the incidence of HIV infection among sex workers in this sprawling east African city, Plummer, a microbiologist who for years had been studying sexually transmitted diseases (STDs) in sub-Saharan Africa, counseled against it on the grounds that there had been no reported cases of AIDS in Kenya. But Kreiss, who now heads her own epidemiology team at the University of Washington, Seattle, persisted. Her persistence was rewarded: She went on to make the then-startling discovery that more than 60% of Kenyan sex workers were infected with HIV. "It came as a bolt from the blue," remembers Plummer, who works for the University of Manitoba in Winnipeg but spends 9 months of each year in Kenya. "It completely changed the focus of the group."

"The group" Plummer is referring to now includes his own team and ones led by Kreiss; Joanne Embree, also of the University of Manitoba; and microbiologist Jackoniah Ndinya-Achola of the University of Nairobi. Besides shifting the group's attention to HIV and AIDS, Kreiss's study also had "worldwide impact," says Ghana's Peter Lamptey, who heads the AIDS research and prevention arm of Family Health International, by helping sound the alert on the grim future of AIDS in Africa.

The Nairobi group, which is mainly funded by the Medical Research Council of Canada and the U.S. National Institutes of Health, is also regarded by many as a model of how to do collaborative science in developing countries, says Richard Marlink, director of the Harvard AIDS Institute. Although some *mzungu*, or Northerners (the Swahili shorthand for Europeans and North Americans), have been accused of "safari science"—a short tour to collect data and then back home to publish it—the Northern members of the Nairobi group are there for the long haul and have a diverse list of accomplishments to prove it.

One of the group's most widely publicized findings is a study of 700 African societies confirming that male circumcision is associated with considerably lower HIV infection rates. Ongoing studies of Kenyan prostitutes and long-distance truck drivers have shown that genital ulcers, often a result of STDs, are associated with greatly increased risk of HIV infection. The researchers are also attempting to lay the groundwork for Kenyan AIDS vaccine trials, gauge the merits of vaginal microbicides for blocking HIV transmission, and evaluate the role breast-feeding plays in transmitting HIV.



CHERYL ALBURQUERQUE

Northern exposure. Canadians and Americans have teamed up with Kenyans to forge a powerful research group.

During the past 2 years, the group has started to untangle why some Nairobi prostitutes who are repeatedly exposed to HIV escape infection. They have discovered that many of these presumably HIV-immune women have rare human leukocyte antigens (HLA), cell surface molecules that the immune system uses to distinguish self from nonself. "It makes intuitive sense," says Kelly MacDonald of the University of Toronto, a microbiologist who works with Plummer. The reason: HIV's lipid coat incorporates HLAs from its human host. So when HIV enters a new host, it "comes into the body wrapped in a foreign HLA," she explains, which means "[a person] who has a rare HLA is more likely to mount a strong immune attack."

The Nairobi team believes its work is making a dent in the Kenyan epidemic. By offering free condoms, counseling, and STD treatments, says Plummer, they've helped drop the annual rate of new HIV infections in the Nairobi sex workers they're following from 40% to 25%. "We've prevented tens of thousands of HIV infections," says Plummer, "which is pretty gratifying."

–R.N.

Human rights and wrongs

Ethical problems dog all types of clinical studies done in Africa. Those that surround AIDS research, however, stand out starkly, in part because of the sheer size of the research enterprise. And unlike other scourges of the Third World, AIDS is a disease that wealthy countries fear within their own borders, prompting the U.S. National Institutes of Health (NIH) alone to devote more than $1 billion a year to AIDS research, more than $10 million of which trickles down to Africa to help support the ever-growing list of ambitious clinical studies (see table).

Most of those trials are directed at finding ways to slow Africa's AIDS epidemic, but they also test drugs and interventions that could be useful in wealthy industrialized countries, which greatly enhances ethical scrutiny. What's more, scientifically, sub-Saharan Africa is one of the best locales to stage large-scale tests of AIDS vaccines and drugs, study the interaction between other infections and HIV, and evaluate ways to block transmission of HIV between mothers and infants.

Why? Because the sheer density of HIV infection turbo-charges clinical trials, amplifying the statistical power of the results and providing massive savings in time and money. "Fifty percent of my patients are HIV-positive," says Craig Cohen, a postdoc at Seattle's University of Washington who is part of a 50-person AIDS research team based at the University of Nairobi (see box). Cohen, who is studying how HIV infection alters the course of pelvic inflammatory disease, says he can do his study in Kenya in 18 months. "At home, to get sufficient power of analysis, it would take 10 years and cost a lot more," Cohen says.

But the poverty that fuels the spread of HIV and helps make Africa a choice setting for AIDS clinical research also challenges attempts to apply U.S. and international standards for informed consent and IRBs. Consider the 1991 Federal Policy for Protection of Human Subjects (often called "the Common Rule"), which states that any U.S. government-funded researcher at home or overseas must "minimize the possibility of coercion or undue influence" of potential trial participants. International guidelines impose similar requirements: In 1993, the prospect of ever-expanding AIDS clinical trials in developing countries spurred WHO to team up with the Council for International Organizations of Medical Sciences, which represents medical research professionals, and hammer out ethical guidelines for clinical trials. Some of the language closely mirrors the wording of the Common Rule, including a statement that "special provisions must be made for the protection of

Testing AIDS Interventions: When Is the Price Too High?

As Africa's AIDS epidemic continues to burn out of control, trials to pinpoint ways of dampening its progress become more aggressive—and risk setting off ethical brushfires. One such controversial trial began last November in the Rakai district of Uganda, where a collaboration of African and American research teams started recruiting 11,000 people for a 5-year study to test whether the spread of HIV can be slowed by treating people en masse for other sexually transmitted diseases (STDs). That's an important question, but there's an ethical catch: If the intervention works, most Africans may not be able to afford the drugs

Most AIDS researchers agree that treating STDs, which cures genital sores and reduces inflammation, can raise the body's barriers against HIV infection. According to a study in the 26 August issue of *The Lancet*, researchers working in rural Tanzania saw the number of new HIV infections plummet by 42% after they improved STD health care, which included making sure that anti-STD drugs were available in the clinics.

In a go-for-broke approach designed to have an even greater impact, Maria Wawer of Columbia University in New York and clinical epidemiologist Nelson Sewankambo of the University of Makerere in Kampala have designed a trial that treats everyone between 15 and 58 years old in approximately 30 Rakai villages. The trial—funded, in part, by the U.S. National Institutes of Health (NIH), the World Bank, and the Rockefeller Foundation—will evaluate an expensive combination of oral antibiotics to cure gonorrhea, chlamydia, trichomoniasis, syphilis, bacterial vaginosis, and chancroid given every 6 months, whether or not participants show symptoms of the diseases.

The main controversy triggered by the mammoth trial is that two of the antibiotics—the broad-spectrum drugs Azithromycin and Ciprofloxacin—are too costly for the average Ugandan. This runs counter to internationally accepted guidelines (see main text) which state that "as a general rule" there should be some assurance that if a therapy proves efficacious, "it will be made reasonably available to the inhabitants of the host community or country."

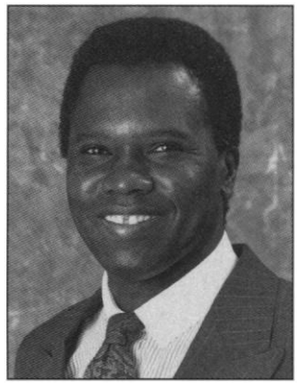
And that is what worries STD specialist Marie Laga of the Institute of Tropical Medicine in Antwerp, Belgium. "The study is very high-tech," she says, "My concern is that they will not be able to implement it anywhere in the developing world. So if they show an effect, what next?"

But the trial did get approved by scientific and ethical review committees at the AIDS Research Subcommittee of the Medical Research Council of Uganda, Columbia University, NIH, and Johns Hopkins University. Wawer says all of these overseers approved the study because it also promises to identify which STDs provide the greatest risk of HIV infection, which "will enable us to develop programs that target specific STDs that could be much more cost-effective in the long run." Team member Fred Wabire-Mangen, a public health expert at the University of Makerere, adds that if the mass treatment strategy works using the best available drugs, then "we'll get in to the operational issues" such as how to make the expensive drugs available or find cheaper alternatives.

–R.N.

the rights and welfare of vulnerable persons."

That's all to the good, but African patients may be very poor, illiterate, speak a local dialect, and have no understanding of the most fundamental medical concepts such as germ theory. In combination, these barriers may demolish informed consent. "There are a fair number of research studies where ... if you interviewed the people in the study, most wouldn't understand what" they have consented to, says Peter Lamptey, a native of Ghana and head of AIDSCAP, an AIDS research and prevention arm of Family Health International.



ALEX TREML/FAMILY HEALTH INTERNATIONAL

Failure to communicate. Peter Lamptey questions quality of informed consent.

To compound the communication gap, many African trials are run by clinicians who have little or no research training, says Stanford University infectious disease expert David Katzenstein, who's working with the University of Zimbabwe to run clinical trials and to set up an AIDS vaccine testing site. Consequently, he says, researchers often treat potential volunteers like patients, which means deciding what is best for them and then "tell[ing] them they are going to give them a medicine. The patients are very happy about that, and they [take] it," says Katzenstein. "It's a very hierarchical society, and I don't think we've developed very good mechanisms for [obtaining] informed consent." Many African patients, for example, are unused to questioning a doctor's wisdom, and that can make them hesitant to ask about the risks associated with a clinical trial.

In the OPRR survey of 25 American and African AIDS researchers and administrators, half of the respondents decried the way informed consent is obtained. A major concern aired in this anonymous survey was that, in violation of all the guidelines, researchers—sometimes inadvertently—use undue incentives to entice volunteers. "Many times [patients] agree to participate in a study for food or money," one African administrator wrote. "The informed consent given in such circumstances is not ethical in my view."

Although survey co-author Gostin contends that several African countries have established exemplary IRBs, he also found that 42% of the survey respondents reported problems with setting up IRBs. The Common Rule, for example, requires institutions funded by the U.S. government to set up IRBs that are diverse in race, gender, and culture, and which include at least one nonscientist and one representative of the local community who is independent of the institution. The IRB must have at least five members with the expertise or background to understand the proposed trial, which usually means scientific or medical training.

To several of the OPRR survey respondents, these requirements are totally impractical in a developing-country setting. "It is simply impossible," complained one U.S. administrator. Another explained that in Africa, the "addition of females or laypersons to human subject review boards ... is not an easy sell." And a third respondent raged that the consequences of these ill-matched requirements are severe: "The indiscriminate application of identical requirements for local IRBs outside the U.S. ... bespeaks an arrogance of approach that turns off foreign investigators."

Ethics are expensive

Many AIDS researchers working in Africa seem flummoxed by the seemingly intractable woes of establishing IRBs in countries where trained doctors and scientists may be few and far between, and obtaining informed consent from patients who may be unused to having any say in their medical care. Yet others are floating a wide range of solutions to improve the situation.

One fix, as Piot suggested, is to work harder at meshing ethical guidelines with each population. For example, he says, for illiterate volunteers, simply putting an X on a typed consent form may be meaningless; instead, extensive one-on-one and group discussion sessions about the pros and cons of the research trial may be needed. The type of informed consent, and decisions about which drugs and vaccines should be tested in a country (see box on p. 1334), should be left to the in-country IRB to decide, says Marlink. Gostin agrees, but stresses that there are some bedrock standards that all human-subject research must adhere to, such as guaranteeing that a patient's autonomy is fully respected. "There's no reason why [Africa] should abide by U.S. ethical standards," says Gostin. "But there is every reason why it should be bound by universal human-rights standards."

With the ethical high ground proving a rough road to travel, some researchers believe that the key is pragmatism. "There's naiveté about what is possible," says Katzenstein. Several researchers say a central obstacle is finding the money and technical assistance needed to educate African researchers about the importance of IRBs and informed consent. They argue that industrial countries that conduct research in Africa should bear this financial burden, for example by expanding programs like the one at the NIH's Fogarty International Center, which during the past 7 years has brought nearly 900 health professionals from more than 60 developing countries to the United States. The fellowships emphasize epidemiology, but "we strongly encourage our program directors to provide ethical training," says Kenneth Bridbord, director of Fogarty's international training division.

Gostin suggests that training, and the bureaucracy needed to run effective IRBs, could be funded by granting bodies such as NIH paying "indirect costs" to foreign grantees, much as they pay U.S. universities for overhead costs. "We recognize the value of ongoing structure and capacity to do research in the U.S., so why not Africa?" he asks. "Some of our most important research is being done there."

Piot is guardedly optimistic that AIDS research in Africa is getting better at sticking to international ethical guidelines. "We are moving more and more away from colonial times, and autonomy for individuals—including in Africa—is more and more respected," says Piot. These principles should be further bolstered by the U.S. National Academy of Sciences' Panel on Data and Research Priorities for Arresting AIDS in Sub-Saharan Africa, which plans to issue a report in December that includes discussion of these issues.

But despite the hope for more improvement, when it comes to the ethics of clinical trials in Africa, many AIDS researchers find the pace of change frustratingly slow. And the sobering reality to them is that African participants in clinical trials are still all too vulnerable to the desires of those who are supposedly working on their behalf.

–Rachel Nowak

EDUCATION

Japan Expands Graduate, Postdoc Slots

TOKYO—The Japanese government is about to take a major step in its continuing effort to become a basic research powerhouse by greatly expanding support for graduate students and postdoctoral scientists. In addition to providing universities with more talent, the rapid growth in the number of postdoctoral positions is expected to give young scientists greater opportunities for independent research. That would be a break from the traditional Japanese practice of having a new Ph.D. take a position as an assistant to an established professor and work for years under close supervision. The new plan will also expand opportunities for foreign scientists who want to work in Japan.

The target figure of 10,000 awards by 2000 would be almost triple the current number of 3775 graduate students and postdoctoral scientists with government funds. The program is expected to get off to a quick start, with 6130 grants available next year.

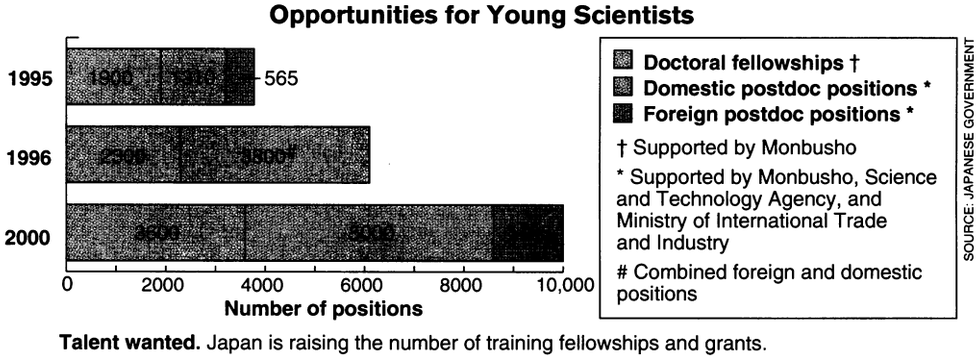
The new positions represent the second stage of a three-step policy adopted in 1991 at the advice of a panel to Japan's Ministry of Education, Science, Sports, and Culture (Monbusho). Japan has made steady progress toward the first goal, to double graduate school enrollment by the turn of the century, with enrollment rising from 98,650 in 1991 to 153,423 this year. But the third step—finding jobs for this growing number of basic researchers at universities, government institutes, or high-tech companies—promises to be the most difficult, especially with the country mired in a lingering recession.

The government programs to be expanded include a range of fellowship and postdoctoral offerings. Individual fellowships, to support either doctoral studies or independent postdoctoral research, are administered by the Japan Society for the Promotion of Science (JSPS), an arm of Monbusho. These awards now provide a monthly stipend of $1950 for graduate students and $2820 for postdocs for 2 to 3 years. "It's enough to live on," says Hodaka Fujii, a doctoral student in molecular biology at the University of Tokyo. "But more would be better." A JSPS fellowship awarded in the course of his training has allowed Fujii to quit a part-time job he held to make ends meet.

On top of the stipend, JSPS fellows can get up to $15,000 a year for research expenses, and foreign postdoctoral researchers can get a 1-year fellowship to work at a national university or Monbusho-affiliated research institute. Foreign fellows get round-trip airfare and a monthly stipend of $2700 plus a housing allowance of up to $1000 per month. The Science and Technology Agency and the Ministry of International Trade and Industry have similar postdoctoral fellowship programs for foreign researchers, which are also being expanded. And there are postdoctoral positions attached to specific institutes affiliated with the three different agencies. Details vary, but they typically run for 2 or 3 years and carry monthly stipends roughly equal to that given JSPS postdoctoral fellows. Many of these positions are also open to foreign postdoctorate-level researchers.

In addition to their increased number, the new slots represent a shift in the balance between graduate and postdoctoral positions, says Makoto Fujiwara, deputy director of the science and international affairs bureau of Monbusho. The current 1:1 ratio will tip sharply toward postdoctorate fellowships and positions in an attempt to accommodate growing numbers of students with advanced degrees.

But Monbusho isn't turning its back on graduate students. Indeed, it wants to start a



Talent wanted. Japan is raising the number of training fellowships and grants.