

A Boost for African Science



SPOTlights
iavi

HOW IAVI BUILT A NETWORK OF LABS Ivory towers can feel pretty confining. That, at least, was what Josephine Birungi had concluded when she learned that the Uganda Virus Research Institute was looking for a senior scientist to set up and run a lab dedicated to conducting clinical or human trials of AIDS vaccines. Birungi, a Ugandan who was completing her post-doctoral studies at Yale University and feeling more than a little homesick, specialized in the molecular biology of the mosquito, and had never before worked on a clinical trial. But she did have the technical skills and scientific training that the Institute sought. She had, besides, already helped establish a molecular biology laboratory at Makerere University in Kampala, Uganda's capital. Setting up another in Entebbe seemed just the prescription for her academic malaise—and much more. Birungi knew that the best way to curb the AIDS epidemic devastating her country would be to develop a vaccine against the disease. “I wanted to be a part of that effort,” she says. “I felt I should contribute. I had spent too much time in school.”

Birungi has left the ivory tower far behind. The laboratory she helped set up in Entebbe beginning in 2002 is one of 11 sophisticated clinical trial facilities that the International AIDS Vaccine Initiative (IAVI) supports and operates in collaboration with local scientists and institutions in India and in five countries in Africa. Their activities are coordinated and monitored by IAVI's Core Labs based in London and Johannesburg. Together, these centers power the organization's primary mission: to create, as quickly as possible, a preventive vaccine against HIV, especially one designed to protect people in the developing world, where 95% of new HIV infections occur. Thanks largely to this network, IAVI has since 2000 helped put six new experimental vaccines to the test in human trials. The labs have also become virtual centers of research into the epidemiology, biology and molecular underpinnings of the AIDS pandemic.



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To run a clinical study, every trial center has to have at a minimum a laboratory that monitors the health of volunteers; if anyone falls ill during the trial, investigators must find out as quickly as possible whether the illness is related to the vaccine, or caused by something else. “If the vaccine is not safe,” notes Jill Gilmour, IAVI’s senior director of clinical research, “it’s going nowhere.” But IAVI had ambitions for the labs it supports beyond overseeing safety issues. Traditionally in vaccine trials conducted in developing countries, samples taken from volunteers were sent directly to labs in the western world where they were analyzed to determine whether and how the volunteer’s immune system responded to the vaccine candidate. IAVI broke that tradition, providing the necessary training and infrastructure locally so that the immunology work would be done on site. The organization also ensures, wherever possible, that trial centers are led by in-country scientists, staffed by in-country technicians and run by in-country

institutions. “IAVI’s approach,” says Dr. Pontiano Kaleebu, principal investigator at Uganda Virus Research Institute (UVRI), “stresses building local capacity for the long term, training people and putting infrastructure on the ground. Not just doing one trial and leaving.”

UNCONVENTIONAL WISDOM

The Kenya AIDS Vaccine Initiative (KAVI) at the University of Nairobi’s Kenyatta Hospital was the first institution to benefit from IAVI’s mission to build scientific capacity locally (UVRI, where Birungi set up shop, was second). A group at KAVI led by Dr. Omu Anzala worked with Oxford University and IAVI to run the first AIDS vaccine trial ever in Kenya. In 2001, “People were not sure we could carry out a vaccine trial in Africa,” recalls Bashir Farah, the lab manager at KAVI. Farah says it was clear to him that many of his colleagues abroad felt that KAVI should send its samples to Europe for

analysis. “They thought we didn’t have the experience,” says Farah. “Well, we didn’t. But we did have the determination.” With the support of Oxford and IAVI, KAVI researchers ran a successful trial, demonstrating that the vaccine candidate proved safe but did not produce immune responses strong enough to warrant further testing.

IAVI contended with similar doubts when it began expanding its trial network. How, skeptics wondered, would it ensure that the data coming from such a large network of labs in developing countries was of consistently high quality? Being a lab in Africa is a bit like being a professional woman says Gilmour, “You’ve probably got to be a little bit better.” To prove that all its partner labs were up to snuff, IAVI had them accredited under the stringent Good Clinical Laboratory Practices (GCLP) scheme, which is based on the legal requirements for conducting clinical trial data analysis in Europe and South Africa. Labs must initially survive two audits one year apart by an outside agency to be granted full accreditation. “We are internationally recognized,” says Birungi, “and that’s important. I’ve worked overseas, and it’s very easy to see data coming from some developing country and doubt its credibility.”

This high level of oversight serves a purpose beyond providing credibility for results: it also provides consistency across the trial network. Because vaccine candidates generally are tested at more than one site, it is vital that trial data generated at



Josephine Birungi and a colleague at work in the Entebbe lab.

one center be comparable to those produced at every other center. This means that technicians need to standardize every aspect of their work—from sample preparation to measurement of immune responses—in exactly the same way, preferably using the same instruments and the same materials. To ensure that this happens, IAVI has created training programs in GCLP and its own standard operating procedures that it runs at both the Core Labs and at trial centers.

The two central labs in London and Johannesburg closely monitor incoming data to make sure the standards are holding. IAVI also regularly sends out samples to external labs as an additional quality control mechanism. These tests show that the labs IAVI supports in Africa perform complex analyses at least as consistently as those in the U.S. “IAVI has established extremely strong training in-country, and incredible laboratory capacity,” says Mark de Souza, a director at the U.S. Military HIV Research Program and one of eight scientists invited by IAVI to conduct an independent review of the trial centers it supports in Africa. “They have amazing quality control programs. They’re kind of the envy of many other vaccine networks.”

CHALLENGES AND REWARDS

Getting there has not been easy. Access to scientific equipment, chemicals and other materials has long been a problem in Africa because many leading manufacturers of such goods don’t have agents dedicated to African countries. (They are more likely to have them in India, which has a booming

pharmaceutical industry.) To address this problem, IAVI’s labs in London and Johannesburg set up a supply network to keep their partners flush with essential materials and diagnostic kits. Many of the labs use identical equipment, so technicians can call each other for advice when trouble-shooting finicky instruments.

Creaky infrastructure poses another set of challenges. At most of the trial centers IAVI supports, the organization has created an information technology platform robust enough to carry IAVI’s web-based data-entry and sample-tracking system. All the labs have had to install generators: in the event of power failure, frozen samples can’t be allowed to defrost.

The reward for overcoming these challenges has been a sequence of successfully conducted clinical trials, as well as a series of research studies, most of them ongoing, meant to prepare the ground for future trials. One research study, for example, examined the prevalence of HIV infection in various countries; another the rate at which HIV infection is spreading. Aside from providing vital public health information, such estimates are key to determining how many people need to be enrolled in trials that assess the efficacy of candidate vaccines: the higher the rate of new infections, the lower the number of volunteers needed. IAVI’s research studies, including one that follows discordant couples (in which one partner is HIV-infected, and the other is not), have the added benefit of providing HIV testing and counseling to participants, who might otherwise get neither.

One study, called Protocol D, looked at the results of various tests—blood cell counts, liver function and the like—conducted with healthy African adults in Kenya, Uganda, Rwanda and Zambia. These tests are used to determine whether volunteers are well enough to participate in clinical trials, but the range defining who is healthy previously had been derived from studies of Westerners. Protocol D found results in Africans differed. Africans with significantly lower counts of white blood cells than the average Westerner, for example, are often perfectly healthy. So many people who were healthy and willing to participate in clinical trials had for years been unnecessarily turned away by investigators relying on inappropriate Western ranges. As a result of Protocol D, and similar research by other organizations, locally relevant ranges are now available. This will both expand the pool of volunteers available for future trials and enable better monitoring of volunteer health, since researchers will be able to compare the results of health checks conducted after the trial has begun against credible local norms.

Two additional studies being conducted at all the IAVI-supported centers in Africa seek to gather information that might improve the design of AIDS vaccines. One examines the course of early HIV infection in a large group of volunteers, tracking how their immune systems respond to HIV and how the virus multiplies and mutates over time. Vaccines are in theory best designed to battle the virus as it appears in the early stages of infection, before it has mutated significantly. The second study focuses on HIV-positive volunteers who have



remained healthy for at least three years after they were infected. Some of them, it turns out, produce broadly neutralizing antibodies to HIV, which destroy many of the subtypes of HIV circulating globally. The identification and analysis of these antibodies could give vaccine designers valuable clues about HIV's vulnerabilities.

INVESTING IN PEOPLE

It could take a number of years before the value of these efforts leads to an effective AIDS vaccine. But the fact that the work is being done in Africa, largely by Africans, has already begun to pay dividends. "One of IAVI's missions," says Gwynneth Stevens, director of clinical laboratories at IAVI, "is to ensure that we leave something behind—that we don't just go in country, take blood and leave. Historically, that's what has happened across Africa and in most developing countries. People are tired of this approach."

When IAVI arrived in Zambia, where two-thirds of the population lives on less than a dollar a day and one of every six adults is infected with HIV, the work done to battle the epidemic in the country had largely been restricted to voluntary testing and counseling. The lab at the country's sole medical school could run basic

clinical and microbiological tests, but had neither the infrastructure nor the trained personnel required to run clinical trials. Dr. Elwyn Chomba, principle investigator and chairperson of the Project Management Group at the Zambia Emory HIV Research Project, notes that IAVI renovated old labs and put up new ones, building almost from scratch Zambia's only complete clinical trial facility. The GCLP-accredited center has already completed its first Phase II trial of an AIDS vaccine. But nothing, says Chomba, has been as valuable as the training IAVI has provided to the laboratory's staff in practical immunology, GCLP and the management of vaccine trials. "When you invest in people, you invest forever. Even if we were to find a vaccine against HIV tomorrow, the capacity to do clinical trials in other fields will always be here," she says. "That probably outweighs everything else."

IAVI-trained scientists and technicians in sub-Saharan Africa are making their presence felt in more ways than one. UVRI, for example, runs a research mentoring program that enables junior clinical trial managers and lab scientists to work alongside more experienced teams. Scientists from government-sponsored research programs in Kenya, Tanzania and Malawi have been mentored by

IAVI's Ugandan coordinators in such areas as designing and managing clinical trials and complying with GCLP. At other centers, scientists from government and academic institutions frequently sit in on IAVI's on-site training workshops on GCLP and standard operating procedures. At the same time, the lab network is changing how African scientists work, expanding professional horizons and seeding a regional scientific community. "Now we can work together with colleagues in Kenya, Rwanda, Zambia, South Africa," says Kaleebu. "We meet often, and we are trying to write joint publications. I think that's important. In the past a lot of the collaboration was with people in the North, not with colleagues in Africa. But with African colleagues you can share your experiences, you can train one another. It opens more opportunities for future collaborations."

As such opportunities multiply, more African scientists who are living in the West, as Birungi was, might find a reason to return home. IAVI alone isn't capable of reversing the brain-drain that has emptied Africa of many of its brightest professionals. But the organization's stress on building capacity in its partner countries is making a difference. After all, many scientists like Kaleebu, Birungi and Chomba could easily find work in the West but would rather not if they don't have to. Certainly not if staying means they can contribute to ending a pandemic that has killed so many of their friends, colleagues and neighbors. "Being Ugandan, and being recognized as someone who is making a contribution in this area—I think that's very satisfying," says Kaleebu. "I don't think I would have had that satisfaction if I had worked abroad."

