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PEPFAR
U.S. President's Emergency Plan for AIDS Relief

Investing in the Future: The Role of Africa in the Search for an HIV Vaccine

Physician-researcher Etienne Karita is standing in his sunlit laboratory in Kigali, Rwanda, looking over the shoulder of one of his lab techs peering through a microscope at cells coaxed from a plastic vial. Nearly 10,000 miles across the globe, in a laboratory with wide windows overlooking the pine bluffs of La Jolla, California, scientist Elise Landais reaches for a similar vial to carefully extract and study the cells that are the workhorses of the human immune system. It's exacting work demanding one's full attention; each drop, after all, could bring the world a step closer to a vaccine critical to putting an end to AIDS.

Together, Drs. Karita and Landais are involved in analyzing samples collected from the largest longitudinal study of HIV infection among Africans. This study, known as Protocol C, is providing scientists with a treasure trove of samples from HIV-infected volunteers and is yielding important insights about the course of infection in Africans, who continue to bear the brunt of the HIV pandemic.

In another study funded by the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) through the U.S. Agency for International Development (USAID) and known as Protocol G, the International AIDS Vaccine Initiative (IAVI)'s African Clinical Research Center (CRC) partners collected blood samples from 1,800 African volunteers, which led to the identification of powerful, infection-fighting proteins called antibodies that are the focus of HIV vaccine development efforts today in laboratories around the world. Thanks to these two large studies, vaccine researchers have tens of thousands of samples to work with toward the discovery of an HIV vaccine. Neither the scientists who embarked on these landmark studies years ago in collaboration with IAVI, nor the advisors at USAID, the primary funder of them, could have predicted the value of these samples or the progress they would spur. The contributions of these two studies to vaccine research are now indisputable even before the world has a vaccine.

"If you want to understand something in order to generate hypotheses, you need to go fishing with a net, not a pole," said Dr. Salim S. Abdool Karim of CAPRISA.ⁱ "Somewhere in there is a beautiful fish. You have to have the patience and the fortitude to go the distance in order to find that fish. The visionaries, such as those who founded these studies, are the ones that make important new discoveries."



Etienne Karita analyzing samples in the early days of the Projet San Francisco lab. Photo by Jean Nepo Nduwamungu.

The End of AIDS?

AIDS is not over. Not by a long shot.

Despite tremendous gains in treating and preventing HIV and AIDS in recent years, the infection continues to ravage communities, particularly in developing countries. In 2014, 1.2 million people died from AIDS-related causes and 2.1 million people around the world were newly infected with HIV. Last year, both two-thirds of the HIV-related deaths and two-thirds of the newly HIV-infected were in sub-Saharan Africa, the hardest-hit region in the world. Globally, AIDS remains the leading cause of death among women of childbearing age.

This is why, more than 30 years into the pandemic, researchers are convinced that a key part of the solution is a vaccine. According to Dr. Anthony Fauci of the National Institute of Allergy and Infectious Diseases (NIAID),ⁱⁱ a vaccine would be "the nail in the coffin of the AIDS epidemic."

After decades of research, an HIV vaccine remains challenging. HIV is a particularly formidable virus; the tried-and-true approaches that led to vaccines against other viruses simply do not work against HIV. It establishes infection rapidly, mutates at a furious rate, and attacks the very cells of the immune system that the body uses to defend against such invaders. However, recent results from

clinical trials and the discovery of powerful antibodies are now fueling real progress and optimism among vaccine researchers.

An eventual vaccine must be effective for the most vulnerable people of Africa, like young women, where the greatest disease burden and the highest HIV infection rates persist. This is why, over the past decade, developing an HIV vaccine for Africa has been the focus of USAID’s partnership with IAVI. With USAID support, IAVI has established a network of Clinical Research Centers and laboratories, primarily in East Africa, led by highly skilled local researchers. IAVI and its partners have focused on building individual, institutional, and national capacity for HIV vaccine clinical trials that can be conducted in accordance with the highest international standards (Figure 1: Map of Sites).

Casting the Net

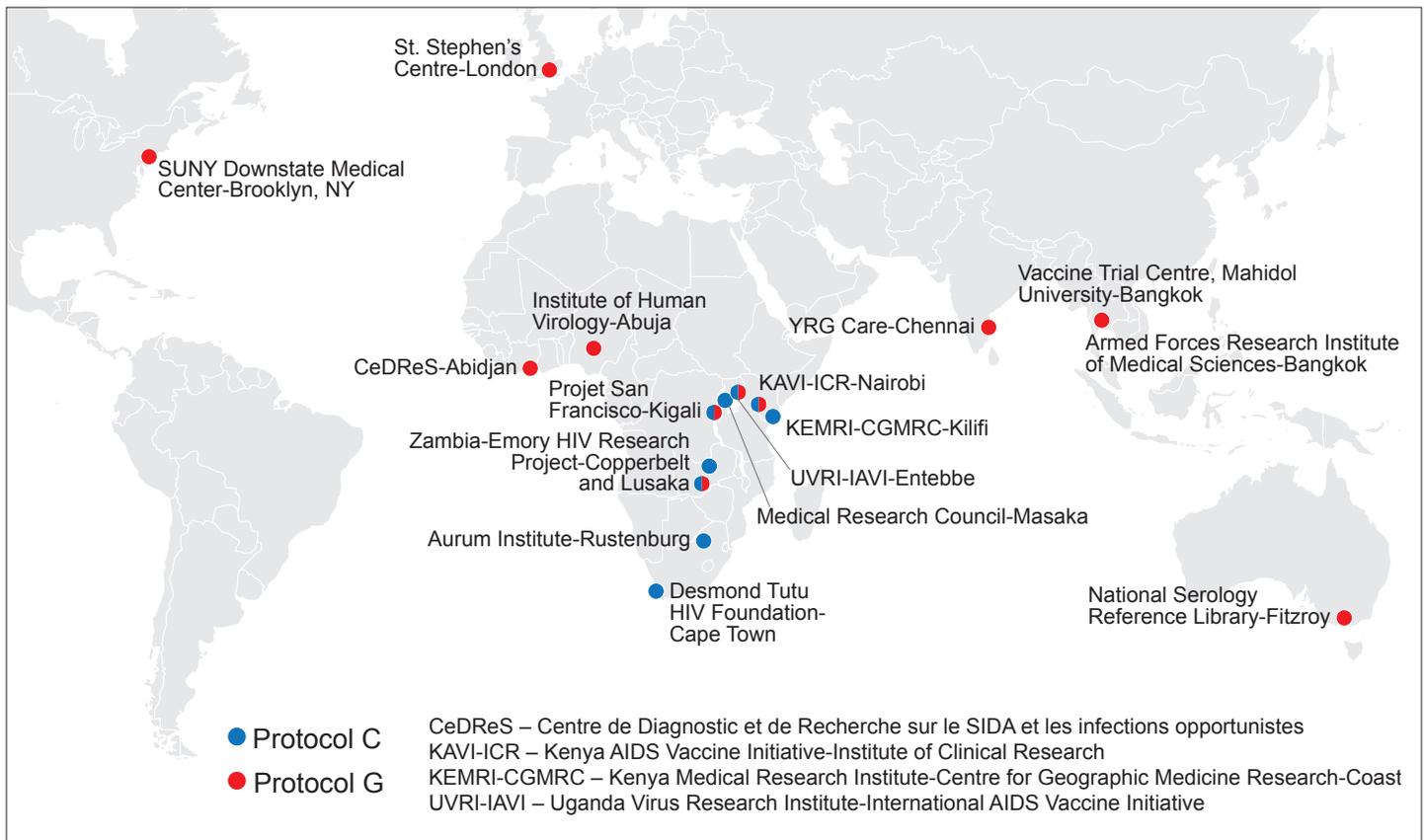
The strains of HIV that circulate in a specific country and how an immune system responds to those viruses may be important to understanding whether, and where, a newly designed vaccine will work. Given this reality and with no HIV vaccine efficacy trials underway at the time, IAVI recommended a series of epidemiological studies in 2006, with stalwart support from USAID. Two of these studies were Protocols C and G.

At the start, the concept of Protocol C was rather straightforward. “The original goal was simply to characterize the health outcomes of HIV-infected Africans in order to plan for vaccine trials,” said Matt Price of IAVI.ⁱⁱⁱ To this end, the study enrolled more than 600 volunteers from Uganda, Zambia, Rwanda, Kenya and South Africa, who were monitored regularly and tracked once they tested positive for HIV. Almost 20,000 samples were collected from these volunteers at the earliest stages of HIV infection. These samples enabled unprecedented insights into both the early events of HIV transmission and the progression of infection over time.

“From this study we have learned so much about the complex interaction between HIV and the immune system: what happens immediately after infection, how the immune system appears to control the initial burst of virus, how HIV changes and escapes from immune defenses, and what are the characteristics of the virus that are able to establish infections,” said Price.

Protocol C has provided a much better understanding of HIV in Africa, revealing differences in how the infection progresses and the distribution of the many HIV variants across regions or countries. “Protocol C is like a gift that keeps on giving,” said Margaret McCluskey of USAID.^{iv} “It’s gratifying to see the new information regarding early viral events that keeps emerging from Protocol C, which promises

Figure 1: Map of Sites



to inform vaccine design in a very real way. The scientific contributions resulting from this work are significant and the teams who have labored over this protocol are a source of great pride for the Agency—and of course, we are forever grateful to the study volunteers.”

Powerful proteins

Antibodies are the reason most common vaccines work. These proteins can work against viruses in many ways, but of particular interest to researchers are antibodies that can latch on to and destroy viruses, the so-called neutralizing antibodies.

But HIV is a moving target. Its rapid mutation rate gives rise to multiple strains of the virus that are in circulation around the world. So, for a vaccine to provide optimal protection, it would need to induce neutralizing antibodies against most if not all strains of HIV—what researchers refer to as broadly neutralizing antibodies. For decades, researchers had only discovered a few broadly neutralizing antibodies. So, IAVI and partners, with USAID’s support, launched Protocol G in an effort to hunt for new, more effective antibodies.

More than 1,800 volunteers who were HIV-infected for at least three years contributed blood samples in this study. Components of their blood were analyzed to see if they could strongly neutralize many different HIV variants. This work led to an important discovery that has changed the landscape of HIV vaccine development. In 2009, IAVI and several partners from academic laboratories and innovative biotechnology companies isolated a new broadly neutralizing antibody from a Protocol G sample. The antibody known as PG9 was the most potent antibody known at that time and the first to be isolated from a study volunteer in a developing country. Since then, researchers at the National Institutes of Health (NIH), IAVI, and others have identified hundreds of new broadly neutralizing antibodies against HIV.

“Before these large studies, most scientists had tested only handfuls of samples at a time,” recalls John Mascola of NIAID.^v “Protocol G and other studies began to test hundreds of people and were able to demonstrate that the immune system can make potent antibodies. That really changed the thinking in the field. It’s just a matter of figuring out exactly how to teach the body to do with a vaccine what happens during infection.” That is now the task at hand: using the information about these antibodies to design better HIV vaccine candidates.

From Samples to Solutions

The involvement of African researchers in Protocols C and G didn’t stop with enrolling, following, and collecting samples from thousands of volunteers. IAVI’s clinical laboratory partners in Africa are now conducting some of the most sophisticated analyses of these samples—work Karita and others take great pride in. And through consortiums and partnerships established by IAVI with support from USAID, NIAID, and others, these researchers are also actively engaged in designing the next generation of HIV vaccine candidates.



Anatoli Kamali discussing Protocol C sample analysis with a lab tech from MRC-UVRI. Photo by Jan de Bont.

“Protocol C has given us a unique opportunity to understand HIV,” said Anatoli Kamali of MRC/UVRI.^{vi} “It gives me a lot of pride that we can turn this data into knowledge and then, hopefully, into an HIV vaccine.”

Building human talent on this level is one of the core results of USAID’s investment to develop an HIV vaccine. By engaging communities devastated by HIV in the solution, USAID is ensuring that the day a vaccine becomes a reality, it will be available to those who need it most. When every day brings 5,600 new HIV infections, that day can’t come soon enough.

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- i Dr. Salim Abdool Karim, Director of the Centre for the AIDS Programme of Research in South Africa (CAPRISA) in Durban and chair of the Joint United Nations Programme on HIV/AIDS (UNAIDS) Scientific Expert Panel
 - ii Dr. Anthony Fauci, Director of the US National Institute of Allergy and Infectious Diseases (NIAID)
 - iii Dr. Matt Price, Director of Epidemiology at IAVI
 - iv Margaret McCluskey, Senior Advisor for HIV Vaccines, USAID, Office of HIV & AIDS, Global Health Bureau
 - v Dr. John Mascola, Director of the Vaccine Research Center at the US National Institute for Allergy and Infectious Diseases (NIAID)
 - vi Dr. Anatoli Kamali, Deputy Director of the MRC/UVRI Uganda Research Unit on AIDS