

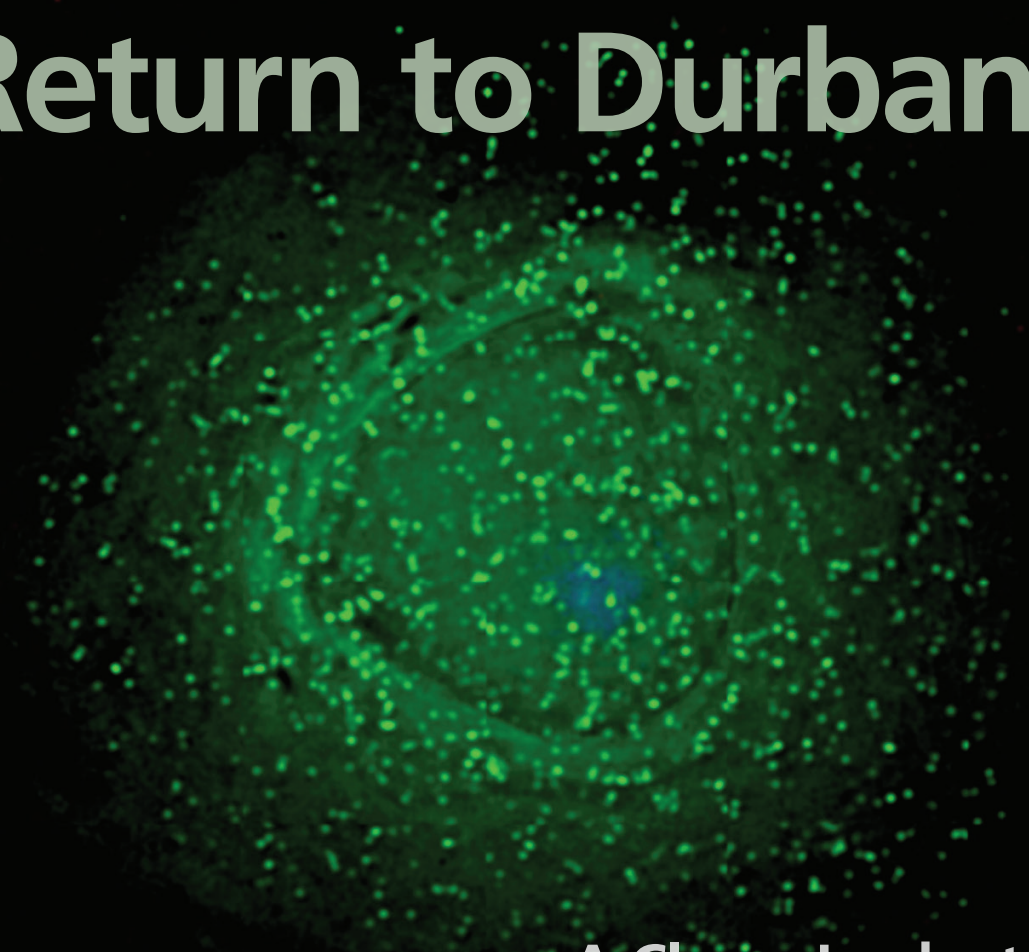
VOLUME 20, ISSUE 3

IAVIReport

The Publication on AIDS Vaccine Research

WWW.IAVIREPORT.ORG | VOLUME 20, ISSUE 3 | 2016

AIDS 2016: A Return to Durban

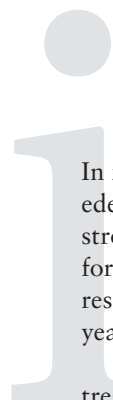


Plus:

**A Closer Look at the EU's
Vaccine Research Grants**

Alex Coutinho on His Career in HIV

EDITOR'S LETTER



In many parts of the world, this season was marked by turbulent events. Whether it be the unprecedented migration crisis, terrorism, the United Kingdom's vote to leave the European Union, catastrophic weather, or emerging pathogens like Zika, there are many priorities these days competing for the attention of governments and international funding agencies. It is within this competitive and resource-constrained environment that AIDS 2016 took place, returning to Durban, South Africa, 16 years after the HIV/AIDS community first gathered in the coastal city.

To be sure, the progress in providing millions of HIV-infected people with life-saving antiretroviral treatment was oft discussed at AIDS 2016. But advocates, public health experts, and government officials are far from resting on their laurels. In fact, experts at AIDS 2016 warned that the hard-won gains against HIV/AIDS are in peril of being lost if financial support isn't maintained and improved HIV prevention efforts aren't implemented. A dozen or more speakers who addressed the conference's more than 15,000 delegates cited a vaccine as a crucial component to achieving the United Nation's goal of ending AIDS. In this issue, we provide our complete coverage of AIDS 2016 (see page 9).

We also look at how the European Union is hoping to stimulate HIV vaccine research efforts across its partner countries with two grants backed by a €45 million investment (see page 4), and provide an update on the imminent HVTN 702 trial, the first large-scale vaccine efficacy trial to begin since the results of the RV144 trial in Thailand indicated that a prime-boost vaccine regimen provided a modest 31% protection against HIV infection (see page 18).

Finally, I had the opportunity to talk with Alex Coutinho, the Ugandan physician, public health expert, and former IAVI Board member about his long and varied career working in HIV and why it was important to him to stay and work in Africa (see page 15). It is through the continued dedication of individuals like him, new and sustained funding, and innovative science that progress in defeating AIDS will be made.

– KRISTEN JILL KRESGE



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The International AIDS Vaccine Initiative (IAVI) is a global not-for-profit organization whose mission is to ensure the development of safe, effective, accessible, preventive HIV vaccines for use throughout the world. Founded in 1996, IAVI works with partners in 25 countries to research, design and develop AIDS vaccine candidates. In addition, IAVI conducts policy analyses and serves as an advocate for the AIDS vaccine field. IAVI supports a comprehensive approach to addressing HIV and AIDS that balances the expansion and strengthening of existing HIV-prevention and treatment programs with targeted investments in the design and development of new tools to prevent HIV. IAVI is dedicated to ensuring that a future AIDS vaccine will be available and accessible to all who need it. IAVI relies on the generous donations from governments, private individuals, corporations and foundations to carry out its mission. For more information, see www.iavi.org.

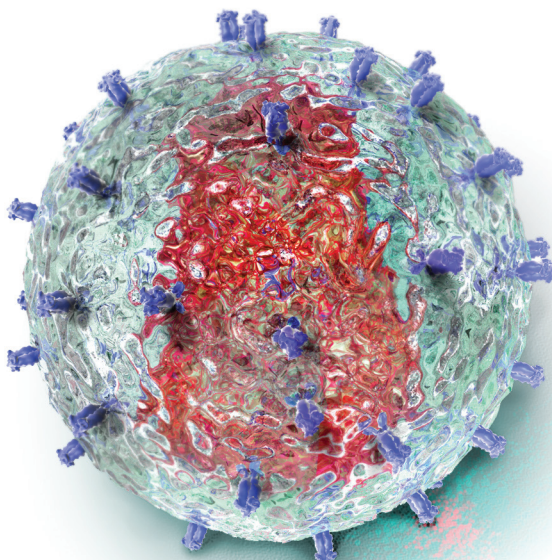
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SENIOR PRODUCTION MANAGER
Nicole Sender

MANAGING EDITOR
Kristen Jill Kresge

CONTRIBUTING WRITERS
Michael Dumiak
Michael Keller
Mary Rushton

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[ON THE COVER]

HIV-1 particles assembling at the surface of an infected macrophage.

Reconfirming the Traditional Model of HIV Particle Assembly. Gross L, PLoS Biology Vol. 4/12/2006, e445. doi:10.1371/journal.pbio.0040445

EUROPE INVESTS *in HIV Vaccine Research*

Talent-rich but comparatively resource-poor and under intense political pressure, the European Union launches a pair of research initiatives under a €45 million umbrella.

By Michael Dumiak

The headlines from Europe this summer paint a picture of a grim and inward-looking place: a continuing struggle to cope with an unprecedented immigration and integration crisis and the United Kingdom's vote to leave the European Union (EU).

The EU, however, is also working to keep its focus on long-term issues in public health, specifically the pursuit of an HIV vaccine. Earlier this year the European Commission launched a pair of research initiatives backed by €45 million (approximately US\$55 million) aiming to produce, compare, evaluate, and test early development-stage HIV vaccine candidates. This is a relatively modest amount: the annual US spending on HIV vaccine research is about \$836 million, with \$595 million of that from the public sector, according to the Resource Tracking for HIV Prevention Research and Development Working Group's 2015 report.

But Europe has many top-flight labs with talented research teams scattered across the continent that consistently make meaningful contributions to basic HIV research, including efforts to develop a vaccine and a cure. The European Commission's most recent funding initiative supports two projects: The European AIDS Vaccine Initiative (EAVI2020) and the European HIV Vaccine Alliance (EHVA). The Brussels-based European Commission intends the initiative to encourage collaboration and discovery, bringing

together dozens of institutions to develop tools to sort and predict the behavior of vaccine candidates, speed the testing process, and contribute to the global effort to expedite the development of an HIV vaccine.

The two five-year projects are meant to be part of a developing portfolio of research projects that the European Commission is building through its Horizon 2020 program. As Brussels continues to try to bridge the fissures besetting the EU, its scientific efforts are attracting higher visibility as a measure of its ability to function. But the HIV researchers involved in EAVI2020 and EHVA are used to high stakes.

The Global HIV Vaccine Enterprise recently partnered with *IAVI Report* to discuss these new projects with four of the key figures involved: Ruxandra Draghia-Akli, director of the Health Directorate at the European Commission's Research and Innovation Directorate General; Yves Levy, chief executive officer (CEO) of the French Institute of Health and Medical Research (INSERM) and coordinator of the EHVA; Giuseppe Pantaleo, chief of the Service of Immunology and Allergy at Lausanne University Hospital, executive director of the Swiss Vaccine Research Institute, and co-scientific coordinator of EHVA; and Robin Shattock, mucosal infection and immunity professor at Imperial College London and the coordinator of EAVI2020.



**Global HIV Vaccine
Enterprise**

The Global HIV Vaccine Enterprise is an alliance of independent organizations committed to accelerating the development of a safe and effective HIV vaccine. The Enterprise, along with its stakeholders, promotes collaboration, coordination, and knowledge sharing to attract interest, resources, and funders to the field. www.vaccineenterprise.org

RUXANDRA DRAGHIA-AKLI

How do you believe the multi-disciplinary nature of EHVA and EAVI2020 will accelerate vaccine development?

The nature of HIV has posed an enormous challenge to the research community that has made endless efforts to develop an effective vaccine and put an end to the AIDS epidemic. There are several bottlenecks which prevent the identification of viable candidate vaccines at an early stage of the development process. These are challenges that no single discipline or research group alone can address. This is a long process and successful vaccine research and development builds on collaborative work, frequently at a global level. It is within this landscape that the EU, with its funding program for research and innovation, Horizon 2020, has invested €45 million in 2015 to support two large and complementary consortia: EHVA and EAVI2020. In these partnerships, European scientists will work together, and in collaboration with researchers from outside Europe, to successfully develop predictive tools and select the most promising vaccine candidates to be tested at an early stage of the process.

With their collaborative structures, the consortia pulled together the necessary critical mass of expertise and complementary skills needed to tackle difficult research challenges—each group bringing its valuable expertise and perspective. In addition, as I believe competition does not prevent collaboration, by funding both consortia the Commission also enhanced the competitive environment in this field which can function as an extra push in accelerating the development of new vaccine candidates.

Therefore, with EHVA and EAVI2020, we offer a triple win: we promote European scientific excellence and global collaborations, accelerate the development of novel prophylactic and therapeutic vaccine candidates, and enhance European competitiveness.

What challenges do you anticipate with the collaborative structure?

Collaboration across disciplines, sectors, and countries can be challenging because of technical, operational, and cultural barriers. However, Europe has a long history of supporting collaborative research, starting with its first framework program for research launched in 1984. The EU funding programs, which are open to the world, have allowed scientists to collaborate together in a joint effort to explore, understand, and provide solutions for the health of patients, including the devel-

opment of an HIV vaccine. Nowadays, most of the academic researchers receiving our grants are used to working together in a multi-disciplinary environment and in teams with civil society, patient organizations, the pharmaceutical industry, and subject matter experts.

What lessons from previous multi- and cross-disciplinary strategic approaches might help guide the EHVA and EAVI2020 collaborative efforts?

For almost thirty years the European Commission has supported multi- and cross-disciplinary consortia. This was done under the cooperation pillar of the framework programs for research and innovation, and continues under the Horizon 2020 societal challenge “Health, demographic change and well-being,” in the public-private partnership Innovative Medicines Initiative (IMI), and the European and Developing Countries Clinical Trials Partnership (EDCTP). The lessons learned from the previous approaches are that to address complex scientific challenges one needs more than the excellence of a single group. What is needed is a well-balanced partnership that includes a broad range of expertise from different disciplines and different types of organizations, ranging from academia to private (small, medium, and large) companies, patient groups, and regulatory bodies, each bringing its own perspective and an open mind to working with others. The investigators in EHVA and EAVI2020 are accustomed to this, as many of them have worked in different partnerships in previous consortia, such as the CUT’HIVAC and IDEA projects, which were successful in advancing the vaccine field.

Does a framework currently exist to maximize knowledge sharing and synergies among the collaborators, including with partners in industry?

Knowledge sharing and synergies are an integral part of our funded collaborative research. A part of all EU-funded grants is dedicated to dissemination, communication, and exploitation of the results and knowledge generated, and this includes information exchange with external stakeholders. Following Horizon 2020’s open access policy, our grantees must ensure that peer-reviewed scientific publications are deposited in repositories and made open access. Also, a novelty in Horizon 2020 to which EHVA and EAVI2020 can apply on a voluntary basis is the Open Research Data Pilot, which aims to improve and maximize access to and re-use of data generated by the projects. In addition, the Euro-



Ruxandra Draghia-Akli is director of the Health Directorate at the Research and Innovation Directorate General of the European Commission

The interview with Ruxandra Draghia-Akli was conducted by the Global HIV Vaccine Enterprise.

“EU-funded research promotes European scientific excellence, it helps to develop new or improved preventive and therapeutic tools for the global benefit of all citizens and patients, and it enhances European competitiveness.”

— Ruxandra Draghia-Akli

pean Commission, which directly manages and monitors the grants, plays an active role to facilitate this process and maximize the synergies among collaborators. For instance, we regularly organize workshops and other meetings around scientific- or policy-oriented themes where representatives from different consortia and organizations are encouraged to work together. And I believe that the Global HIV Vaccine Enterprise, which brings together the main groups working on HIV vaccines and which the European Commission has been a member of since its inception, has a role to play in this regard.

EHVA and EAVI2020 have nine partners in common, including IAVI, which among other roles is responsible for the implementation of the dissemination plan. The two consortia also have links with projects funded under the Innovative Medicines Initiative, the largest public-private partnership between the European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA) that brings together relevant stakeholders to drive the development of better and safer medicines and other interventions in an open innovation ecosystem. I trust that all these elements together will ensure a productive environment among the collaborators for sharing the knowledge generated, further strengthening the synergies, and helping establish new collaborations.



Yves Lévy (top) is CEO of the French Institute of Health and Medical Research (INSERM), and coordinator of EHVA. **Giuseppe Pantaleo** (bottom) is chief of the Service of Immunology and Allergy at Lausanne University Hospital, executive director of the Swiss Vaccine Research Institute, and co-scientific coordinator of EHVA.

The interviews with Yves Lévy and Giuseppe Pantaleo are based on conversations with IAVI Report and the Global HIV Vaccine Enterprise.

How can EHVA and EAVI2020 best build meaningful capacity—specifically, in sub Saharan Africa—for sustainable development, such as establishing long-term translational research programs?

In 2003 the European Commission together with several European member states and sub-Saharan Africa countries established the EDCTP. This was an important step towards the creation of a long-term and sustainable partnership to fight the three main poverty related diseases: HIV/AIDS, tuberculosis, and malaria. Based on its successes in 2014 we have renewed, reinforced, and extended this partnership with the second phase of EDCTP, which has a broader scope, including the engagement with other international funders. EDCTP2 has now become one of the crucial facilitators in capacity building and accelerating the clinical development of new or unproven products against these diseases, including HIV vaccines. Therefore, when we opened the call for proposals for HIV vaccine development, we specifically requested the applicants establish close links with EDCTP2. Both EHVA and EAVI2020 have included several investigators which have been working with EDCTP2, thus ensuring that the promising vaccine candidates generated during the implementation of the program will be proposed to EDCTP2 for advancement in clinical development.

YVES LÉVY AND GIUSEPPE PANTALEO

How will EHVA integrate a multidisciplinary approach to address challenges in HIV vaccine research?

YL: EHVA brings together 39 partners from Europe, Africa, and the US across a very diverse set of disciplines in discovery research and product development. The alliance includes expertise in the fields of molecular and structural biology, vector design, adjuvant delivery, immunology, clinical research, and biostatistics. The aim for this team is to develop an efficient platform for developing, evaluating, and selecting prophylactic and therapeutic HIV vaccines. Core components in the Alliance are the immune profiling and data management platforms to rank novel and existing vaccine candidates and ensure efficient selection of candidates during pre-clinical and clinical development.

What are the components of the platform that the EHVA will use to develop prophylactic and therapeutic vaccine candidates?

YL: The Multidisciplinary Vaccine Platform (MVP) comprises four components: discovery, immune profiling, data integration and down-selection, and clinical trials. Each brings together relevant expertise within the field. The discovery arm will generate immunogens able to induce potent non-neutralizing and neutralizing-antibody responses and T-cell responses. The immune profiling arm will standardize a set of assays and rank the novel vaccine candidates against existing ones. It will also continue to develop novel assays to further enhance this process. The data integration arm will develop statistical tools to interpret the data generated and build a data warehouse system for hosting the preclinical and clinical datasets. And the clinical trials arm will conduct Phase I trials to inform candidate selection and support prediction of success and failure in early stage research. This serves not only as a platform for selecting candidates developed within EHVA, but can also serve the vaccine field beyond the EHVA project lifespan.

Can you explain a bit more about the immune profiling?

GP: Immune profiling identifies the uniqueness of the phenotypic and functional properties of the immune response elicited by the vaccine under development. A variable number of methodologies are used to profile the vaccine-induced immune response qualitatively and quantitatively. The availability of validated assays is critical in profiling the immune response. The immune profiling platform includes a set of 28 assays encompassing humoral, cellular, and innate immunity including the set of six assays measuring the immune correlates of efficacy identified in the RV144 trial. The immune profiling platform will be instrumental for ranking the different vaccines under investigation, the down-selection of the best-in-class vaccine candidate based on pre-established criteria, and the cross-comparison with other vaccines developed in other programs.

How will the EHVA build on the results of RV144, the only trial so far to show any efficacy?

YL: EHVA builds on the learnings from the RV144 trial by developing tools to help identify the correlates of immunity, optimize vaccine regimens, and aid the selection of novel vaccine candidates for further development. The aim is to develop prophylactic HIV vaccine candidates that generate more durable and potent immune responses. To this end, EHVA is building on technologies and insights generated in the field and will focus on the development of RNA-based vaccine candidates, novel protein candidates, novel delivery system and adjuvants, as well as head-to-head comparisons of different vaccine regimens already developed by partners in the Alliance to optimize them. EHVA will also focus on developing therapeutic vaccine candidates and help elucidate mechanisms for a functional cure.

What novel vaccine candidates are you prioritizing?

GP: EHVA will aim to bring one RNA-based vaccine candidate and one protein based vaccine candidate to early phase clinical testing within the grant's five-year timespan. The primary goal of these new vaccine candidates is to elicit antibody responses directed against vulnerable sites of HIV Env. The combined use of the novel vector with protein-based vaccines will hopefully also induce durable antibody responses that are necessary for long-term protection. These novel vaccine combinations will be compared head-to-head with a number of benchmark candidates that have already been in clinical development thus representing another unique strength of the EHVA program.*

YL: Several RNA-based vaccine candidates will be compared in preclinical studies including replicon RNA, replicon RNA delivered as naked DNA, and messenger RNA. The modified HIV Envelope proteins that will be developed and compared include stabilized existing Env trimers and trimers with added glycans to silence immunodominant, non-neutralizing surfaces of the viral spike. The improved envelope trimers will be coupled with virus-like particle (VLP) or dendritic cell (DC)-targeting delivery systems.

Those that perform best in preclinical studies (small animals and nonhuman primates) will be selected for clinical trials and evaluated in a prime-boost combination to develop regimens with improved antibody and T-cell responses. Other approaches, including VSV [vesicular stomatitis virus] vectors and adjuvants will be more upstream and part of the discovery track.

GP: There are also a number of new adjuvants that are going to be evaluated. Right now there are only three adjuvants that are approved for clinical use by the US Food and Drug Administration (FDA). It's a very difficult field because there are major regulatory issues in bringing a new adjuvant into clinical development. Within the scope of our program, our work is going to focus predominantly on the pre-clinical evaluation of new adjuvant preparations that are similar, but not identical, to those that are approved by the FDA.

What does EHVA anticipate will be the collateral benefits of this approach?

YL: We plan to deliver an immune profiling platform and a central data analysis platform with state-of-the-art statistical tools for the analysis and interpretation of complex data and algorithms for the effective selection of vaccines. The field will be able to benefit from these tools to better predict poor or low efficacy of a candidate early in the process. This can also provide value for other vaccine efforts. Furthermore, the support from the European Commission and Swiss Government to develop vaccines against HIV/AIDS and other global health threats, we hope, will send a positive signal to the EU member states and other international funders about the importance of supporting these efforts.

How does EHVA seek to build meaningful capacity, specifically in sub-Saharan Africa?

YL: EHVA includes partners from Uganda, Tanzania, Mozambique, and Côte d'Ivoire. They bring extensive expertise and robust capacity for AIDS vaccine R&D to the Alliance, and will help

* These benchmark candidates include two DNA vaccines: the EuroVacc DNA Env/Gag/Pol vaccine and the GTU DNA vaccine developed by Finnish biotech FIT in Helsinki. There are also two poxvirus-based vaccines that have undergone previous testing: the NYVAC Env/gag/pol and the InSerm-ANRS MVA-HIV-B vaccine. For more information go to clinicaltrials.gov.

provide further training for African researchers. Furthermore, we liaise closely with the European and Developing Countries Clinical Trials Partnership (EDCTP) to help ensure that sufficient capacity is available for the further development

of HIV vaccine candidates that are generated by EHVA. It is anticipated that any promising vaccine candidates, prophylactic or therapeutic, that warrant further development in larger scale clinical trials will be supported by the EDCTP.



Robin Shattock is a professor of mucosal infection and immunity at Imperial College London and is the coordinator of EAVI2020.

ROBIN SHATTOCK

Is this program meant to supplement other HIV research initiatives or is it a singular effort?

It is funded as a one-off, standalone piece. We are encouraged to use these resources to leverage further collaborations and potentially further funding. We're very much integrated into a wider international program, but we are making sure that we're not duplicating work done by the CHAVI-IDs [Center for HIV/AIDS Vaccine Immunology-Immunogen Discovery grants] in the US. We are closely linked to the CAVD [The Collaboration for AIDS Vaccine Discovery] and we have representation on our advisory board from the US National Institutes of Health. We've taken great effort to make sure this isn't a me-too approach where we are all building similar versions of the same space rocket. We have tried to make sure that we're working in a unique space so that we can provide a unique contribution to the field.

What kind of infrastructure is in place? What's needed?

There are 23 partners across Europe, all with very different but complementary skill sets. We took to heart the original challenge that was put out by the European Commission, which was to try and generate 10 new vaccine candidates and put them into the clinic within five years. That's ambitious. We made a deliberate policy that we would not work on any existing candidates that were already in the field, and I think this is one of the things that makes us a little more unique. We have tasked ourselves to get eight new, next-generation, stabilized, native-like trimers and two novel T-cell vaccine approaches into the clinic within that five-year time period.

What can you tell us about the different candidates?

For the B-cell candidates, we are building on what came out of the very elegant work John Moore and Rogier Sanders did that led to the development of the BG505 SOSIP immunogen.*

As a consortium we are working to improve the breadth of the antibody response. We are trying to induce breadth by looking at conserved and mosaic immunogen approaches in collaboration with

Bette Korber from the US. Rogier Sanders and the consortium are also using viral isolates derived from HIV-infected volunteers that developed broad neutralizing responses to the virus within the first six months or so (rather than one to two years) and using these as a road map for driving B-cell responses toward neutralizing breadth. Our intention is to select a series of B-cell immunogens with potential to do the same in non-infected subjects over a short period of time. Essentially, we are looking to develop approaches that have translational potential in a real-world setting.

Then we will move immunogens that have been shown to induce quite a good level of breadth from pre-clinical study to early clinical/experimental medicine Phase I trials, and try to do it quickly. A significant part of our focus is to be in humans as fast as possible so that we can get an early readout on human immunogenicity. Understanding how to engage the right B cells in humans, and particularly germline B cells, will be critical to solving this problem. We're not anticipating that these first shots at goal will be a score, but they will help us get better at predicting what makes a good immunogen and how to focus the immune response towards making broadly neutralizing antibodies.

In parallel to our dash to the clinic, we have a slower, considered, iterative, rational design where human immunogenicity will feed back into the design in the earlier stages. The goal is that by the end of the program we will have built up a really extensive experience with B-cell immune responses in humans that will generate a further generation of immunogens that will be ready to go and significantly better than anything we can design right now. That's the ambition.

How will you be able to begin clinical trials so quickly?

All of these candidates will be tested in non-human primate studies. Some of the early primate studies will be what we call a para-clinical approach—we will test the same immunogens in macaques alongside humans to be able to understand the utility of macaques in predicting useful antibody responses.

We are already comparing the B-cell response to

Continued on page 19

* The BG505 SOSIP is a stabilized trimeric HIV Env protein. John Moore of the Cornell Medical College and Rogier Sanders of the University of Amsterdam did pioneering work in creating BG505 SOSIP and testing it in animal studies as an antibody-producing immunogen.

AIDS 2016: Significant Progress BUT STILL AN UPHILL BATTLE

Faltering prevention efforts and funding questions combine with excitement about cure and vaccine research to paint a complex picture of the AIDS epidemic in its fourth decade.

By Michael Keller

In 2000, when the international AIDS community gathered in Durban, South Africa, no less than Nelson Mandela gave the marching orders. “In the face of the grave threat posed by HIV/AIDS, we have to rise above our differences and combine our efforts to save our people,” he implored the audience. “History will judge us harshly if we fail to do so now, and right now. Let us not equivocate: a tragedy of unprecedented proportions is unfolding in Africa.”

Nearly two decades later, some 15,000 researchers, advocates, and policymakers flooded into the city’s International Conference Center for AIDS 2016. This meeting, the 21st International AIDS Conference, started, appropriately enough, on the Rainbow Nation’s Nelson Mandela Day. If the great man were present in the halls and exhibition spaces to take in the events that swirled about Durban on July 18-22, he would likely have had mixed feelings. Researchers presented sobering findings about the increase in new infections in several countries, the failure to reach marginalized people at the highest risk of contracting HIV, and the virus’s emerging drug resistance. At the same time, vaccine trials are moving forward and work continues toward developing a cure that eliminates the virus or provides long-term remission. During a time when AIDS must com-

pete with terrorism, other emerging diseases, and turbulent politics for the world’s attention, the week of the AIDS 2016 conference brought the complexities and realities of the global epidemic into relief.

From despair to progress

In the intervening 16 years since Durban last played host, huge strides have been made in treating those infected with HIV. At the time of the 2000 conference, a watershed moment that got the international community working in concert to face the epidemic, a meager 690,000 HIV-infected people were receiving antiretroviral therapy (ART). By 2015, those receiving the lifesaving drugs had jumped to 17 million in a herculean feat of scaling that many thought was impossible. Because of that, the number of people dying from AIDS fell from 2.8 million in 1999 to 1.1 million in 2015. Mother-to-child transmission rates are also falling around the world, with many countries close to stopping it, and others like Thailand and Armenia eliminating it entirely. In South Africa alone, efforts over the last five years have reduced mother-to-child transmission by 84 percent. Because of these and other prevention efforts, 2.1 million people acquired HIV in 2015 compared to 5.4 million in 1999.



“Sixteen years ago, Nelson Mandela addressed the International AIDS Conference here in Durban. He called it, ‘A gathering of human beings concerned about turning around one of the greatest threats humankind has faced,’” said UN Secretary-General Ban Ki-moon. “He called for access to treatment equity and human rights. That was a turning point that led to remarkable global progress. For every one person who received lifesaving treatment back then, there are now 17 who have it today.”

The massive scale-up in access to ART is encouraging, but much more remains to be done. There are still nearly 20 million people around the world in need who aren’t receiving ART. And just getting more and more people on treatment may not be enough to end the epidemic.

Many researchers had hoped that increased access to treatment as early as possible after a person discovers they are HIV infected would be an effective means of prevention. The idea behind this strategy is that the drugs would decrease virus levels enough that HIV would not be transmitted as readily, and therefore new infection rates would decline. A previous study had shown that providing ART to the HIV-infected partner in a discordant couple could reduce virus transmission by 96 percent (*Curr. Opin. HIV AIDS* 7, 99, 2012). But this treatment as prevention (TasP) approach suffered a major blow in Durban.

Investigators released findings during the conference from the first phase of a large study called ANRS 12249, which was evaluating TasP in South Africa. In this study, researchers used the “test and treat” strategy of universally testing people for HIV and immediately offering ART to those infected (*PLOS Med.* 2016, doi: 10.1371/journal.pmed.1002107). The work involved almost 13,000 volunteers in a rural part of KwaZulu-Natal province. Randomized communities of participants were broken into two arms—one where all HIV-infected participants were offered immediate access to ART, and a second where only those whose CD4⁺ T-cell counts fell below 350 (the South African standard for ART initiation) received treatment. All participants were given at-home HIV testing and those who were infected were sent according to their study arm to a TasP clinic within a 45-minute walk from their home.

An initial survey by investigators offered hope that infected people would quickly start on treatment. Ninety-three percent of participants said that they would want to start ART as soon as possible if they learned they had HIV. Those who actually sought treatment once they learned their status, though, fell far from expectations. In fact, easy

access to testing and ART did not incentivize the majority to begin treatment. Only 47.5 percent of infected participants sought care within the first six months of learning they had HIV and new infection rates did not go down among this group. The authors said reluctance to start treatment by those who found out they were HIV infected could be the result of at-home testing, which may have identified infection before symptoms occurred. They are also investigating whether stigma could play a role in reluctance to get treatment, since community members know that only those who are HIV-infected go to the clinics.

Prevention efforts failing

So while the number of people accessing ART has increased dramatically, the end goal—made concrete by the Joint United Nations Programme on HIV/AIDS (UNAIDS) objective of ending the epidemic by 2030—hinges on keeping people from getting infected in the first place. And if Mandela were in attendance at AIDS 2016, he would have noted delegate after delegate proclaiming how much work remains to be done to do just that.

“Let me say clearly that I am scared,” said Michel Sidibé, the executive director of UNAIDS. “We are back in Durban in difficult times. The world is facing many competing priorities. Terrorism. Migration. So many issues.”

He continued: “I am seeing for the first time the decline in financing from donor countries—13 out of 14 reduced their contribution to the response... If we continue with this trend, we will not be able to end AIDS by 2030. The risk is that we will have a rebound in this epidemic. We will have resistance. We will lose our investment and we will have to pay more later.”

Indeed, a number of researchers and analysts revealed evidence at conference sessions that substantiated Sidibé’s fears. Perhaps the most troubling came from a new epidemiological study published on July 19 in *The Lancet HIV* that took a second look at how the rate of new HIV infections is calculated. Whereas statistics on the number of people living with HIV and annual deaths caused by the virus are benchmarks for the success of treatment efforts, the rate of new infections is a major indicator used to measure progress in prevention.

In 2005, 4.9 million people became infected with HIV, a number that began decreasing rapidly because of education and behavioral changes. But in the most recent UNAIDS update that came out before June’s UN High-Level Meeting on Ending AIDS, the organization reported that “declines in new HIV infections among adults have slowed

alarmingly in recent years,” with the total number of new infections remaining basically unchanged at around 2.1 million since 2010. Now, according to the new study, the picture is significantly bleaker. More than 1,700 collaborators from 124 countries poured over data from the comprehensive 2015 Global Burden of Diseases, Injuries, and Risk Factors Study (GBD). Researchers improved the estimation process, they said, by updating and including prevalence rates from national surveys and antenatal care clinics, demographic input on fertility and migration, mortality on and off ART, and background HIV-free mortality. They also improved how UNAIDS’s epidemiological programs are integrated into the analysis to improve estimates of HIV incidence for countries not included in UNAIDS’s process. Their work, which they say are “the most comprehensive and internally consistent assessments of the levels and trends of HIV/AIDS incidence, prevalence, and mortality worldwide so far,” concluded that 74 countries actually had an increased rate of new infections over the last decade. Countries as diverse as Egypt, Mexico, Russia, and the Philippines all had an uptick in infections (*Lancet HIV* 3, e361, 2016).

Haidong Wang, a University of Washington demographer and lead author of the study, said the findings point to the size of the challenge to meet the UN goal of eradicating AIDS by 2030. “The obvious conclusion is that much still needs to be done,” he said. In fact, he and his colleagues say their findings cast significant doubt on whether the world can even achieve UNAIDS’s 2020 interim goals, collectively known as the 90-90-90 targets: getting 90 percent of all people living with HIV to know their status, 90 percent of all people with diagnosed HIV infection on ART, and 90 percent of all people receiving ART to have their virus successfully suppressed.

Peter Piot, who is the director of the London School of Hygiene and Tropical Medicine, agreed, saying the stubbornly high rate of new infections was staggering. “It’s still an enormous burden,” Piot, a former head of UNAIDS who was not involved in the study, said. “It’s very hard to imagine that we can reduce new infections to 500,000 in the next few years.”

In a commentary published alongside Wang’s study, Sorbonne University’s Virginie Supervie and Dominique Costagliola say this new way of tracking incidence is far more than an update that opens a new avenue for understanding the epidemic (*Lancet HIV* 3, e337, 2016). According to Supervie and Costagliola, the refined model also points to significant blind spots and incongruities with the offi-

cial UNAIDS data that must be corrected. “The GBD estimates of HIV incidence are significantly lower (two to ten times) than the reported number of newly diagnosed HIV cases for most countries in North America, Europe, Central Asia, and Australia,” they write. “The study reveals that there are still large uncertainties and gaps in knowledge about the HIV incidence in many settings. Without timely and reliable assessment of HIV incidence it will be impossible to end the HIV epidemic.”

Highest risk communities forgotten

As community advocates took the stage on ensuing days, it became clear that one of the largest hurdles to preventing new infections—absent an effective cure or vaccine—is reaching the most vulnerable communities. Speakers repeatedly called for meaningful access to prevention and treatment programs for men who have sex with men (MSM), young women, the transgender community, sex workers, injection drug users, and prisoners. Reaching these people is key to getting the epidemic under control since 90 percent of new infections in Central Asia, Europe, North America, the Middle East, and North Africa in 2014 occurred in these groups.

Ben Plumley, CEO of Pangaea Global AIDS, said he and many others had been greatly disappointed with the outcome of June’s UN High-Level

Resistance peaks its head

The unprecedented public health effort to identify HIV-infected individuals and get them on antiretroviral treatment has kept millions alive. But the spread of drug resistant virus, which occurs when the virus develops mutations that make it less susceptible to certain antiretrovirals, is on the rise globally.

A World Health Organization (WHO) technical report released in July found that HIV drug resistance is now being found in more than a fifth of people just starting antiretroviral therapy (ART) in some low- and middle-income countries. In Cuba, drug resistance was observed in 22 percent of treatment-naïve patients. And perhaps more alarmingly, drug resistance was found in up to 37 percent of patients who have stopped and then restarted treatment in some countries.

WHO modeling has determined that if drug resistance rises to more than 10 percent of treatment-naïve patients in sub-Saharan Africa alone, an additional 420,000 deaths and 300,000 new infections could follow in the ensuing five years. Since those with drug-resistant HIV would continue spreading the virus to others while on first-line treatment and would need to be put on more expensive second- and third-line therapies, the WHO estimates that ART program costs could balloon by nearly US\$3 billion.

“These are early warning signals popping up in countries around the world,” said Silvia Bertagnolio, medical officer with the WHO’s HIV Drug Resistance Team. “We can say that, as of 2013-2014, we’ve started seeing alarming levels of drug resistance.” She says the WHO is now recommending countries perform resistance surveys. “The only real answer to stop the spread of HIV drug resistance is a vaccine,” said Bertagnolio. —M.K.

Meeting. During a pre-conference session, he and others voiced concern that the tone of officials is that the page has been turned on AIDS. “All the governments at the [UN High-Level] meeting said the fight against HIV is over—all that is left is the AIDS benefit concert,” Plumley said. “Yes, we have had some progress in treatment since 2001, but we’ve failed fundamentally in prevention. Yet again, our governments couldn’t bring themselves to speak of the communities that will turn this epidemic around.”

Perhaps the most invisible of the key populations that need access to prevention and treatment are the world’s 10.2 million men, women and children being detained as prisoners. According to a special edition of *The Lancet* released in time for AIDS 2016, this population is at especially high risk of HIV. Modeling showed that 3.8 percent of the population have HIV, compared with a global prevalence rate of 0.8 percent in 2015 (*Lancet* 2016, doi:10.1016/S0140-6736(16)30466-4). One reason for this is the drug laws that criminalize intravenous substance abuse, forcing many already HIV-infected individuals to concentrate in prisons.

Also at particularly high risk are girls and young women aged 15 to 24. UNAIDS’s official statistics show that in sub-Saharan Africa, this group now accounts for 25 percent of new HIV infections among adults, and women of all ages make up 56 percent of new infections among adults. The organization says this unequal burden is the result of harmful gender norms, insufficient access to education and sexual and reproductive health services, poverty, food insecurity, and violence. “Fifty-six percent of people with HIV are women. Funders must put their money where the problem is,” said activist Yvette Raphael. “Women are at the center of this and I can say we are nowhere near the end of HIV/AIDS. We are still dealing with some of the same issues we were dealing with 15 years ago when I was diagnosed.”

The plight of girls and women resurfaced throughout AIDS 2016, with experts from different specialties saying that as women go, so too goes the effort to eradicate the disease. “We must think gender,” said Elizabeth Bukusi, co-director of the Kenya Medical Research Institute-University of California, San Francisco Training Program. “Gender matters for prevention. Gender matters for treatment. The goals we’ve set for 2020 are off-track. A reason for that is our inattention to gender.”

Realizing the need, many projects are taking a more aggressive approach to controlling HIV in these at-risk populations. Some start organically, like a Kenyan advocacy group securing ART for its community that began as a group where ostracized

women with AIDS took care of others as they died. Vancouver, meanwhile, is now one of dozens of cities around the world offering injection drug users supervised injection sites, safe fix rooms that give them access to clean needles and healthcare services. San Francisco and other US cities are now considering launching their own. Meanwhile, Thailand has launched an online program that offers supervised HIV self-testing, counseling, and registration at treatment clinics. The program hopes to reach more MSM and transgender women where they already network in the digital space.

Improving prevention

Leaders in the research and advocacy communities agreed that at-risk people, especially those comprising the now globally recognized key populations, need access to every prevention tool currently available: clean needles for injection drug users, condoms, pre-exposure prophylaxis (PrEP), and voluntary adult male circumcision. But having the tools, getting them into the hands of those who need them most, and then seeing they are used effectively and consistently are three very different things.

Nduku Kilonzo, the director of Kenya’s National AIDS Control Council, lamented how her country has not yet effectively gotten the message out about using protection during sex. “We invest a lot in the new kid on the block and remove money from older things we know work well like condoms,” she said. “In Kenya, every single young person knows where to go to get more airtime for their mobile phones. What have we done wrong that they don’t know where to get a condom?”

New evidence also reinforced that social changes can themselves act as protective measures. One recent study looked at whether increasing schooling in Botswana had any effect on new infection rates (*Lancet Glob. Health* 3, e470, 2015). Researchers found that each additional year of schooling reduced the risk of infection by 8.1 percent in study participants. Women benefitted more than men, seeing a risk in reduction from the country’s baseline prevalence by almost 12 percent.

Researchers also discussed a new way to use PrEP, which they say increases the options for those who might not want to take a pill every day. Early studies showed that administering the antiretroviral Truvada (a combination of tenofovir disoproxil fumarate and emtricitabine) one, three, or seven days before and two hours after rectal exposure to a simian immunodeficiency virus (SIV)/HIV hybrid (SHIV) protected rhesus macaques as well as a daily dose (*Sci. Transl. Med.* 2(14), 14ra4,

2010). Another study found that pigtail macaques given a Truvada dose a day before and two hours after vaginal virus exposure were all protected from infection, whereas all controls were infected (*PLoS ONE* 7(12), e50632, 2012).

Then last year, the ISHEGAY study involving 400 MSM showed that when participants took Truvada before and after sex, there was an 86 percent relative reduction in the incidence of HIV acquisition (*N. Engl. J. Med.* 373, 2237, 2015). Specifically, volunteers were told to take two pills two to 24 hours before sex, another pill a day after taking the first two, and a fourth pill a day after that. Jean-Michel Molina at the University of Paris Diderot, who led the ISHEGAY research team, said the availability of on-demand PrEP isn't for everyone since it requires premeditation and planning in advance of sexual encounters. Robert Grant, an investigator at the University of California, San Francisco School of Medicine, said that while sexual event-driven dosing is complicated, it might find a receptive audience among those who have "seasons of risk," where higher-risk behavior happens infrequently. "There are some who do very well with on-demand, particularly older gay men," Grant said. "If you're having risky sex once a month or less, there's really no call to take a pill every day."

Hope in the vaccine research community

Even if all existing HIV prevention options are implemented well, at least a dozen speakers at AIDS 2016 said an effective vaccine would be humanity's best chance to end AIDS. "The only way we'll eliminate HIV in the next 100 years is with a vaccine. There's no other way," said Paul Stoffels, the executive vice president and chief scientific officer of Johnson & Johnson.

The energy propelling the scientific search for a vaccine has ebbed and flowed over more than three decades of cyclic excitement followed by dashed hopes. One period of heightened enthusiasm was driven by the unexpected efficacy seen in 2003's now well-known RV144 trial of a prime-boost genetically engineered viral vector and protein, which lowered the rate of infection by a modest 31 percent in participants over the three-and-a-half year study. These results offered the first evidence of vaccine-induced protection against HIV.

Now, interim results announced in Durban from HVTN 100, a small ongoing study of 252 people in South Africa that was designed to test a modified RV144 vaccine regimen in a high-risk population, has green lighted the next step. Later this year, researchers will start enrolling partici-

pants in South Africa in the HVTN 702 study, a Phase III randomized controlled trial of 5,400 adults aimed at preparing the experimental vaccine for licensing in South Africa (see *In Brief*, page 18). "All the criteria were met unequivocally and, in many instances, the HVTN 100 outcomes exceeded both our own criteria and the immune responses seen in RV144," said Linda-Gail Bekker, chair of the HVTN 100 protocol and deputy director of the Desmond Tutu HIV Center. Results of HVTN 702 are expected in 2020.

Another area of vaccine research generating buzz is the recently started large-scale trial involving passive administration of broadly neutralizing antibodies to uninfected individuals in the hope of preventing HIV infection. Antibody-mediated prevention (AMP) turns the idea of vaccination on its head—instead of the normal method of presenting the body with an immunogen so that it starts making antibodies, it arms participants with the antibody itself. The research community has shown that introducing antibodies into nonhuman primates can confer protection against the monkey equivalent of HIV, but there has not yet been enough human data to support the idea that it also works in people. One such broadly neutralizing antibody, VRC01, prevented infection in animal models, and was found to be safe and well tolerated during three Phase I trials with 140 human participants. This antibody is now being tested in Phase IIb clinical trials. During the project, called the AMP Study, 2,700 MSM and transgender participants in the Americas (HVTN 704/HPTN 085) and 1,500 heterosexual women in sub-Saharan Africa (HVTN 703/HPTN 081) will receive the VRC01 antibody. As of the conference's start, 19 of 24 sites in the Americas had been activated and 249 participants were enrolled. In Africa, five of 15 sites had been activated and 29 women were enrolled. During the double-blinded, randomized study, patients will receive either a low- or high-dose of the antibody or a placebo. In the studies, participants will receive a total of 10 antibody infusions, one every eight weeks, with a follow-up 20 weeks after the last infusion. Final results are not expected until 2022.

Another approach undergoing clinical testing involves a different viral vector/protein prime-boost combination than that being studied in HVTN 702. One study published last year showed that using an adenovirus serotype 26 (Ad26) vector prime loaded with clade B HIV Gag, Pol, and Env viral protein sequences followed by a purified HIV clade B HIV Env gp140 boost, protected half of inoculated rhesus monkeys against multiple rectal SIV challenges

(*Science* 349 (6245), 320, 2015). An ongoing Phase I/IIa trial called APPROACH is assessing this regimen's safety, tolerability, and immunogenicity with the addition of a modified vaccinia Ankara (MVA) poxvirus vector carrying HIV Env, Gag, and Pol proteins (see *The Confidence Booster, IAVI Report*, Vol. 20, Issue 2, 2016).

At the conference, Hanneke Schuitemaker, the head of viral vaccine discovery and translational medicine at Janssen Pharmaceuticals, said all 400 participants in the APPROACH study were recently given their third vaccination at the trial's six-month mark. A fourth booster injection that includes combinations of Ad26, MVA, and gp140 will be given at the 48-week mark, with a 12-month follow-up. She said another Phase I/IIa study, called TRAVERSE, enrolled its first volunteer in July. This trial will test a candidate that does not include MVA, and adds a clade C Env insert into the Ad26 prime and boost. A third trial, called ASCENT, is expected to begin in the fourth quarter of 2016 and will test a clade B mosaic gp140 insert in the boost. Mosaic HIV immunogens are computationally derived proteins designed to maximize coverage of the many circulating strains of HIV. The collaboration running these trials hopes to find, among all the different combinations, a regimen that elicits a balanced immune response against HIV variants in clades A, B, and C.

Yet one more strategy is using replicating vectors to induce sustained immune response against HIV. Nicole Frahm of the Fred Hutchinson Cancer Research Center said a few different designs centered on replicating vesicular stomatitis virus (VSV) vectors, including one created at IAVI, are in, or will soon be moving into, clinical trials after showing efficacy in animal studies.

Even with all of this, many speakers modulated their enthusiasm about the current state of vaccine research in acknowledgement of the long road still ahead and the formidable challenge presented by the rapidly mutating and diverse virus. "If our efforts in developing an HIV vaccine are successful, this feat will represent the most creative, elegant, and complex approach toward vaccine development in scientific history," said Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases.

And getting there will require serious funding, a state of affairs that is not a given.

Funding the tools

Advocates and authorities sounded an alarm that decades of advances against the disease could be reversed without countering mounting indifference among donors, governments, and the public. A

major report released by the Kaiser Family Foundation and UNAIDS just ahead of Durban found that donor government funding for HIV programs in low- and middle-income countries fell by more than a billion dollars in 2015, the first decline in five years. The analysis found that funding from 13 of 14 donor governments fell or remained the same last year. The US continued to provide the vast majority of funding for the global AIDS fight, contributing \$5 billion last year, or 66.4 percent of the global total.

Meanwhile, the investment in global HIV prevention research has also been declining from a 2012 high of \$1.31 billion to \$1.18 billion in 2015. "We've heard a lot of talk about the end of HIV during this conference," said Thomas Fagan, a health financing and policy analyst at Palladium. "I think we need to temper that a little and find the donors and find the funding to move us forward."

During a time of tightening purse strings, many low- and middle-income countries will need to find more money domestically to maintain funding levels for AIDS programs. But a major obstacle to increasing a country's domestic contribution to health programs or any other services, especially in Africa, is the rampant corruption that sees billions of dollars diverted every year. "We have the money. Our people are suffering not because we are poor, but because we are mismanaging our resources," said Ruth Labode, a member of Zimbabwe's parliament. "We have corruption. Zimbabwe is not poor. Kenya is not poor. But the national budget in Zimbabwe is \$5 billion and \$15 billion walked out of the country."

The international and domestic funding situation is just one obstacle to contend with. The messages coming out of Durban were clear: to achieve the UN target of eradicating AIDS by 2030, access to treatment must expand, prevention efforts must improve, key populations must be reached, and new infection rates must come down. "We are not going to end AIDS with the tools we have," said David Wilson, the World Bank's global AIDS program director. "What an extraordinary success we've already had in treating the infected. But it's also increasingly clear that in the real world tablets are not going to stop this epidemic. We have to reinvigorate R&D. We've never stopped a disease without a vaccine or a cure." ■

Michael Keller reports from the frontiers of science, technology, and international affairs. His writing has appeared online and in newspapers, magazines, and books, including the graphic novel Charles Darwin's On the Origin of Species.

A CAREER *Defined by AIDS*

The Ugandan physician and global health champion
Alex Coutinho talks about his career in HIV/AIDS
and his belief in the importance of a vaccine.

By Kristen Jill Kresge

Alex Coutinho speaks with authority and conviction. His authority comes from more than three decades of working as a physician in Uganda battling HIV, malaria, and tuberculosis (TB); implementing programs to improve maternal health; and most recently, applying the lessons learned from battling HIV in East Africa to scale up services for treating non-communicable diseases and neonatology, among other areas. His conviction to end AIDS comes from the personal experience of losing friends and family members to this horrid disease.

Like many others, Coutinho's early career was defined by a virus. He graduated as a doctor in 1983 just as HIV and its deadly consequences were coming to light in Uganda. He served as the executive director of The AIDS Support Organization (TASO), a non-governmental organization established in 1987 and based in Kampala, Uganda, which provides HIV prevention, care, and support services throughout the country. During Coutinho's tenure as executive director, TASO's budget grew from US\$3 million to \$22 million annually. TASO currently provides antiretroviral (ARV) treatment for more than 50,000 HIV-infected individuals across its 11 service centers throughout Uganda.

After TASO, Coutinho was executive director of the Infectious Diseases Institute (IDI) in Kam-

pala, where he oversaw an extensive research portfolio and the Institute's programs to provide training in HIV, malaria, and TB. Coutinho was also a founding board member of The Global Fund to Fight AIDS, Tuberculosis, and Malaria, and joined IAVI's board in 2008, becoming its chair in 2013, a post he recently vacated.

In 2013, Coutinho was awarded the Hideyo Noguchi Africa Prize from the Japanese government for his "pioneering efforts to expand access to life-sparing medicine for people infected with HIV." He won the ¥100 million prize in the medical services category, alongside Peter Piot, winner of the medical research award, who now serves as the director of the London School of Hygiene and Tropical Medicine.

Now, at age 57, after trying out retirement for a short time, Coutinho is working with Partners in Health in Rwanda to scale up services in oncology

and non-communicable diseases at the organization's sister organization, Inshuti Mu Buzima.

Through all of this Coutinho remains passionate about the need for an HIV vaccine and committed to living and working in Africa. His deep voice and his hearty laugh resonate over phone lines and through conference halls. He is direct but immediately likable. His knowledge, experience, and compassion come through effortlessly. He commands a



Alex Coutinho

global stage, speaking recently at AIDS 2016 in Durban, South Africa, but his concerns remain local. “I chose to be based where the problem is,” he says.

On the occasion of his recent departure from IAVI’s board, Managing Editor Kristen Jill Kresge spoke with Coutinho about his decades-long career battling HIV.

What was it like when you first started working as a young doctor in Uganda and people were first realizing what HIV was and its dire implications? How did this time help shape your career?

It was back in 1982 when I saw my first case of HIV—even though I didn’t know what I was seeing—in Uganda, in the cancer wards. Then in the next couple of years after that we started seeing a lot of people dying in the wards, and even some of my own friends getting this strange disease. It wasn’t until 1984 that we realized that this was HIV.

In Uganda, I was there right from the very beginning. I graduated as a doctor in 1983, and for 33 years HIV defined who I was as a doctor. But, also, HIV was killing my friends, it was killing my own relatives, and I was feeling pretty helpless. In 1986, I started going around the country trying to educate the population, educate young people, about what HIV was. At the time there wasn’t any effective treatment or any effective prevention, so it was a bit frustrating.

We were talking about the vaccine in 1986 as being 10 years away. Of course, 30 years later we don’t have a vaccine, and they’re still saying it’s 10 years away. So it is really frustrating for me as a doctor. We had antiretroviral therapy in Africa in 2001 and it made a big difference. But even then I knew this was not the total solution. The total solution needed to include both treatment and HIV prevention tools.

So when I was approached to go to Lake Como, Italy, to a meeting IAVI was holding in Bellagio in 1994 to sort of regroup after more than 10 years of knowing HIV was the cause of AIDS, I was one of the external people to give my perspective about what IAVI was trying to do to drive the urgency for a vaccine.

Then, when the opportunity came for me to join the IAVI board, I was ready and I wanted to contribute. I believed then, as I still do now, the importance of getting a vaccine, because regardless of what other technologies exist, we know that without a vaccine this is not going to work.

It was during your time at TASO that there was really a sea-change in the way people viewed the viability

of ARV treatment in Africa. This of course came after the 2000 AIDS conference that was held in Durban, South Africa. What was it like during that time?

Well, there was a lot of optimism. We never really believed that we would be able to get treatment at those kind of prices, and in a way, the change was very sudden. One year the likelihood of getting treatment was not there, and then within a couple of years, The Global Fund, etc. were created, and suddenly the question wasn’t whether we would get treatment, because there was money for treatment. The limiting factor was not about money. It was getting capacity.

We were under a lot of pressure because people were dying every day. People whose immunity had declined, and at that time we didn’t have viral loads, but we could measure their CD4 counts. We saw CD4 counts of four or 10, and we knew these people were going to die if the anti-retrovirals were not in the stores.

So there was a lot of exhilaration as antiretroviral therapy kicked in, but there was also a lot of anxiety in trying to save as many as we could, and that wasn’t happening because of systemic challenges in getting things moving.

This past July, after 16 years, the International AIDS Conference returned to Durban. Things are vastly improved since the last Durban conference in 2000 but still less than half the HIV-infected people in the world who are in need are getting treatment. How do you view the current situation?

I think Durban in 2000 was a landmark because it was really at that conference that the possibility of treatment in Africa was the greatest, and where Africans were saying and demanding that this is not acceptable. Sixteen years ago there were maybe 800,000 people on treatment, most of them outside Africa. Today, there are 17 million people on treatment, most of them in Africa. That alone tells you how far we’ve come, so the glass is half full. But the glass is also half empty. There is another 20 million people and counting who need to get on treatment. So this should be celebrated, but we also have to recognize the soberness of how half the world has treatment and the other half doesn’t.

You were a plenary speaker in Durban this year. What was it that you emphasized in your talk?

I was part of a plenary that looked at what health systems are needed to achieve universal access. Starting from today, what do we need to get so we can get people on treatment, and what can we do to make sure that the 17 million on

treatment stay on treatment and how do we make sure that they don't fail treatment, don't develop resistance, and don't need secondary treatment.

The longer HIV-infected people are on treatment, there is also a greater likelihood that they will develop non-communicable diseases, such as heart disease and cancer. What is your perspective on how important that issue will become in Africa and how already strained healthcare systems will manage this additional burden?

Well, technically, it's a good problem to have. I call it a good problem because the only reason it's become a problem is because people are now living longer. Previously, we didn't see this connection between HIV and non-communicable diseases because people died—there was premature death. But now as people stay on ARVs for five, 10, 15 years, people grow older, and non-communicable disease and oncology/cancer start rearing their heads.

And yes, it generates significant challenges in terms of managing one chronic disease and then adding another chronic disease. But it's really a reflection of the success of getting people on treatment and keeping them alive. I think the opportunity is to develop a system that can be used for chronic diseases, whether they be oncology, non-communicable diseases, genetic diseases, or HIV. It's really getting a chronic care platform that builds in the complexity of life-long management of disease.

Or in the case of HIV, lifelong management among people who are healthy. You're really telling them, based on the lab tests, you are unwell and you need to take medication for the rest of your life because your lab tests say you're HIV positive. That's very different from someone who is sick or has been dying and they understand that, 'Wow, I was nearly dying, and now I need this medication.' That's a major challenge we are faced with.

Going back to vaccine research, have you seen the interest in or the momentum toward a vaccine change over the years?

I think there's a tight audience that understands the imperative for HIV prevention generally, and the fact that a vaccine is essentially the pinnacle of what we're looking for. But I think there's also a fair percentage of people that say, look, it's unlikely that you're getting a vaccine in the next 20 years, and in the interim, we have treatment that's prevention. There are all these other prevention approaches and many of them involve antiretroviral therapy, such as preventing mother-to-child

transmission and PrEP [pre-exposure prophylaxis]. So in some groups I feel there is almost a sense of giving up on the vaccine and feeling that the other alternatives are just as good, which I don't agree with. I think they are complementary.

So what are you doing these days?

Well, I have retired. But after a year I discovered that golf and traveling are not sufficient substitutes for an active mind in global health. So I went back to work, and I'm the Country Director for Partners in Health in Rwanda. My work is essentially about large scale, scale up for conditions other than HIV. It's essentially taking the lessons from HIV and using them to scale up access to oncology services, neonatology, and the treatment of non-communicable diseases. So I guess that's what I'm up to.

So is this the first time in three decades or more of your career that you've not been working directly on HIV in any way?

When I was working on HIV at IDI, we also did maternal and child health. I was leading the project in one of the districts where we were scaling up maternal and child health programs and were able to reduce maternal mortality. And of course, in working with HIV, we were also strengthening health systems across Uganda. So it's not the first time, but it is the first time to use these approaches to scale up services in oncology, neonatology, non-communicable diseases, and mental health.

Was it important to you to stay in Africa throughout your career and make a difference there?

Well, global health can be practiced anywhere in the world. All the players, whether they be in New York or Geneva or London are important. In my case, I chose to be based where the problem is. I chose to be based in Africa where many of these issues, like HIV and so on, are having the greatest impact. So my primary ambition was that when I attended global health forums and global meetings, my contributions were validated by the front-line experience that I had. Some of the discussions I would listen to were very theoretical, and I was then able to intervene and sort of say, listen, yes, this sounds okay on paper, but the truth be told, it's not as straightforward as this. And so my experience was that working from Africa gave me much more credibility—made me much more of a credible spokesperson for Africa than if I had been based with UNAIDS [The Joint United Nations Programme on HIV/AIDS] in Geneva or at any other place. ■

In BRIEF

HVTN 702 Efficacy Trial Ready to Launch in South Africa

Seven years ago, a large-scale HIV vaccine trial in Thailand known as RV144 surprised scientists and funders alike when it provided the first and thus far only example of vaccine-induced protection against HIV. Now, a long-awaited follow-up study that is trying to improve upon RV144's modest 31.2 percent efficacy result is preparing to launch in November. This new Phase IIb/III efficacy trial, led by the HIV Vaccine Trials Network (HVTN), is known as HVTN 702 and will enroll 5,400 HIV-uninfected men and women at risk for HIV in South Africa, which remains the country with the greatest HIV/AIDS burden in the world.

"We're obviously looking to this trial with a great deal of interest," says Anthony Fauci, director of the US National Institute of Allergy and Infectious Diseases (NIAID), which is funding the US\$130 million study along with the Bill & Melinda Gates Foundation. "You know HIV is not an easy vaccine to make for the simple reason that the body does not naturally make a good immune response. So the fact that we did get that first positive signal with RV144, even though it was modest, the idea of being able to improve that and sustain it is exciting. Hopefully we will get enough data over a reasonable period to determine whether we have something or not."

There are some notable differences between the HVTN 702 vaccine regimen and that tested in RV144 that investigators hope will improve the efficacy of the prime-boost candidates and also increase the durability of the immune responses they induce. Like RV144, HVTN 702 will test a canarypox vector-based candidate prime, ALVAC-HIV (vCP2438), made by Sanofi Pasteur. This time, however, the ALVAC candidate contains clade C HIV genetic inserts to match the predominantly circulating clade in South Africa. The boost in HVTN 702 is a genetically engineered HIV gp120 protein also derived from subtype C (manufactured by GlaxoSmithKline) that is co-formulated with the adjuvant M59, whereas in RV144 alum was used as the adjuvant.

The dosing schedule for HVTN 702 also differs. In HVTN 702, the vaccine candidates will be administered sequentially in a series of five injections over 12 months. The dosing schedule for RV144 consisted of four injections over six months. A fifth dose at 12 months was added to HVTN 702 in hopes of extending the early protective effect observed in the RV144 trial, which was as high as 60 percent after the first year, but waned over time.

Glenda Gray, president and CEO of the South African Medical Research Council and principal investigator of HVTN 702, said there is a huge sense of relief that this trial is finally coming to fruition and also excitement about its potential. "We have new products—a new protein and a new adjuvant—so although the approach is the same, pox-protein prime boost, there are distinct differences," says

Gray. "Scientifically, we hope that we can improve on RV144 and that our choice of proteins and adjuvant address this. Logistically, there are new sites, new investigators, places that have never done trials before, so it will be a big learning experience for all of us."

Delayed start

HVTN 702 was a long time in coming. It is the first large-scale efficacy trial of any HIV vaccine candidate to begin since the RV144 results came in. Larry Corey, principal investigator of the HVTN, says he is happy to see the efficacy trial finally move forward after five and a half years. "People have worked very hard to get us this far," he says.

The trial is part of the Pox-Protein Public Private Partnership or P5, which formed in 2010 to test variants of the RV144 regimen in future trials as well as to learn more about the immune responses induced in the RV144 trial. The P5 consists of representatives from NIAID; the Gates Foundation; the South African Medical Research Council; the HVTN; the drug companies, Sanofi-Pasteur and GlaxoSmithKline; and the Military HIV Research Program (MHRP), a key collaborator in the RV144 trial.

Multiple factors are responsible for delaying 702's start, some logistical and others scientific. On the logistics, VaxGen, which manufactured the gp120 protein used in the RV144 trial, no longer exists, so a new commercial partner had to be found to manufacture the modified protein candidate for 702. Preliminary studies of this candidate also had to be conducted.

On the scientific side, researchers worked diligently in the seven years since the RV144 results were first reported to try to understand what immunological mechanism might be responsible for the modest 31.2 percent efficacy afforded by the RV144 vaccine regimen. This included analyzing the RV144 samples as well as conducting a myriad of follow-up studies in animals and humans.

In 2011, scientists identified two so-called "correlates of risk" associated with the experimental vaccine regimen: immunoglobulin (Ig)G antibodies that bound to the V1/V2 loops of HIV Env were correlated with a 43 percent reduction in HIV infection rate, and plasma IgA antibodies that bound to HIV Env were correlated with a 54 percent increase in HIV infection rate among vaccinated volunteers (see *A Bangkok Surprise*, *IAVI Report*, Sep.-Oct. 2011). The following year, researchers found two genetic signatures in a specific region of HIV's surface protein that closely correlated with vaccine efficacy (see *A Slew of Science in Seattle*, *IAVI Report*, Mar.-Apr. 2012).

Researchers also conducted a small safety and immunogenicity trial in South Africa known as HVTN 100 that served as a litmus test for whether another efficacy trial was warranted. As a secondary objective, the South African trial of 252 HIV-uninfected men

and women needed to meet certain immunogenicity parameters in order for the vaccine candidate to “graduate” to HVTN 702.

Last May, an interim analysis found that the vaccine regimen tested in HVTN 100 induced a comparable if not better immune response profile (using the same assays run in the same labs) than what was observed in vaccine recipients in RV144. “The HVTN 100 study clearly showed that V2 responses seen in RV144 are even more robustly elicited in South Africans with the new ALVAC and gp120 vaccine products developed for the region,” says Nelson Michael, director of MHRP. He added that the HVTN 702 trial in South Africa is the next logical step.

Corey shares some of this optimism. “The results from HVTN 100 are quite gratifying, with some areas of immunogenicity better than what we saw in RV144. That’s good.” However, Corey notes that it remains to be seen how well the candidate protects against

clade C viruses in South Africa. “Why the clade C virus is so rampant, why the prevalence rates are so high has never been fully explained,” says Corey. “Whether that will be played out in this vaccine trial we don’t know yet, but we are excited to do the experiment.”

Mitchell Warren, executive director of AVAC, the HIV prevention advocacy group based in New York City, agreed that the field needs to settle the question about whether this vaccine regimen can provide high enough efficacy to be licensed, but says the AIDS vaccine field should keep its options open. “You don’t leave a positive result on the table,” says Warren. “That said, a 50 percent efficacious vaccine that requires five doses over a year is not the ultimate vaccine that we want, and there is no disagreement that even as 702 goes forward we have to accelerate other vaccine candidates.” —*Mary Rushton*

Mary Rushton is a freelance writer based in Cambridge, MA.

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immunization across rhesus macaques and cynomolgus macaques to see which of those two models best fits our purpose. We also have a collaboration with Kymab, which has a mouse model that expresses the human immunoglobulin repertoire. We’ll look at that as well with the same immunogens. We will then have a really clear picture of how predictive these models are, where they are useful in terms of prediction, and where they may be misleading. A second aim or second challenge is to reduce the risk of late-stage failure by improving the predictive utility of what is taken into larger clinical trials. That’s our intention.

What other paths are you pursuing?

We have a parallel track looking at novel T-cell immunogens. There we have two main groups driving two different concepts. The first one is from Tomas Hanke and Andrew McMichael at Oxford, who have been working on developing what they call a conserved mosaic immunogen design. These immunogens are based on computational algorithms, again developed by Bette Korber, that select all the conserved parts of the virus. These immunogens have been put into a range of nucleic acid and viral vectors to move into clinical trials, and earlier versions have already shown a greater breadth of T-cell recognition, which looks quite promising. We are partnering with IAVI, which is funding some of the manufacturing costs, and we’re hoping that additional partners may come in to support that part of the project.

The other group is led by Christian Brander from Barcelona, and his approach is similar but different. He’s selected conserved epitopes that have shown beneficial control in HIV-infected individuals. Our expectation is that they will do the same in healthy volunteers and infected subjects that have not mounted similar responses.

We’re going to compare those two approaches side by side in clinical trials to see what strengths or weaknesses they have. In the past, the field’s really just focused on magnitude of T-cell response and hasn’t really grappled with the issue that greater breadth may be much more important in constraining viral replication.

Outside of the very promising data that Louis Picker has with his rhesus CMV [cytomegalovirus] approach, we think these two are probably the best two T-cell strategies that can be taken into

humans within the timeframe that we have.

It’s refreshing to hear about some European initiatives. How would you describe the status of HIV vaccine research in Europe overall?

I would say there’s a lot of talent but a lot less funding. That means we have to be smarter about what we do. We think quite carefully before we move into an area, and I think that the less money you have, often the more creative you have to be in order to make an impact. Obviously, one doesn’t want to talk oneself out of funding. It’s good to have. It certainly is daunting in terms of trying to be competitive against some of these very large networks in the US.

But to kind of offset that, rather than trying to compete, where possible we’re trying to collaborate and be partners. If we collaborate, we can really add to the field, and I think that’s the way to be most successful. In Europe, I think people are definitely likely to take risks and I think there’s perhaps more diversity in approach at the very early level. But because there’s less funding, many of these concepts don’t get very far, even though they may have some merit. Still, nothing’s done in isolation. A lot of the investigators in Europe are also funded by international organizations and involved in other international consortia.

How are you managing the ambitious plans for EAVI2020?

We’ve got really a very well mapped-out plan, and because of the ambitious scope our milestones and our planning is really very tight. We’re monitoring on a weekly basis where we are in the program and constantly reviewing the timelines to make sure that everything is in place. When you talk about trying to move products into humans, everything that could go wrong usually does go wrong and timelines always slip. We’re having to make decisions now about things that will be tested in humans in three or four years’ time. If any of those decisions are delayed it will start to push the trials off past the end of the program, so we can’t afford any slack. ■

Michael Dumiak reports on global science, technology, and public health and is based in Berlin.

Upcoming HIV-Related Meetings



OCTOBER 2016

HIV/AIDS Research: Its History & Future

October 13-16; Cold Spring Harbor, New York, USA

More information: meetings.cshl.edu/meetings.aspx?meet=BIOHIST&year=16

5th Latin American Meeting on Hepatitis & HIV

October 14-15; Rio de Janeiro, Brazil

More information: www.virology-education.com/event/upcoming/latam2016

HIVR4P: HIV Research for Prevention

October 17-20; Chicago, Illinois, USA

More information: www.hivr4p.org

HIV Glasgow 2016

October 23-26; Glasgow, United Kingdom

More information: hivglasgow.org

DECEMBER 2016

National HIV PrEP Summit

December 3-4; San Francisco, California, USA

More information: hivprepsummit.org

MARCH 2017

Keystone Symposia: HIV Vaccines

March 26-30; Steamboat Springs, Colorado, USA

More information: www.keystonesymposia.org/index.cfm?e=web.Meeting.Program&meetingid=1440

For a full list of meetings and their descriptions, go to www.iavireport.org/meetings.