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Antibodies:



Treatment, prevention, and cure?

EDITOR'S LETTER

As the mother of a four-year old, I have plenty of occasions to talk about germs and viruses. Let's be honest, I enjoy it. Add to that the number of times my daughter hears me talking about my work and it isn't too difficult to understand why she's been using the word antibody since she was two.

We've reported extensively on antibodies over the past few years as they have come to revolutionize efforts to prevent or treat HIV infection. And progress on this front continues. In this issue we report on the major findings presented at the HIV Research for Prevention (HIVR4P) conference held in October (see page 8). At this meeting, as in many of recent memory, antibodies were a prominent theme. From the trials testing the ability of directly administered broadly neutralizing antibodies to prevent HIV infection to the latest efforts to engineer a series of vaccine immunogens that could induce these powerful proteins, antibodies are fueling scientific developments in many areas. Now the search for a functional cure can be added to the list. Just prior to the opening of HIVR4P, researchers from Emory University and the US National Institute of Allergy and Infectious Diseases, including esteemed head Anthony Fauci, reported that a small group of monkeys were put in sustained remission for a period of almost two years following receipt of an antibody and standard antiretroviral therapy. This result, though not yet fully understood, raises hopes that a similar response might be seen in humans with an already licensed antibody. Trials are now underway.

Progress in preventing the spread of HIV or in alleviating the burden of daily HIV therapy can't come soon enough. Emilio Emini, director of the HIV program at the Bill & Melinda Gates Foundation, warns that the AIDS response is at a particular crucial juncture—particularly in sub-Saharan Africa where there is a large population of young people about to enter the age range when their susceptibility to contracting HIV is the highest. Emini and I spoke recently about this situation and how it provides the lens through which the Gates Foundation, the world's largest charitable foundation, views all of its funding decisions (see page 4).

It is within these vulnerable populations that the Centre for the AIDS Programme of Research in South Africa (CAPRISA) is striving to halt the epidemic through a variety of options. In this issue we also profile their impressive commitment to turning the tide against HIV and tuberculosis (see page 12).

Taken together, the articles in this issue showcase the steadfast commitment of some of the field's leading funders, scientists, and community research centers to seeing an eventual end of AIDS. We hope it fills you with hope and a renewed sense of optimism too. Happy holidays and best wishes for the new year.

– 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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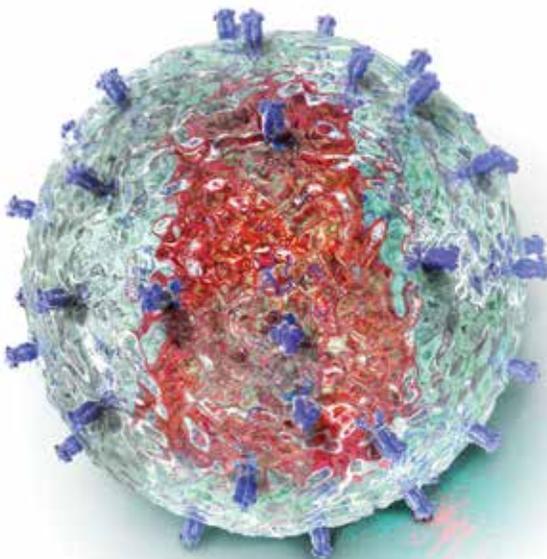
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Act Now or Risk *HIV Rebounding*

Long-time pharmaceutical company veteran Emilio Emini took over the reins of the HIV program at the Bill & Melinda Gates Foundation over a year ago. Here, he describes the Foundation's efforts to combat HIV and why this task is more important than ever.

By Kristen Jill Kresge

Bill and Melinda Gates call themselves “impatient optimists.” Backed by a big purse and led by a group of talented and driven individuals, the Bill & Melinda Gates Foundation (BMGF) is striving to make the complex happen. And quickly.

When it comes to HIV, their goal is “to accelerate the decline in HIV infection worldwide and save lives by ensuring expanded and simplified HIV treatment and improved and effective use of interventions to prevent new infections.” It sounds simple, but as with almost everything to do with this virus, it never is.

There is no question that BMGF is a huge player in global health. They are the world's wealthiest charitable foundation and have already invested billions of dollars in grants focused on improving the health and wellbeing of the world's poorest. To date, US\$3 billion has been invested in HIV alone, with another more than \$1.6 billion going to The Global Fund to Fight AIDS, Tuberculosis and Malaria, which supports the expansion of programs offering life-saving antiretroviral (ARV) treatment to the millions of HIV-infected individuals worldwide.

Within BMGF there is a team of influential individuals making their grant decisions and determining how they can work with or through others, whether it be product development partnerships or companies, to drive change. Since last July, the HIV program has been led by Emilio Emini, a seasoned pharmaceutical industry leader with decades of experience in both HIV research

generally, and vaccine development in particular. During his career at Merck, Wyeth, and then Pfizer, Emini amassed experience in developing and licensing both drugs and complex vaccines. While at Merck, he led the research team that developed one of the first ARVs against HIV. He also led the company's vaccine development effort, helping usher HIV vaccine candidates into clinical trials and working on the development and licensure of their vaccines against rotavirus and human papilloma virus. His work in vaccines continued at Wyeth and Pfizer, where he led the effort that resulted in the licensure of the pneumococcal vaccine, Prevnar 13. In between his decades-long experience in the pharmaceutical industry, Emini also served as senior vice president of vaccine development at the International AIDS Vaccine Initiative (IAVI).

In all these roles, Emini brought his vast experience, agile mind, and calm nature to bear on a daunting scientific challenge. In his current position, he remains as determined and practical as ever. When we spoke recently, he emphasized how important it is that efforts to stem the rate of new HIV infections in the hardest-hit places and populations continue to accelerate. “This is not the time to back off,” he says. “I believe we are on the edge of losing control of the epidemic. This is the premise upon which we look at everything that we're trying to do.” Accelerating a continuing decline in new infections requires sustained funding, improved access to existing treatment



Emilio Emini

and prevention options, and more research into newer and better options to both treat HIV infection and prevent the virus's spread. And although the goal is ensuring that happens as quickly as possible, Emini understands the heftiness of the task. "The effort that's going to be required is going to be even harder and more expensive than the efforts we've made in the past."

What is the vision for the HIV program at the Foundation?

Our priorities go across quite a broad range. Our overall priority is to accelerate the decline of the global HIV burden and to continue to accelerate the decline in incidence of new HIV infection.

Obviously, that's a very broad statement. To do that, we have investments across a large range of activities. Also, and it's important to note, that while we have the word "global" in our vision statement, our primary focus, albeit not exclusively, is on Southern and Eastern Africa, because that is where we have two-thirds of the burden of HIV infection worldwide. We decided to focus predominantly in those parts of the world because one of our perspectives is that if you're going to do this well you have to go in depth. Not just in terms of the research and development areas in which we're focused, but also geographically.

What are the priorities for accomplishing this vision and which of them do you see as the most promising?

Let me describe the challenge first. We know that the global incidence of infection over the last five years has been pretty flat. It's not continuing to go down substantially as was the case prior to this five-year period. At the same time, in the last 15 years there has been a noted improvement in infant mortality, particularly in Southern Africa. As a result, Africa is right now a very young continent. There is a large population of young people that have grown up and are now entering into that age range—15-24 years of age—in which they are most susceptible to HIV infection.

So if you do the math, given a flat incidence and a substantial increase in the population of young people who are entering into the susceptible age range, the modeling suggests very strongly that 15 years from now we're going to wind up having, in an absolute sense, a greater number of individuals living with HIV than we currently have, or even had 15 years ago.

It may sound dramatic, but I believe we are on the edge of losing control of the epidemic. And

so, when we take a look at where we need to place our investments, we do it in the context of looking towards the next 15 years. If we don't manage to lower the incidence of HIV infection, especially in high-incidence populations, we will have more people living with HIV, particularly in sub-Saharan Africa, than we have right now. This is the message that Bill Gates delivered at the AIDS 2016 conference back in July when he gave the keynote address. This is the premise upon which we look at everything that we're trying to do.

Another premise is that you can't just focus on prevention or treatment. You need to focus on the entire spectrum of what we call the treatment and prevention cascades—you have to look at both ends. When we re-articulated our strategy over the last 12 to 18 months, we divided it into a series of strategic areas that reflect both the treatment end of what needs to be done and the prevention end.

What is the main focus of the treatment work the Foundation invests in?

On the treatment side, we focus first on how to find those people who are living with HIV but who don't know it, and therefore are not linked to antiretroviral therapy. About 50 percent of individuals who are living with HIV don't know it, so the first question is how do you find that 50 percent and how do you link them to treatment? We have a number of existing and pending investments in this area.

The next question is, once you have individuals on treatment, and hopefully on fully virally-suppressive treatment, how do you keep them on treatment? There are many sub-questions associated with this area, including how treatment delivery actually is done and the cost of treatment delivery. We focus on improving the efficiency of treatment delivery, the effectiveness of treatment delivery, and the effectiveness of using diagnostic methods such as virus load assessments to determine if treatment is successful.

Our overall focus is on improving end-to-end patient management because the objective is to keep people on fully virus-suppressive treatment for the rest of their lives. We have a broad series of investments in this strategic area.

And what about within prevention?

Our first area of focus in prevention is centered on making the best use of the prevention interventions that we currently have available. There are three efficacious biomedical interventions: volun-

GATES FOUNDATION HIV AREAS OF FOCUS

Improving Diagnosis and Expanding Treatment Coverage

BMGF supports the development and appropriate use of novel tools that can greatly increase the number of people who know their status and who seek treatment.

Improving Treatment Retention

BMGF supports partners who are working to simplify the delivery of HIV treatment and introduce models of care that are more tailored to the needs of particular populations and their circumstances.

Expanding the Use of Existing Preventive Measures

Effective existing measures in preventing HIV infection include voluntary medical male circumcision, condoms, and drugs that reduce the risk of acquiring the virus after exposure. These measures can be effective only if they are affordable and reach high-risk populations—and only if those populations are aware of their risk of contracting HIV.

BMGF supports circumcision-related efforts in several high-burden countries in Sub-Saharan Africa.

They also support efforts to improve consistent condom use and the use of drugs that reduce the risk of contracting HIV.

Developing Long-Acting Prevention Measures

BMGF supports efforts to develop, evaluate, and introduce innovative approaches to protecting those at risk. These include potential long-acting prevention interventions that can provide continuous protection over a period of time.

Developing an HIV Vaccine

BMGF continues to invest in efforts to develop an HIV vaccine. Although developing a highly effective vaccine remains a substantial scientific challenge, even a vaccine with partial efficacy and limited duration could help dramatically reduce the global incidence of HIV.

—*Courtesy of GatesFoundation.org*

tary medical male circumcision, so we look at how we could enhance its use; condoms, which are incredibly effective if used consistently, so we look at how to enhance appropriate use and improve condom social marketing; and, most recently, oral pre-exposure prophylaxis, which is just now being introduced in specific at-risk populations in sub-Saharan Africa. Again, the focus here is to do this in the most effective and efficient ways possible.

In addition to these biomedical prevention tools, there are behavioral and structural interventions that are critically important as well. Using all the available prevention tools together to achieve the greatest possible effectiveness and efficiency is the aim of many of our investments.

The next area of prevention focus involves looking towards the future at potentially new biomedical interventions, particularly the development of long-acting anti-HIV prophylactic agents. I am not referring here to vaccines but passively-administered anti-HIV drugs or antibodies that are delivered parenterally to provide a prolonged period of prophylactic protection. There are various manifestations of this approach, including the use of broadly anti-HIV neutralizing monoclonal antibodies and anti-retroviral agents that are formulated in ways to give rise to long-acting protection. In essence, we took a page from our family planning colleagues. Contraception becomes very effective when users are provided multiple choices. One can either have the pill once a day, parenteral administration of a contraceptive agent that lasts two to three months, or one can have long-acting implantables. We've committed significant investments to help develop the equivalent choices for HIV prevention.

Our final area of HIV prevention focus continues to be centered on the development of a highly effective vaccine. I don't think I need to say anything more about this other than noting that we continue to very heavily invest in HIV vaccine basic research and basic development efforts. These early development efforts are designed to obtain an understanding of whether a specific vaccine approach that may be potentially effective can, in fact, be successfully developed. While a considerable amount relating to the design of a potentially effective vaccine has been learned over the last 15 years, we still don't know how close or how far we are to achieving our goal.

Are there developments in the past few years that stand out within the vaccine arena or that you feel particularly optimistic about?

Much of the vaccine-related research work of

the past 10 years is clearly encouraging, but until we obtain human clinical data regarding some of the currently more interesting vaccine approaches, I am going to reserve my opinion in terms of optimism. This is an important consideration when it comes to the overall HIV vaccine research and development effort. Human data, by definition, can only be obtained in human clinical studies and, for some of the more promising approaches, these will involve clinical efficacy studies to determine whether promising preclinical observations can be recapitulated in humans. Even with the one clinical study that gave a suggestion of potential efficacy—the RV144 study—the question persists as to whether that specific vaccine approach will yield the same results in high-incidence populations in Southern Africa. We don't know. We have to do the clinical studies.

This isn't a trivial issue because human efficacy studies are expensive. We're talking \$100 million to \$150 million each. When you look at the list of studies that need to be done eventually in terms of human efficacy, the list may become long. And at \$100 million to \$150 million per study, this approach represents a significant investment that needs to be made by the HIV vaccine research and development community over the next five to 10 years. Nonetheless, it's an investment that needs to be made or we won't know where we stand. We have a lot of preclinical data, a lot of promise, but until we get those human data...

Of course, the human evaluations do not all involve efficacy assessments. There are many clinical studies that need to be done to address earlier questions. For instance, can one come up with a set of immunogens that will elicit broadly neutralizing antibodies? It's a possibility, but whether or not it can actually be accomplished can only be assessed to a limited extent in pre-clinical animal models. Until the approaches that have been devised are studied in the context of the human immune system, one cannot provide a reasonable guess as to the likelihood of success.

Given that the research into long-lasting antiretrovirals and passive administration of broadly neutralizing antibodies is already being tested in humans, do you still see a vaccine as being a necessary component of an eventual end to AIDS?

Absolutely. All of the non-vaccine approaches have, at the moment, significant uncertainties associated with them. Even if some of these approaches will be able to demonstrate reasonable efficacy moving forward, that's just the first step.

The next step is to actually get them used. There remain multiple questions with respect to cost effectiveness and delivery. One of the issues about all preventative interventions is that they have to be used sustainably. The same is also true for vaccines. One has to sustainably maintain the immunization status within a population or protective effectiveness will be lost at both the individual and population level.

Sustainability is an important issue. Underlying all of the strategic focus areas in the foundation's HIV program is an added strategic focus on sustainability, whether it be for treatment or prevention, for new interventions or the interventions that we currently have. When treatment or prevention interventions are introduced, they have to be introduced in ways which will allow the end-user population to use them sustainably. And the donors who pay for the interventions, including the individual country governments who will have the longer term responsibility for their use, need the information and the data to understand how to maintain the use of these interventions in a sustainable fashion.

Specifically, this entails performing analyses of how incidence of infection is impacted when you introduce a new intervention or when you change how a current intervention is used, and how this information can be used to calculate cost effectiveness to determine whether paying for a given intervention over many years is worthwhile. We don't ignore the economic aspects of our work. It's a fundamental part of the work that we're doing in all of our focus areas. In the absence of doing so, we're not going to be able to introduce effective interventions in a way that will ensure sustainability over the longer term.

How have you found that the Foundation's approach has changed or evolved since you took the reins as director of the HIV program?

Well, honestly, a lot of this work was already going on and was going on in very significant ways. I think the only thing that my colleagues and I did since I joined the Foundation was to re-articulate the strategy and place it into defined strategic focus categories. The re-articulation helped because it placed what we're doing into context. I wouldn't call it a fundamental sea change—I would say that it is just contextually different.

Given your extensive background in the pharmaceutical industry, is there any more emphasis now on attracting industry or working with them on

HIV vaccine research in particular?

We work with different partners and a number of them are industry partners. Some of them are large, some of them are smaller, and we've worked with them as needed within our strategic areas. Is the emphasis any more so than it was in the past? No, I think it's the same.

In addition to industry partners, the foundation works collaboratively with other donors in the HIV area to maintain the research and development focus needed in the field. Some of our biggest partners include: UNAIDS [the Joint United Nations Programme on HIV/AIDS], PEPFAR [the US President's Emergency Plan for AIDS Relief], USAID [the US Agency for International Development], the NIH [US National Institutes of Health], and the WHO [World Health Organization].

We're also trying to enhance our engagement with community groups as the importance of community engagement is paramount to our overall effort.

How does the Foundation evaluate its past investments and determine the success of those in spurting progress?

All investments have milestones associated with them, and we evaluate the achievement of the milestones over the life of the investment, and ask where we want the investment to be in terms of its achievements over a defined period of time. In the end, the primary measure that we use is whether the investment has yielded knowledge or an actual intervention that will impact the decline in the incidence of new infection. We then decide whether or not continued investment is worthwhile and appropriate.

In October you were a keynote speaker at the HIV Research for Prevention conference in Chicago. Were there any other key messages you shared with that audience?

One final and critical message is that that this is not the time to step back from our collective global financial commitments related to the control of the HIV epidemic. Even though the successes of the last 15 to 20 years have been pretty remarkable, we're on the edge of losing control of this epidemic in substantial parts of the world and in some significant populations. The tools that we have are good tools in many cases, but we have to be able to use them better. We also need new tools for the future. The effort that's going to be required is harder and more expensive than the efforts we put in in the past. We've got to keep it up as a global community. This is not the time to back off. ■

Many Keys to Protection, *But Many Locks Remain*

October's HIV Research for Prevention conference highlighted the abundance of pathways that investigators are pursuing in the quest for an effective vaccine.

By Michael Keller

In mid-October, researchers in South Africa were finalizing plans to launch HVTN 702, the first large-scale efficacy trial of an HIV vaccine candidate since the landmark RV144 trial in Thailand showed that two vaccine candidates in a prime-boost regimen provided 31 percent efficacy after three years. Investigators hope that the modified regimen now being tested in HVTN 702 will be able to protect at least 50 percent of the 5,400 South African participants from HIV over the same period.

As the last arrangements were being made for this trial, more than 1,400 leading scientists, advocates, and government officials gathered in Chicago for the biennial HIV Research for Prevention (HIVR4P) conference. While South Africa was half a world away, the trial's start was one element in the universe of vaccine discovery that imparted excitement and optimism for the development of useful and long-acting HIV prevention strategies. Another was the multi-country Antibody Mediated Prevention (AMP) Study, a second major trial that is testing whether regular infusions of a potent broadly neutralizing antibody (bNAb)—one of many isolated that can neutralize a broad swath of HIV isolates in circulation—can provide protection against HIV. This trial is testing the strategy researchers refer to as passive administration: rather than relying on the immune system to make the antibodies, the antibody itself is directly injected into the susceptible individual. Presenters at HIVR4P also showcased efforts to design vaccine immunogens that could train the immune system to make its own HIV-destroying antibodies. Taken together, the conference's speakers presented incremental work toward the goal of developing an effective vaccine and other prevention modalities.



“This is a good year,” said William Snow, the former director of the Global HIV Vaccine Enterprise who recently stepped down from this post (see sidebar, page 9). “Now, after long preparation, the field has embarked on a number of efficacy trials. They should, in a short, comfortable number of years, clarify what really works and why, which in turn will set the best direction for truly effective products, be they bNAbs, potent vectors, native trimers, or rational immunogen design. The questions have been posed and the answers are forthcoming.”

bNAbs in the spotlight

The Phase III AMP Study, which started earlier this year and is expected to run for about two years, is just one application for the bNAbs that have recently become a major focus of HIV treatment and prevention. In this trial, around 3,900 participants in the Americas and sub-Saharan Africa will receive infusions of the bNAb VRC01, a potent monoclonal antibody that targets the highly conserved CD4⁺ binding site where HIV docks to infect T cells. More than 700 volunteers had been enrolled in the AMP study as of mid-October. Larry Corey, president and director emeritus of the Fred Hutchinson Cancer Research Center and co-chair of the study, said the best-case outcome of the trial would be that a low dose will provide a sufficient concentration of antibody *in vivo* to protect against infection. That result would open the door to creating a marketable subcutaneous or intramuscular injection that could protect against HIV. If it turns out that protection is only imparted at higher *in vivo* concentrations, it bodes less well for developing this approach and also suggests it may complicate vac-

cine efforts, he warns, as this concentration may be challenging to achieve. In fact, with a growing playbook of bNAbs now in hand, Corey was asked whether there were any plans to test a cocktail of antibodies. He said the idea is to eventually use a combination of bNAbs, but AMP is specifically designed to employ only one as a test of concept and to tease out its immunological functioning.

In the meantime, several researchers are working on tweaking bNAbs to improve their chances at protecting. John Mascola, director of the Vaccine Research Center (VRC) at the National Institute of Allergy and Infectious Diseases (NIAID), spoke at HIVR4P about various modifications VRC researchers are making to antibodies to increase their potency and half life. “We have now discovered hundreds of antibodies that are extremely potent,” said Kevin Whaley, the CEO of Mapp Biopharmaceuticals, a company developing and marketing antibody-based therapies and vaccines. “VRC01 came out so far ahead of the other candidates, but we need to look at these others. I think we have a revolution going on in the world of antibody discovery.”

The recent boom in antibody discovery might make it seem like bNAbs are common, but they are in fact naturally produced by a small subset of all HIV-infected people, and even then, typically only after years of infection. Part of the reason that bNAbs are rare and take so long to develop in HIV-infected individuals is that they are extensively mutated. B cells are the components of the immune system that recognize pathogens and give rise to antibodies. B cells with defined specificities exist before the body is ever exposed to a particular pathogen. Once these cells come in contact with a specific pathogen such as HIV, a chain reaction process begins that results in the induction of so-called germline antibodies that target specific sites on HIV Envelope (Env) protein. These germline antibodies do not, however, typically bind to or neutralize HIV Env. It is only after the B cells undergo successive rounds of somatic hypermutation, which involves B cell stimulation and the process of affinity maturation, that these B cells are capable of producing the types of bNAbs vaccine scientists are interested in.

Such bNAbs can target and bind to specific sites on multiple regions of the virus and some have protected nonhuman primates (NHPs) against infection with a simian immunodeficiency virus (SIV)/HIV hybrid known as SHIV (*PNAS* 109, 18921, 2012; among others). Many researchers think that a vaccine that induces a long-lasting and potent bNAb response would protect against HIV. Therefore, understanding bNAb specificities

and determining how best to elicit them via vaccination has become a major focus of HIV vaccine research in recent years.

Dennis Burton, scientific director of IAVI’s Neutralizing Antibody Center (NAC) and chairman of the immunology and microbial science department at The Scripps Research Institute (TSRI) in La Jolla, CA, spoke at HIVR4P about progress in developing neutralizing antibody-based vaccine candidates. He said bNAbs have been identified that individually target widely conserved areas on the virus’s trimeric Envelope (Env) protein, including the apex, high mannose patch, CD4⁺ binding site, gp120-gp41 interface, and membrane-proximal external region.

Researchers studying bNAbs are now using a reverse vaccinology approach to try to develop vaccine candidates that can induce bNAbs. They start by determining what the unmated or germline form of the antibody is and then design a series of vaccine immunogens to stimulate B cells to induce these germline antibodies and then shepherd B cells through the process of making more mature, mutated antibodies that will hopefully be able to broadly neutralize HIV. If that sounds complicated, that’s because it is. But researchers are making progress using this step-wise approach to inducing bNAbs in animal models.

“We’ve been seeing if we can steer germline antibody maturation,” said Burton. “This field has made incredible progress. We now have many different rationally designed immunogens and immunization strategies that are being evaluated. Some of these are going to make it into humans.”

Devin Sok, an IAVI research scientist, presented research at HIVR4P on one approach to design immunogens that elicit bNAbs. Since 2013, William Schief of TSRI and IAVI’s NAC, Burton, Sok, and others have been designing a self-assembling nanoparticle immunogen called eOD-GT8 60-mer. The plan, what the team refers to as a “multi-step reductionist vaccine strategy,” is to use an engineered germline-targeting immunogen like eOD-GT8 to prime VRC01-class precursor B cells, then use successive booster immunogens that are increasingly more native-like to induce further rounds of somatic hypermutation, eventually inducing bNAbs with the ability to recognize and neutralize native HIV Envs.

In previous studies, the eOD-GT8 60-mer immunogen was shown to activate the presumed B-cell precursors of the VRC01 class of antibodies (*Science* 349, 156, 2015). Then in a paper published earlier this year, researchers showed that more native-like boosting immunogens designed to guide the genetic and functional maturation of VRC01-

ENTERPRISE APPOINTS INTERIM DIRECTOR

Gerald Voss, former head of GlaxoSmithKline’s (GSK) HIV Vaccine program and vice president of the Enterprise’s Board of Directors, is now interim director of the Global HIV Vaccine Enterprise Secretariat, replacing longtime AIDS vaccine advocate William Snow, who has stepped down. Voss will oversee the Secretariat while the organization charts its future direction. After conducting a strategic review, the Enterprise will seek a permanent director. Snow will remain a senior advisor to the Secretariat and the Board of Directors.

Snow said he decided to take a step back because he felt someone else was needed to take the Enterprise to a new level. “I’m thrilled to say that Gerald has plenty of experience to take the reins,” says Snow. “His base of experience is much broader than mine and his connections are long-standing.”

Voss has spent much of his career working on AIDS vaccines, primarily at GSK, but his work also involved malaria and tuberculosis research. As interim director, Voss says he will be seeking ways for the Enterprise to further the work that Snow and his team began. This includes capitalizing on recent developments. “There has been a lot of scientific progress and so we want to make sure that the Enterprise evolves to meet these new and exciting developments,” says Voss. —*Mary Rushton*

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

class precursors induced by eOD-GT8 were able to induce antibodies that were similar to a partially mature VRC01-class antibody in transgenic mice (*Cell* 166, 1, 2016). Although these antibodies could only weakly neutralize native HIV, the researchers concluded that this sequential immunization strategy was capable of guiding maturation of antibody responses and is therefore “a significant milestone in HIV vaccine development.”

At HIVR4P, Sok showed that they were also able to use eOD-GT8 to boost the number of VRC01-class precursors in transgenic mice that can produce human immunoglobulin (Ig; *Science* 353, 1557, 2016). These VRC01-class precursors naturally appear very rarely in the body, so getting B cells to produce more of them is a critical early step. In the study, the team immunized mice with a dose of eOD-GT8 or a control. Twenty-nine percent of those that received the immunogen started producing a VRC01-class precursor, with tell-tale characteristics of VRC01-type antibodies, compared to none of the control group. “It looks like we’re not only activating them [VRC01 precursors], but that we are selecting for productive mutations that would enable higher affinity,” Sok said.

Bart Haynes, director of the Duke University Human Vaccine Institute, is also testing the sequential immunization strategy. At HIVR4P, he noted recent data showing there is less overlap in sequences of Ig genes in NHPs and humans, suggesting that NHP data resulting from sequential immunization strategies may not translate directly into humans.

Trimer mimics

Another approach to potentially induce bNAbs is immunizing with proteins that mimic the natural trimeric structure of HIV gp140, so-called native-like trimers. For years researchers struggled to obtain a stable, trimeric form of this notoriously floppy protein, but now with the structure in hand, researchers are testing trimeric immunogens. Marit Van Gils, a postdoctoral researcher at the University of Amsterdam’s Academic Medical Center, presented work using one of these trimeric immunogens, BG505 SOSIP.664 (see *Research Brief, IAVI Report*, Vol. 19, No. 2, 2015). Recently, she and a multinational team found that rabbits vaccinated with the immunogen produced neutralizing antibodies that targeted a vulnerable hole in the glycan shield, the protective carbohydrate molecules that are densely packed around HIV Env and shield the virus from antibody-mediated neutralization. These antibodies were found to be able to neutralize moderately resis-

tant autologous viruses, but did not possess broad activity because the location of the hole in the glycan shield was specific to the HIV isolate used to create the immunogen (*Cell Reports* 16, 2327, 2016).

During the conference, Van Gils presented data extending this line of inquiry, showing that two rhesus macaques immunized with BG505 SOSIP.664 produced narrowly directed neutralizing antibodies, confirming results seen in the earlier rabbit study. She said this is a first step in an iterative vaccine design process that includes vaccinating animals and humans with the immunogen, isolating the antibodies that develop from it, characterizing them, and then redesigning the immunogen to get closer to the broadly neutralizing response that a vaccine would ideally induce to protect against diverse strains of HIV. Understanding how to broaden the response to effectively target HIV isolates with differing glycan shields will be key to this process.

Exploiting holes in HIV’s glycan shield is an emerging theme, according to Penny Moore, senior scientist at South Africa’s National Institute of Communicable Disease’s Centre for HIV and Sexually Transmitted Infections. In one study, a team including John Moore and Rogier Sanders of the Weill Medical College of Cornell University engineered native-like recombinant SOSIP.664 trimers that were based on Env genes from clade A, B, and C HIV isolates (*PLoS Pathog.* 9, 1005864, 2016). The trimer immunogens were given either at the same time or in sequence and effectively induced neutralizing antibodies in rabbits, but with limited neutralization breadth. Researchers found that antibodies elicited from different trimers primarily recognized holes in the glycan shield, and that in some cases the location of the holes was shared between the different isolates. With this knowledge, the group hopes that multiple trimers could induce broader neutralizing antibody responses that can home in on shared weak points.

These are just a sample of the bNAb-eliciting vaccine development routes under active investigation. But even with these promising developments, much still remains to be learned about how the ever-mutating virus might evade even bNAb responses. Jinal Bhiman, a postdoctoral fellow in South Africa’s National Institute for Communicable Diseases, presented evidence that CAP256-VR26—a class of antibodies that bind to the V1 and V2 regions on Env first isolated by the Centre for the AIDS Programme of Research in South Africa—could still attach to Env even after the virus had mutated to be resistant to neutralization. Further, those antibodies with higher levels of somatic hypermutation actu-

ally bound better to Env, but did not effectively neutralize the virus. This means that HIV can escape the neutralizing activity of a bNAb, while still allowing the antibody to bind to the viral Env protein, which is a surprising result. “This goes against everything I’ve ever been taught about neutralization,” said James Bradac, the chief of preclinical research and development at the US National Institute of Health’s (NIH) Division of AIDS.

Vector-based approaches

While researchers plug away at vaccine strategies to induce bNAbs, there is also considerable progress in advancing viral vector-based vaccine strategies into human clinical trials. Georgia Tomaras, research director of the Duke University Human Vaccine Institute, presented results from HVTN 100, the Phase I/II trial that served as a preliminary safety and immunogenicity test of the HVTN 702 regimen. The prime-boost study tested the ALVAC canary-pox-based vectored vaccine used in the RV144 trial, which had been modified to be specific to southern Africa’s clade CHIV strains, along with a bivalent HIV subtype C gp120 protein boost. In still unpublished data she presented at the conference, her group found that the regimen used in HVTN 100 elicited a robust mix of immune responses, some of which were higher and some lower compared to those seen in RV144.

Results that appeared superior in HVTN 100 included titers of IgG and IgG3 antibodies capable of binding the Env protein included in the vaccine, and HIV-specific CD4⁺ T-cell polyfunctionality. The latter is significant because in a separate presentation at HIVR4P, Nicole Frahm from the Fred Hutchinson Cancer Research Center reported that CD4⁺ T-cell polyfunctionality correlated with protection in RV144. However, antibodies recognizing the V1/V2 region of Env had less breadth in HVTN 100 compared to RV144 when tested against multiple HIV clade C Envs. IgG3 antibody responses against V1/V2, which were reported to be potentially important in RV144 (*Sci. Transl. Med.* 6, 228ra39, 2014), were also lower in HVTN 100. In terms of antibody functionality, antibody-dependent cellular phagocytosis was generally similar between the two trials, and assays for antibody-dependent cellular cytotoxicity (ADCC; the process by which antibodies facilitate destruction of virus-infected cells) produced evidence of better recognition of HIV-infected cells among HVTN 100 participants. Most importantly, however, all of the pre-defined immunogenicity criteria for launching the HVTN 702 efficacy trial were met.

Several other vector-based vaccine regimens

are also being advanced post-RV144. In one Phase I trial, designated HVTN 094, researchers are evaluating a DNA prime and a modified vaccinia Ankara (MVA) boost made by biotech company GeoVax that produce virus-like particles. This approach has been shown to reduce the risk of SIV and SHIV infection in macaque studies.

In 48 HIV-uninfected volunteers, the 094 research team found that a regimen consisting of two or three doses of MVA was well tolerated and produced cellular and humoral immune responses. Susan Buchbinder, a University of California, San Francisco epidemiologist who led the investigation, presented unpublished data at the conference showing that the regimen induced ADCC. This regimen’s immunogenicity will be tested in the HVTN 114 trial involving 100 participants starting in December. “What’s unique about these vaccines is that they produce these virus-like particles that we believe presents the envelope in a more conformationally intact structure and, therefore, may generate more functional antibodies than what we might see with some other vaccine regimens,” said Buchbinder.

The virus’s rapid mutation and the resulting variability of circulating virus remains a challenge for vaccine development. One strategy scientists are using to counter this involves employing mosaic immunogens, which are a bioinformatically derived set of HIV gene sequences that encode whole HIV proteins that are designed to match those made by the majority of circulating HIV strains worldwide. Mosaic immunogens are meant to trigger a broad cellular immune response, and previous studies indicate that the mosaic approach can partially protect rhesus monkeys from SHIV through the action of both neutralizing and non-neutralizing antibodies (*Cell* 155, 531, 2013).

Lindsey Baden, director of clinical research at Brigham and Women’s Hospital’s Division of Infectious Diseases, discussed unpublished data from a Phase I trial called IPCAVD-006, which was the first in-human clinical trial of the mosaic approach. Twenty-five participants were split into two groups: those who had never been given an HIV vaccine candidate and those who had received an adenovirus serotype 26 (Ad26) vectored vaccine candidate up to five years before that was meant to elicit HIV Env-targeted antibodies. Volunteers in both groups received an MVA vector containing the mosaic insert by intramuscular injection. The vaccine candidate was found to be safe and well tolerated, and it elicited Env-directed B- and T-cell responses. This response was still seen up to a year after the vaccine was given, though response to Gag and Pol

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The Centre for the AIDS Programme of Research in South Africa, **CAPRISA**, has been working to unlock the secrets and weaknesses of **HIV and TB** for years. With a spate of ongoing and planned trials, researchers hope to soon **turn the tables on the deadly diseases.**

IN THE



EPIDEMIC'S



HEART

By Michael Keller

In a waiting room inside Durban, South Africa's eThekweni research clinic, Dr. Nigel Garrett, wearing a white lab coat and a couple of days of facial stubble, talks with five waiting volunteers. Between Garrett and the volunteers is a side table stacked with slices of white bread for noshing as they wait for their names to be called. A television mounted to the pinkish-beige institutional walls buzzes with a daytime show over Garrett's shoulder.

Nurses and case workers emerge from and enter the door to a small examination and treatment room connected to the waiting area. Inside that room, one woman sits at a table and records numbers on spreadsheets, the anonymized identifications of the people outside and the trial biopharmaceuticals they are about to receive.

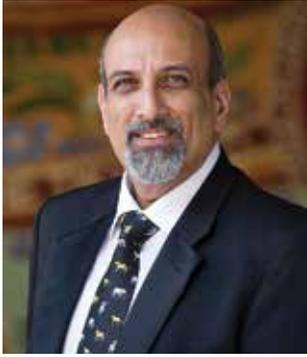
The waiting volunteers, all HIV free, are some of the first to receive an experimental prevention approach—passive transfer of broadly neutralizing monoclonal antibodies to prevent transmission of HIV. These volunteers are enrolled in the multinational Phase IIb Antibody-Mediated Prevention (AMP) Study and will receive repeat infusions of a broadly neutralizing antibody (bNAb) known as VRC01 (*J. Virol.* 85, 8954, 2011). This antibody is one of several that has recently shown early promise in preventing infection in monkeys (*Nature* 533, 105, 2016). The Centre for the AIDS Programme of Research in South Africa (CAPRISA), a consortium of five institutions in South Africa

and the US, started enrolling participants in May at eThekweni clinic and will eventually recruit more than 100 people in this two-year trial. The facility is one of 15 sub-Saharan African sites chosen to be part of the randomized, placebo-controlled study. Volunteers will receive the VRC01 antibody or placebo by intravenous infusion every eight weeks and be monitored to see if they contract HIV.

"How are you doing today?" Garrett asks a woman who is sitting closest to him. She smiles and nods her head amiably. The two make small talk.

Later, to a visitor, he says, "These people are really so generous with their time. For the AMP Study, the first infusion takes an hour and then we monitor them for negative reactions for another 30 minutes, then it takes 30 minutes for every infusion after. We have a party every three months to give people updates about these studies, and they're generally very positive about them. These participants are making a real contribution."

Volunteers for trials that CAPRISA runs at eThekweni clinic, which involve testing HIV vaccine candidates and other prevention approaches, as well as possible treatments, enroll either after walking into the clinic or through community recruitment efforts, Garrett says. To recruit participants, teams canvass neighborhoods to identify people willing to take part. Each volunteer is paid up to US\$25 per



Salim Abdool Karim, CAPRISA's
Director



Quarraisha Abdool Karim,
Associate Scientific Director at
CAPRISA



Nigel Garrett, Head of vaccine
and HIV pathogenesis research
at CAPRISA

visit, depending on travel time and the onerousness of the procedure. Recruiters don't stress the compensation, though, because "we don't want to give people the wrong incentive to take part," Garrett notes.

Inside the clinic, all is peaceful. Nurses and technicians quietly shuttle patient samples to the on-site laboratory for analysis. Outside the facility's walls is a different matter. eThekweni clinic is situated in the heart of the city's transportation hub. Trains and buses arrive at their respective stations throughout the day from the outlying townships. Minibuses and taxis take the people who arrive there to and from work all over Durban. And the whole hub rises up amidst the city's main outdoor markets, where sellers, in stalls and out on the street, hawk fruits, incense, beads, and music. Charcoal smoke and the smell of cooking meat waft through the air as several old men play a game of pool on a table that has been wheeled onto the sidewalk.

eThekweni adjoins the Prince Cyril Zulu Communicable Disease Center, the largest outpatient tuberculosis (TB) and sexually transmitted infection (STI) treatment facility in Durban. Their location is strategic—some 460,000 commuters and at least 6,000 street vendors come through the area on an average day. The two clinics receive the sick who are city residents or coming into Durban to shop or work from villages in the surrounding KwaZulu-Natal province. Patients start lining up for diagnosis or treatment beginning at five in the morning, and more than 300 can come through the door in a day. Many have TB, and 80 percent of the people presenting with that disease also have HIV.

"Here you see the worst because they're coming in on their own after symptoms start occurring," says Garrett, an HIV and sexual health specialist who relocated from the UK because he said he wanted to be at the center of the epidemic. "Most people come in with persistent coughing, weight loss, bringing up sputum. We need to get their TB symptoms under control a bit and then quickly start them on ART [antiretroviral therapy]."

One of CAPRISA's main research focuses is HIV and TB coinfection. In 2012, 88,000 South Africans living with HIV died of TB. That's more coinfection deaths than in the next three African countries with the highest coinfection rates combined. The widely cited 2010 CAPRISA 003 TB-HIV treatment study helped optimize the starting time of ART during TB therapy (*NEJM* 362, 697, 2010). Up to that point, many clinicians had delayed ART because it could negatively interact with TB drugs. But the researchers found that treating both deadly infections at the

same time reduced overall patient mortality by 56 percent. This evidence helped accelerate the international adoption of new treatment guidelines. CAPRISA says the combined therapy now saves an estimated 10,000 South African lives a year.

"The problem in South Africa is that we started HIV treatment very late—that's why we've got such a problem here," says Garrett. "The idea now is to test as many people as possible for HIV, treat as many as possible, and keep the virus suppressed in their system. We treat TB at the same time."

Just before noon at the eThekweni clinic, business has settled down since the morning and only a dozen people wait in the communicable disease center. Upstairs, up to 6,000 patients are being treated for HIV and TB. Garrett, CAPRISA's head of vaccine and pathogenesis research, strides through the communicable disease admission area with his disposable respirator covering his mouth and nose, taking it off when he enters the prevention wing. The day is just beginning for his team.

On the frontline

eThekweni is one of three research clinics CAPRISA runs. It also operates the nearby Springfield clinic at Durban's King Dinuzulu Hospital, which focuses on clinical studies to treat drug-resistant TB, and the Vulindlela clinic outside Durban in rural KwaZulu-Natal province, the epicenter of the decades-long AIDS epidemic. In 2012, the last year for which official data is available, the southeastern province had an HIV prevalence rate among all people age two years and older around 17 percent. If looking at only people 25 years and older, the prevalence in the province shoots up to 30 percent. By comparison, the global rate was around 1 percent. These provincial numbers represent the highest percentage of people living with HIV in South Africa, which itself has the world's most infected people—around 7 million.

It is these stark realities, along with CAPRISA's work on understanding the virus and developing prevention and treatment approaches, that have made the organization and its 200 scientists and graduate students a renowned research and educational center on the frontline of the epidemic. The effort is coordinated from an office on the campus of the University of KwaZulu-Natal's Nelson R. Mandela School of Medicine. The headquarters is a modern work of glass-and-concrete architectural art.

In the waiting area outside CAPRISA's offices on the second floor stands a working child's toy—a maze where anyone can pick up a marble from below, drop it in at the top, and watch as it careens

down wire pathways like a roller coaster ride. Plastic arms randomly send the marble down different avenues to the bottom—perhaps a fitting analogy for CAPRISA’s scientific pursuits. The organization currently lists 24 trials and studies ongoing or in some stage of approval or data analysis. Promotional materials proudly announce that institute researchers have been authors of more than 350 articles published in peer-reviewed journals, and produce an average of 50 new journal articles a year.

With so much research news to share, it is understandable that Salim Abdool Karim, an infectious diseases epidemiologist who is CAPRISA’s director and cheerleader-in-chief, could rarely be found around the office when the 21st International AIDS Conference (AIDS 2016), the preeminent meeting on the epidemic, came to town in mid-July. During that week, he and wife Quarraisha Abdool Karim, another infectious diseases epidemiologist and CAPRISA’s associate scientific director, were a blur. The power couple remained in motion except when planted on one of the stages inside Durban’s International Conference Center. Between them, they were featured speakers in eight sessions over the conference’s five days. Other center researchers like Garrett spoke at another nine sessions.

On the last day of AIDS 2016, the two finally got a chance to sit down for a quiet working lunch at the center’s headquarters. A couple of days before, Salim’s lunch hour was spent on a stage with Bill Gates in front of thousands of researchers and advocates packed into a dark auditorium. Now Salim and Quarraisha shared quiche and salad while providing a narrative of CAPRISA’s past and future for a couple of visitors. Salim, in a tan suit and light blue, short-sleeved shirt, leaned back into the office chair. His face seems to be permanently open in a warm smile beneath his salt-and-pepper goatee. While Quarraisha comes off as quieter, studious, and more comfortable rattling off deeply complex biomedical research data, Salim appears relaxed and gregarious as he lists the recognitions his team has earned.

He takes special pleasure in informing guests of the overwhelming number of women—82 percent of the staff—working throughout CAPRISA. “We are essentially a women’s organization,” he says. “We have a policy of giving women preference, and it just turns out that we get a lot of women who apply. We don’t have a male statistician or pharmacist in the organization.”

An approach targeted at women

CAPRISA’s focus on women extends beyond its internal staff. The organization is also heavily



invested in countering the unequal burden AIDS places on girls and young women. In 2012, more than 14 percent of all South African women had contracted the virus compared to a prevalence rate of under 10 percent of men.

During AIDS 2016, researchers released findings that illuminated a reality in South Africa’s epidemic that at least partially answers why this is so. From population studies, investigators could see that women were getting infected years before males of the same age. CAPRISA scientists analyzed the genetic code of HIV found in 1,589 people living in either rural or urban settings. In their still unpublished study, the team was able to connect new infections in girls and young women to men eight years older than them on average. This characteristic perpetuates a cycle of infection that continues when the newly infected females transmit the virus to males of similar age. “It’s not about having sex at this young age. Sex with peers gets you pregnant and other STIs,” says Salim. “Having sex with older men gets you HIV. Older men allow HIV’s entry into younger women. If you can keep the 15- to 24-year-old group uninfected, you can break the chain of transmission.”

CAPRISA has been developing tools specifically for young women to prevent HIV transmission. A study whose results were released in 2010, the CAPRISA 004 tenofovir gel Phase IIb trial, was the first to show that an antiretroviral-based microbicide could be used to prevent sexual transmission of HIV (*Science* 329, 1168, 2010). The product, a vaginal gel, was meant for women to take prevention into their own hands, and the initial results excited the scientific community. The team of scientists from CAPRISA, Family Health International, and South Africa’s National Institute of

Lenine Liebenberg, Ph.D. is a research associate at the CAPRISA Mucosal Immunology Laboratory.



Professor Quarraisha Abdool Karim, Ph.D., with women in the community of Vulindlela where the CAPRISA research clinic is located.

Communicable Diseases found that vaginal administration of a gel containing one percent tenofovir up to 12 hours before sex and as soon as possible within 12 hours afterwards reduced HIV infection in women by 39 percent. It also reduced genital herpes infection by 51 percent. When it was announced during AIDS 2010 in Vienna, the crowd broke out into applause and a standing ovation.

This unabashed optimism was tempered later by a series of studies showing the approach was ineffective. A study published in 2013 called Vaginal and Oral Interventions to Control the Epidemic (VOICE) failed to show tenofovir gel's efficacy among more than 5,000 women in sub-Saharan Africa. "The data on tenofovir gel and tablets in women has been all over the place," says Salim. "It's about adherence. The participants don't know how to use the products. You have to focus on drug levels—if a woman misses one dose out of seven, her tenofovir levels are wiped out."

Those who used the gel and had detectable drug levels in blood saw a significantly lower risk of contracting the virus. But subsequent tests of stored blood samples in 2014 found that only 30 percent of participants used the products regularly, and follow-up interviews found widespread inconsistency in use. Undeterred, researchers at CAPRISA and elsewhere are working to produce a PrEP product for women that isn't as dependent on user adherence. Current candidates include a vaginal ring and an injectable antiretroviral (ARV). The center contributed to one study called ASPIRE, which used a vaginal ring containing the experimental ARV dapivirine. Results published in February showed the ring modestly reduced the rate of infection by 27 percent

(*NEJM* doi: 10.1056/NEJMoa1506110). Another analysis of the ASPIRE data released in July at AIDS 2016 showed that, in those women who used it as directed, the ring reduced the infection rate by 65 percent across all age groups. Meanwhile, CAPRISA is also taking part in another, ongoing Phase III dapivirine ring study called MTN 020.

"We know the more you use a product, the more protection you have," says Quarraisha. "But even among high adherers, you don't get complete protection. What else is a factor? We know the amount of ART at the point of infection is important because commensal bacteria in the vagina are depleting the drug. So we have to look beyond adherence to the biology of women."

These considerations have led CAPRISA's researchers to investigate how the bacterial microbiome in the vagina may play a role in HIV infection, protection, and drug interaction. In a small, unpublished analysis of the vaginal bacterial community of 119 South African women, scientists recently found that an overgrowth of *Prevotella bivia*, an opportunistic pathogen, increased the chance of HIV infection 13 times over those with less or none of the bacteria. This may be due to the bacteria's release of lipopolysaccharide, an immune system stimulant that can increase genital inflammation up to 20 times and therefore make people more susceptible to HIV infection. *Prevotella bivia* has long been associated with bacterial vaginosis and pelvic inflammatory disease (*Clin. Infect. Dis.* 20, S271, 1995). Salim and his colleagues published studies last year that showed how the inflammation cascade, including elevated inflammatory cytokines in the female reproductive tract, recruit more HIV-susceptible immune cells to mucosal surfaces (*Clin. Infect. Dis.* 61, 260, 2015). Once there, they provide a target-rich environment for the invading virus (*Mucosal Immunol.* 9, 194, 2015).

Another cohort analysis showed how the complexities of the microbiome can impact the efficacy of HIV prevention approaches. A collaboration between the Public Health Agency of Canada, CAPRISA, and the University of Washington investigated cervicovaginal lavage samples from 688 women who took part in the tenofovir gel study and had 50 percent adherence to the gel application schedule as evidenced by monthly returned empty applicators. They found 188 unique bacterial species in the samples. Of these, the gel protected 61 percent of women who had a more typical genital microbiome dominated by bacterial species of the *Lactobacillus* genus, reported study team member Adam Burgener of the Public Health Agency of Canada during an AIDS 2016 session. But in women whose

microbial communities had shifted to become dominated by other non-Lactobacillus species, such as Gardnerella vaginalis, the protective efficacy was only 18 percent, which was not statistically significant. An unpublished follow-up study showed that G. vaginalis can absorb tenofovir, diminishing the drug's availability at the infection site. "It turns out that a healthy vagina is important for this prophylactic to work," says Salim. "So how do you make a healthy vagina? Can we supplement with Lactobacillus? And why does somebody's microbiome look one way versus another?"

This work has opened up new research pathways that could aid in creating more effective prevention approaches. Among a host of possibilities, Salim posits that combining antibiotics or probiotics with antiretrovirals could make PrEP more forgiving in the event a woman misses a dose. Of this new view into microbial interplay, Quarraisha said: "Here we are three decades into the epidemic and we are trying to find preventions in women when we haven't figured out some of the basics of women's biology. If the genital tract's health is playing an important role in infection, it behooves us to understand this better."

Pushing forward with new insight and greater hope

Walking through CAPRISA's clinic downtown and its headquarters gives a small view into how the organization and its research partners work. Within its headquarters, there is a lab that analyzes samples from a network of nine laboratories all over the country. The overflowing space is crammed with sequencers, refrigerators, shelves of reports, walls of cell-sorting machines, and microscopes of both the optical and electron type. One room is dedicated to performing cytokine analysis, another just for DNA preparation.

Taped to a hood, an illustrated procedure checklist shows the proper dissection and manipulation of cervical tissue. Salim notices a visitor reading it and comes over to offer some context. "We grow human vaginas here," he says proudly. "We get tissue from surgical theaters. We put HIV on them. We put drugs on them. It's all done here. We have equipment that would be the envy of any university."

Outside the laboratory's doors hang pictures of marching protestors taken during the Apartheid era. In one, the camera is focused on a young Salim, who fought against the system since his boyhood in Durban and through his days in medical school until it finally collapsed. That long battle is a fitting lesson about perseverance for the young scientists who pass the picture every

day, and then hunker down at their desks trying to find an exploitable chink in HIV's armor.

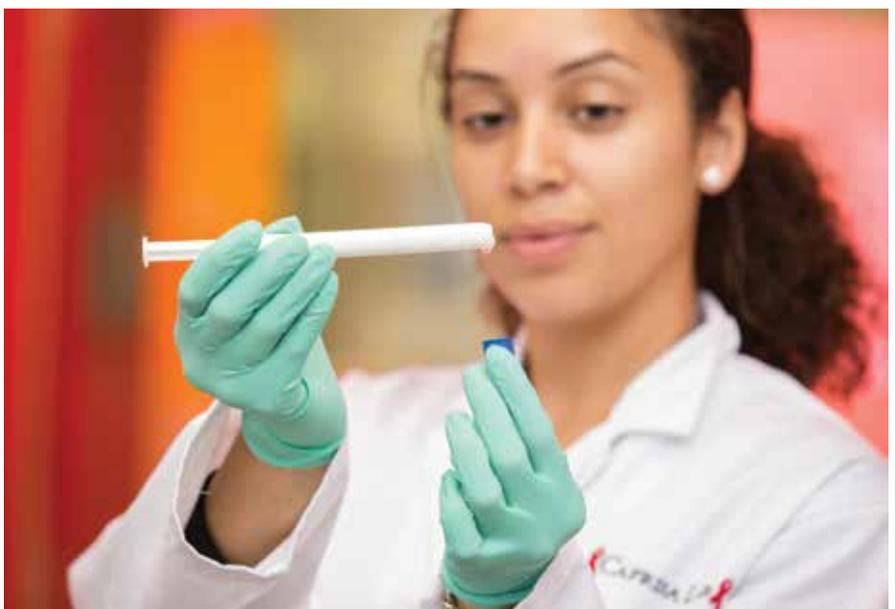
Taking several turns after the picture, the space opens up into a bullpen where graduate student researchers sit when not out at field sites working on their projects. Nearby, in an adjacent room cluttered with keyboards and denuded computer towers, information technology specialists are managing the raw information from previous and current trials that is growing every day. Back in the bullpen, giant blown-up front pages from international newspapers like *The New York Times* that trumpet the center's studies adorn the walls. They are likely meant to serve as inspiration to the young researchers. One from the *Times*'s Celia Dugger in 2010 heralded the results of the tenofovir gel trial as a promising tool that could empower women to keep themselves from getting infected.

A search for the ultimate

But to the Karims and the rest of the CAPRISA staff, any means of prevention that requires daily, monthly, or sexual-activity-based maintenance to impart protection from infection is not the ultimate breakthrough against the epidemic they're hoping to find. Of course, it is well understood that there will be no silver bullet against the virus, and multiple behavioral and pharmacological tools will need to be used together. Still, the most tantalizing aspect of their work, says Quarraisha and Salim, is the possibility of developing an effective and long-lasting vaccine to impart immunity against HIV.

To this end, CAPRISA has become a study site

Masters fellow Cheli Kambaran examines the tenofovir gel in the CAPRISA laboratory.





“I have never been as optimistic about our prospects of developing a safe and effective vaccine than I am today. Now that I see what we can do with these broadly neutralizing antibodies, I am full of hope.”

– Salim Abdool Karim

and research partner for several vaccine candidates. During AIDS 2016, the partnership running HVTN 100, a Phase I/II safety and immune system-response trial of the ALVAC/gp120 prime-boost vaccine candidate, released preliminary safety and immunogenicity data from the approximately 250 South African participants, of which 44 were given the experimental vaccine candidates at the eThekweni clinic. These candidates are similar to those tested in the RV144 trial in Thailand, which showed the combination was 31 percent effective at preventing HIV infection. The HVTN 100 vaccine candidates, however, were formulated based on HIV clade C, the more common strain across Africa. Based on the results of this trial, officials green-lighted the large-scale follow-on Phase III efficacy trial HVTN 702. CAPRISA intends to enroll 400 of HVTN 702’s 5,400 participants.

“People wonder how South Africa has made such an investment in finding a vaccine. It all started when we set up CAPRISA in 2001,” says Quarraisha. “This consortium let us follow cohorts before, during, and after infection.”

Salim is particularly excited about the burgeoning field of research into bNAbs, the class of immune system proteins that can target and destroy a wide range of HIV strains around the world and are being investigated as crucial components for a new crop of vaccine candidates. One multiyear study, called CAPRISA 002, continues to provide insights into HIV’s progression into AIDS and led to the identification of individuals who naturally made bNAbs (*Nat. Med.* 18, 1688, 2012). Investigation into how the immune system started producing these potent antibodies found they were triggered because a sugar molecule on the virus’s surface switched posi-

tions, opening up a window for a bNAb to reach the virus particles and neutralize them.

CAPRISA researchers isolated a family of bNAbs called CAP256 from a local schoolteacher who was a volunteer in the 002 study (*J. Virol.* 87, 4882, 2013). She was HIV free for several years over the course of the study period and then became infected. As the immune response evolved, they noticed she was making antibodies that targeted similar epitopes on the virus as in the RV144 trial (*Immunity* 38, 176, 2013). One study found that one of these antibodies, CAP256-VRC26.25, neutralized 70 percent of clade C isolates and 57 percent of various clade isolates (*J. Virol.* 90, 76, 2016). Salim said the promising bNAb should go into trials next year.

Right now, Salim says their work suggests a bNAb-based vaccine of this type would need to be given to a person every four months. But since the average time that girls and young women are vulnerable to infection is around eight to 10 years, he says that would translate to a total of no more than around 40 doses. “If we can protect these girls, then we can break the cycle of transmission,” he says. That is what Salim, Quarraisha, and the CAPRISA network are focused on for now.

“I have never been as optimistic about our prospects of developing a safe and effective vaccine than I am today,” says Salim. “Now that I see what we can do with these broadly neutralizing antibodies, I am full of hope.” ■

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.

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remained limited throughout the study period. Those who had previously received the Ad26 candidate had higher levels of immune response than those who had not, suggesting the Ad26 candidate had effectively primed the immune response.

Tomaras and colleagues also tested another prime-boost vaccine regimen in a study involving 184 South African participants (*PLoS ONE*, doi:10.1371/journal.pone.0161753). This regimen, an MVA vector-based prime containing genes encoding Gag, Reverse Transcriptase, Tat, Nef, and clade C Env HIV proteins followed by a Novartis-engineered subtype C envelope gp140 boost with an MF59 adjuvant, proved to induce the strongest peak neutralizing and binding anti-

body responses out of four vaccine regimens tested. Inclusion of the MVA prime contributed to both humoral and cellular immune responses, while a DNA-based candidate alone did not.

A path to remission?

In an unexpected twist, the study that garnered the most attention at HIVR4P was not about prevention at all. Rather it was about a treatment approach that led to sustained remission in NHPs. Just prior to the start of the conference, a study by Emory University and NIAID scientists revealed that ART along with administration of a mouse monoclonal antibody engineered for NHPs called Act1, which blocks the cellular receptor called $\alpha 4\beta 7$ integrin on CD4⁺ T

cells, had diminished SIV levels in infected monkeys to undetectable for as long as 23 months, even after they stopped all treatment (*Science* 354, 197, 2016). Their experiment started 18 infected macaques on 90 days of ART five weeks after infection. Then, nine weeks after infection, researchers initiated infusions of the recombinant monoclonal antibody on 11 animals every three weeks until week 32. The animals that received Act1 maintained “robust” virologic control for the rest of the study period, while viremia in the control group animals rebounded within two weeks. In addition, the experimental group’s diminished CD4⁺ T-cell count replenished to normal levels after ART and antibody treatment, a phenomenon not seen in the ART-alone group.

“Infusions of anti-alpha 4 beta 7 in nonhuman primates together with a course of ART post-infection with SIVmac239 induced long-term virological suppression following discontinuation of all therapy,” Anthony Fauci, a study author and head of NIAID, told an audience of hundreds during the conference’s first plenary. “CD4-positive T cells were restored in gut, blood, and certain peripheral lymphoid tissue.”

The $\alpha 4\beta 7$ integrin is known to be a homing receptor that lymphocytes use to migrate to the gut. For years, Fauci’s lab has been looking into whether HIV gp120 binds to $\alpha 4\beta 7$ on CD4⁺ T cells. In previous studies, they found that CD4⁺ T cells expressing high amounts of $\alpha 4\beta 7$ were preferential targets for the invading virus (*PNAS* 106, 20877, 2009). In 2014, Fauci’s group also found that targeting $\alpha 4\beta 7$ integrin prevented or delayed SIV transmission when given before repeat low-dose vaginal challenges (*Nat. Med.* 20, 1397, 2014).

How the antibody helped the study animals clear the virus for nearly two years remains unclear, but since August Fauci said they have been running an experiment to see if a similar effect will be seen in humans. They are performing a small open-label study of 15 to 25 volunteers using vedolizumab, a humanized anti- $\alpha 4\beta 7$ monoclonal antibody already approved by the US Food and Drug Administration to treat Crohn’s disease and ulcerative colitis. “These studies may provide insight into potential mechanisms that could be pursued in the prevention of HIV infection and/or the maintenance of sustained virological remission following interruption of ART,” said Fauci. “All of this in my mind as a human immunologist and HIV clinician will only be important if it works in humans.”

David Margolis, director of the University of North Carolina School of Medicine’s HIV Cure Center, who was not involved in the research, said he was as surprised as other experts in the field at the

study’s findings. “The work is impressive, and unexpected,” Margolis said. “This might lead to a way to prevent infection, or allow durable control of infection without lifelong antiviral drug therapy.”

Treatment is potent prevention

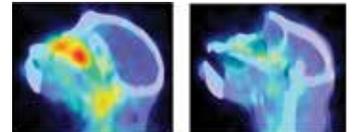
Another thread discussed at HIVR4P was the use of treatment as prevention. Myron Cohen, the University of North Carolina School of Medicine’s Associate Vice Chancellor for Global Health, offered more data from the HIV Prevention Trials Network (HPTN) 052 study at HIVR4P (*NEJM* 375, 830, 2016).

Cohen and his team analyzed data from almost 1,800 serodiscordant couples (where one partner is HIV-infected and the other isn’t) in nine countries and found a 93 percent HIV transmission reduction between partners when ART was started early compared to the late-starting ART group. This protective effect was stable over five years. “What’s really important is that we saw no transmission, zero transmission, when HIV replication was suppressed,” he said. “The only linked transmissions we saw were when the drug failed for whatever reason, and that was a rare event.”

The prospective, observational PARTNER (Partners of People on ART—A New Evaluation of the Risks) study found similarly good news (*JAMA* 316, 171, 2016). In this one, researchers followed 1,166 serodiscordant couples in 14 European countries and found no phylogenetically linked transmissions.

Cohen views the results of these treatment as prevention studies as just one of many rays of hope in defeating HIV. “Prevention research is really rapidly on the move. That’s the best way to look at it,” he said. “The ongoing studies in treatment as prevention are going to inform how to maximize this approach, and that’s exciting. Long-acting antiviral agents are almost certain to serve as critical new tools for treatment and prevention of HIV. The bNAbs are going to provide novel treatment and, in addition, they’re going to inform vaccine development in a way that’s not heretofore been possible. And, ultimately, all these new tools are going to lead to the kind of combination prevention that’s required to get to an AIDS-free generation.” ■

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.



This SIV-infected monkey shows far less virus (red-yellow) after treatment with an antibody to $\alpha 4\beta 7$ (right). Courtesy: Philip J. Santangelo/Francois Villingier of Emory University

Upcoming HIV-Related Meetings



JANUARY 2017

19th Bangkok International Symposium on HIV Medicine

January 18-20; Bangkok, Thailand

More information: www.hivnat.org/bangkoksymposium

FEBRUARY 2017

7th International Workshop on HIV & Women

February 11-12; Seattle, Washington, USA

More information: www.virology-education.com/event/upcoming/7th-hiv-women-workshop/

CROI 2017

February 13-16; Seattle, Washington, USA

More information: www.croiconference.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

APRIL 2017

HIV & Hepatitis in the Americas

April 6-8; Rio de Janeiro, Brazil

More information: www.hivhepamericas.org

Keystone Symposia: B Cells and T Follicular Helper Cells – Controlling Long-Lived Immunity

April 23-27; Whistler, British Columbia, Canada

More information: www.keystonesymposia.org/index.cfm?e=Web.Meeting.Program&Meetingid=1462

MAY 2016

Cold Spring Harbor Laboratory: Retroviruses

May 22-27; Cold Spring Harbor, New York

More information: meetings.cshl.edu/meetings.aspx?meet=RETRO&year=17

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

