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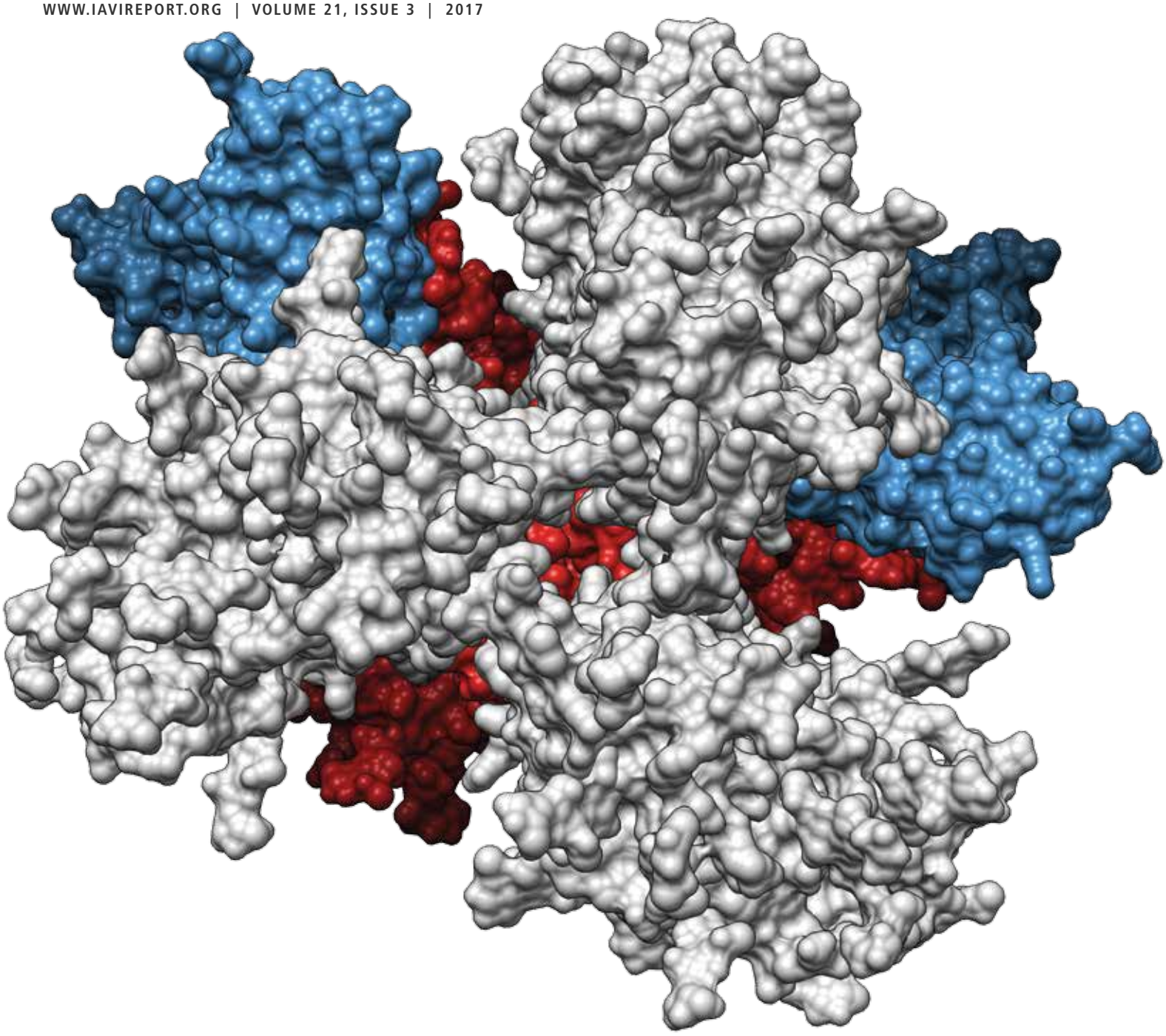

Research Updates from IAS Conference

Expanding PrEP in Kenya

Funding Concerns for HIV R&D

EDITOR'S LETTER

It is September again in New York City, which ushers in Autumn, sends kids back to school, and brings the United Nations (UN) General Assembly to the city for its annual meeting. Most of the HIV/AIDS-related stories coming out of last week's UN session touted significant progress in HIV/AIDS treatment.

As of 2016 there are 36.7 million people worldwide living with HIV. Roughly half of them are now receiving life-saving antiretroviral therapy. A major achievement to say the least, and newer and better drug options will now be available in many of the countries hardest hit by HIV/AIDS. There was an announcement during the UN assembly that two Indian companies will make the fixed-dose antiretroviral combination of three drugs (tenofovir disoproxil fumarate, lamivudine, and the newer drug dolutegravir, a combo known as TLD) available in 92 poor countries for only about US$75 per person a year. This will bring a newer first-line therapy to many more in need and may help alleviate the growing problem of drug-resistant virus that renders treatment ineffective.

But scientists, funders, and HIV prevention advocates who gathered at the New York Academy of Sciences on September 22, just after the a meetings finished, warned that this progress, while significant, is incomplete and fragile. There were still 1.8 million people newly infected with HIV last year, which is why HIV prevention remains paramount. Newer and better HIV prevention options, particularly those that are longer acting, are still sorely needed (see page 18).

At the same time, efforts to increase access to existing prevention strategies such as oral pre-exposure prophylaxis are underway. In this issue we feature a story about Kenya's valiant efforts to scale up PrEP access within the country's most at-risk populations (see page 13). We also detail the latest research presented at the International AIDS Society's conference this summer (see page 4), and talk with IAVI scientist Devin Sok about his research in HIV and beyond (see page 9).

Development of any new prevention options is, of course, dependent on continued funding, which is by no means a guarantee these days as governments struggle with competing priorities. Spending for HIV research and development seems to be on everyone's minds (see page 17). Some worry that success in rolling back HIV rates and expanding access to treatment may come at a cost. Mitchell Warren, executive director of the HIV prevention advocacy group AVAC, states it best: "These are great times but we shouldn't overstate success because the minute we do, funding dries up."

– KRISTEN JILL KRESGE

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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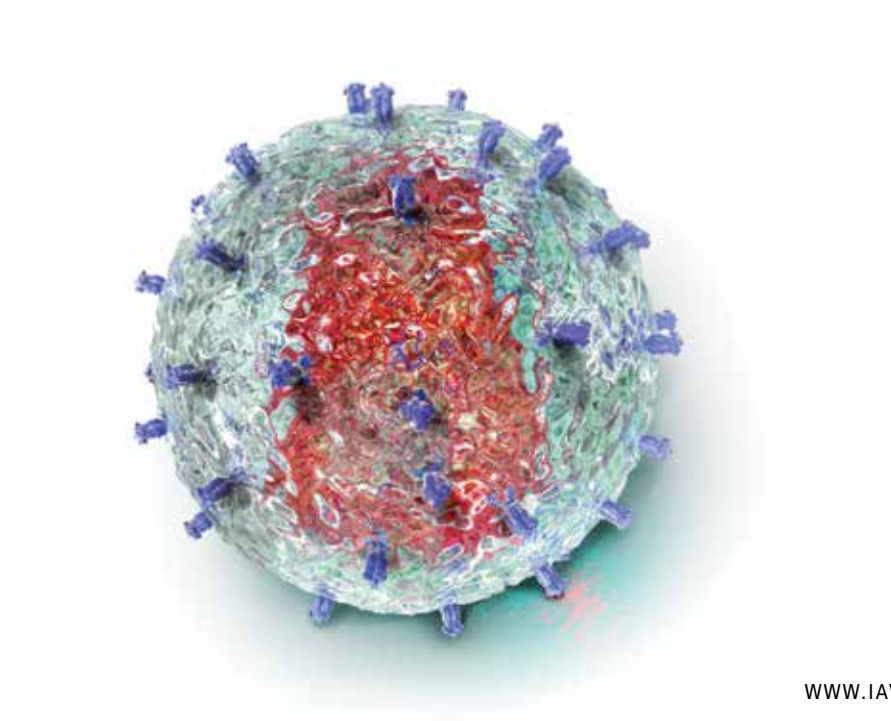

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[ON THE COVER]

Overall structure of a soluble HIV-1 envelope glycoprotein trimer in complex with the broadly neutralizing antibody PGT151. The gp120 and gp41 subunits of the trimer are depicted in white and red, respectively. The antibody (Fab) is shown in blue. The "native-like" ConM SOSIP trimer was generated at the Academic Medical Center Amsterdam for the EU H2020 EAVI2020 program and will be tested in experimental medicine trials in the near future.

Image prepared by Alba Torrents de la Peña, PhD candidate in Rogier Sanders' lab in the department of medical microbiology at the Academisch Medisch Centrum, Amsterdam, the Netherlands.

Decisive Moments in Wake of Paris

The themes and research brought up at the International AIDS Society's annual gathering may set the tone for years to come.

By Michael Dumiak

Glenda Gray, chief executive of the South African Medical Research Council and a well-known HIV researcher is, like most scientists, not given to hyperbole. Even so, Gray thinks that clinical trials either already underway or about to start this fall will set the stage for the design and development of HIV vaccine studies for the next decade. "The HIV vaccine field is at a pivotal moment," Gray told a large audience at the Palais des congrès in Paris, where the 9th International AIDS Society's (IAS) Conference on HIV Science took place over five humid and rainy midsummer days from July 23-27.

Whether or not these trials become heralds for the next decade, the Paris meeting underscored several themes that will play out in coming months and years and will likely set the direction toward developing an HIV vaccine.

New efficacy trials, but more vaccine concepts a must

The HIV epidemic is in the middle of its third decade. Life-saving antiretroviral therapy is accessed by more and more people around the globe, yet with concerns about the virus developing resistance to these therapies, and a less certain funding environment (see page 17), prevention remains paramount. "The ultimate control of the worldwide HIV epidemic will likely require the development of a safe and effective vaccine," says Dan Barouch, a founding member of the Ragon Institute and director of the Center for Virology and Vaccine Research at the Beth Israel Deaconness Medical Center. "Only four different vaccine concepts, though, have been tested for clinical efficacy in the 35-year history of the epidemic."

Barouch's team aims to add to that number. He came to Paris to report on some key data from ongoing experiments. Barouch's group and his partners at Janssen are approaching crucial points in a 14-year effort pursuing HIV vaccine candidates based on adenovirus vectors. The team is well into parallel preclinical studies as well as early-phase clinical studies in humans with their Phase IIa APPROACH, TRAVERSE, and ASCENT trials, gauging the safety, tolerability, and immunogenicity of a variety of vaccine formulations. All use a strain of the common cold virus, adenovirus serotype 26 (Ad26), as the priming vector. The vaccines also use either HIV clade C or clade M and C gp140 as the boost to increase antibody titers, as well as, in APPROACH, a modified vaccinia Ankara (MVA) vector-based boost in certain groups (see *AIDS 2016*, *IAVI Report,* Vol. 20, No. 3, 2016; *Science* **349** (6245) 320, 2015; *The Confidence Booster*, *IAVI Report,* Vol. 20, No. 2, 2016). The vaccine payloads are so-called 'mosaic' antigens, which are synthetic proteins derived by algorithm to be effective against the many different strains of HIV in circulation.

"The goal is to develop a global vaccine," Barouch says, meaning a single vaccine that is effective against multiple strains of HIV. In Paris, Barouch showed data from preclinical studies in rhesus macaques employing mosaic vaccine candidates like the ones which will be tested in humans. The results showed 66 percent efficacy in preventing infection following a series of viral challenges with an HIV/simian immunodeficiency virus (SIV) hybrid, or SHIV, while all the control animals became infected.

The study results are not yet published but Barouch reported in Paris that this study involved a group of 72 rhesus monkeys, which is significant in terms of size and cost. The idea was to conduct an

experiment that would parallel the A004/Phase IIa APPROACH study as closely as possible. Monkeys were inoculated with six different variations of the vaccine candidate, with 12 monkeys receiving each variant. All received the Ad26 Env/Gag/Pol prime, with differential boosts. The boosts consisted of Ad26 alone, Env protein alone, Ad26 plus Env, Ad26 plus MVA, and Ad26 plus both MVA and Env. There was also a 12-monkey placebo group. The vaccine components came from the clinical seed stocks at Janssen. The Env tested was clade C gp140 with alum as an adjuvant. The prime shots came at week zero and week 12, with the boosts at weeks 24 and 52, modeling APPROACH as closely as possible. Because the study employed HIV antigens instead of antigens against SIV, researchers challenged the animals with low doses of SHIV-SF162P3 six months after the final boost.

The results show that the monkey groups receiving Env protein boosts produced higher antibody responses than the groups receiving only vector immunizations. These groups also had the highest level of non-neutralizing functional antibody activity, as well as an augmented Tier-1 neutralizing antibody response. The MVA boost, for its part, increased T-cell responses. The group showing the best protection data against the SHIV challenge, Barouch says, is the one immunized with the Ad26 prime and Ad26 plus Env protein boost, with 66 percent of animals remaining completely uninfected through six challenges, or an equivalent 94 percent per-exposure risk reduction versus placebo. Barouch says one of the most important aspects of this large monkey study is that the responses and immune profiles in the immunized macaques are similar and comparable to those they believe are protective in humans.

Hanneke Schuitemaker, Janssen's head of viral vaccine discovery and translational medicine, was also in Paris to characterize the company's lead vaccine candidate, developed with Barouch, that should soon be heading into a Phase IIb efficacy trial. If everything proceeds as planned, Janssen will advance a regimen consisting of a four-valent Ad26-based double-prime expressing Gag/Pol and Env mosaic inserts, followed by a double boost consisting of a mix of the four-valent Ad26 candidate co-formulated in a one-to-one-to-one-to-one ratio with a clade C gp140 protein, and a clade C mosaic protein.

Schuitemaker says the APPROACH trial, which tested eight Ad26-based vaccine regimens, is producing data showing favorable safety and immunogenicity profiles. "All vaccine regimens that we tested were very immunogenic," she says. The upcoming Phase IIb trial will be known as HVTN 705, but first researchers are awaiting data from the TRAVERSE trial of Janssen's lead candidate, which should wind up in the next several weeks.

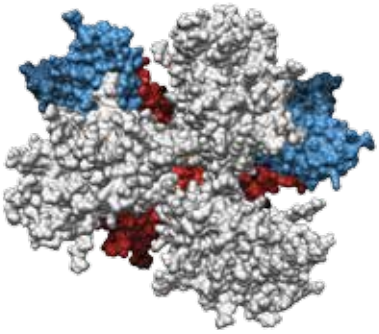
"We don't know whether this vaccine will protect humans," Barouch says. But the data to date, he says, supports moving the vaccine candidate into an efficacy trial, which the group hopes to start before the end of the year pending that last bit of crucial data. He also expressed his wish that there were more and different kinds of advanced studies taking place. "We need more shots on goal," he says. "We're delighted that multiple different vaccine concepts are moving ahead." Barouch is by nature confident but even-keeled—the HIV vaccine field is nothing if not humbling—and in Paris he allowed himself a bit of tempered hope. "These promising preclinical and early-phase clinical data, together with advances from many other investigators in the field, support a new sense of optimism that the development of an HIV vaccine might, in fact, be possible."

HVTN 702 update and EAVI progress

Another pox virus vector is of course under study in HVTN 702, the field's only ongoing Phase III efficacy trial. It is based on the canarypox and protein candidates tested in the RV144 study in Thailand, which is the only regimen to date to show any efficacy in preventing HIV infection—albeit a modest 31 percent. In Paris, Gray, protocol chairwoman on the HVTN 702 trial, described the aspirations for a perfect vaccine: it should be effective in a single dose, durable enough to provide lifetime protection, or at least protection for several years, should have minimal side effects, offer cross-clade protection, be administered simply and co-administered with other vaccines, and employ preparation and a supply chain that does not require special handling such as a long and intense cold chain.

However, an imperfect vaccine building on other imperfect vaccine strategies with moderate efficacy will suffice, Gray then told her audience with a smile. The 702 trial, started late last year, aims to build on RV144 and its follow-on study HVTN 100 by testing a clade C-specific candidate, a newly constructed protein boost, a new adjuvant, and an additional boost in a bid to make whatever immune responses are induced more durable. The scheme of the study calls for a prime with ALVAC-C, the canarypox-based vaccine, boosting with ALVAC and gp120 proteins, with the addition of an aluminum hydroxide gel adjuvant, and another booster at the 12-month

These promising preclinical and early-phase clinical data, together with advances from many other investigators in the field, support a new sense of optimism that the development of an HIV vaccine might, in fact, be possible.
– Dan Barouch



HIV Envelope trimer in complex with PGT151. Image courtesy of Alba Torrents de la Peña, PhD candidate at Rogier Sanders' lab in the department of medical microbiology at the Academisch Medisch Centrum, Amsterdam, the Netherlands. See full description, page 3.

mark, this one a GlaxoSmithKline-produced gp120 mix with a squalene-in-water emulsion adjuvant. Now 39 weeks in, Gray says HVTN 702 has enrolled 997 participants, averaging 26 a week, and is about to double capacity in the next phase. The study calls for 5,400 volunteers and its goal is to reach greater than or equal to 50 percent efficacy after three years. Results are expected in 2020.

Echoing Barouch's call for more vaccine concepts to undergo testing, Robin Shattock, a mucosal infection and immunity researcher at Imperial College London, was in Paris to keep an eye on all the options and to propose testing them more efficiently, a theme he's been touting for some time. "While studies are going on into these perfect vaccines," says Shattock, referring, partly tongue-in-cheek, to the HVTN 702 regimen, "if they fail to realize the level of efficacy that the investigators would hope to reach, we need some alternatives." Shattock is now in a place to develop potential alternatives as coordinator of EAVI 2020, the European Commission-backed European AIDS Vaccine Initiative, which launched last summer with about US$20 million in seed funding for basic research.

"It's prudent to have approaches that can continue irrespective of what the findings of the [current] trials are, and if they are spectacular, we can move on to something else," he says. Shattock endorses the use of experimental medicine trials of promising HIV candidates. "These are not different from Phase I studies—they are still about safety—but they are specifically designed to test hypotheses, and they do not have the purview of being part of a product development strategy," he says. "That means in some ways they can move faster and be smaller scale and that allows us to accelerate some of the things we want to do."

With funding becoming more and more fraught, Shattock expects it to become harder to put more candidates into efficacy trials. Better prevention technologies, such as oral pre-exposure prophylaxis, should also bring down incidence of HIV, which will make it necessary to do larger and larger efficacy trials to gather data properly. This will be more expensive. "We will still urgently need an HIV vaccine. That sense of urgency needs to be maintained," he says. "Refining vaccines early in the pipeline makes sense."

Shattock says these efforts should speed development and decrease risk of late-stage failure in other trials; address questions that can't be definitively answered in animal models; and enable validation and sequential iteration for structural design, of which there has been an extreme blossoming of late. "The bottleneck now is getting those design concepts into humans," Shattock says. Hypothesis testing of novel concepts prior to formal product development should be the purview of experimental medicine trials, with results set up to deliver in-depth analysis of human immune and antibody repertoire responses. And they should involve the kinds of intense sampling of blood, mucosal layers, lymph nodes, and bone marrow that are impractical in large-scale studies.

"We have no vaccine that produces any neutralizing antibodies of any breadth in humans, so a lot of work needs to be done to start changing immunization schedules that may go out for many years to types of schedules applicable to a real-world setting." Shattock is particularly interested in utilizing experimental medicine trials to evaluate recombinant trimers that resemble HIV's native Env structure and to understand how they can be used through sequential immunizations or as defined cocktails to drive B-cell responses towards neutralizing breadth. The idea is to be able to reproduce the chain of events that happens in those very rare infected people that produce broadly neutralizing antibodies (bNAbs), but to do it proactively in vaccinated individuals in a compressed period of time.

One approach that EAVI participants are pursuing is the use of a series of trimers isolated from an infected individual that developed bNAbs within a period of months. Shattock and the EAVI team (see *Europe Invests in HIV Vaccine Research*, *IAVI Report*, Vol. 20, No. 3, 2016) are currently producing a recombinant protein every six months, Shattock says, in service of creating a pipeline sufficiently nimble and cost effective to get things into trials faster. Some 18 months into the EAVI program, teams in Rogier Sanders' lab at the Academisch Medisch Centrum in Amsterdam and Quentin Sattentau's lab at Magdalen College in Oxford are preparing two candidates based on a consensus Env sequence, one that is meant to provide coverage against the majority of circulating HIV strains. These stabilized trimers will be manufactured in small batches in Austria by a company called Polymun. The trials will be Phase I safety and immunogenicity studies involving between 30 and 50 volunteers. Shattock says the first trials will examine the B-cell repertoire response, or how the protein subtypes in the adaptive immune system react toward the protein candidate after exposure. "In later developments we'll look at lineage design approaches or approaches to broaden the response," he adds.

Shattock is keen to close the loop between human trials and structural vaccinology. "We

can link structural design to human immunogenicity and have an iterative cycle where the human response can feed back into the structural biology, and we can design better immunogens to elicit the type of responses we want to achieve."

Moove over mice!

Things might look quite different, though, if humans made antibodies like cows. "They make fantastic antibody responses, very quickly, with broadly neutralizing activity," Shattock says.

Shattock and everyone else knows this thanks to recent experiments conducted by researchers at IAVI, The Scripps Research Institute (TSRI), and Texas A&M. It all started with a discussion between Devin Sok, director of antibody discovery and development at IAVI and Vaughn Smider, a bovine antibody expert and protein engineer at TSRI. Sok had been exploring and characterizing antibodies in rabbits, mice, and guinea pigs, but after discussions with Smider began thinking about cow antibodies. Smider has been studying cow antibodies for some time. Bovine antibodies have unusually long and diverse protein chains as part of their antigen recognition sites. "We thought, well, why don't we just immunize the cows and see if we generate antibodies," Sok says.

The two pressed ahead, and the results are impressive (*Nature* **548**, 108, 2017). "The level of response—the titers that we saw, how potent the serum was against the virus—I've never seen that before," a still-amazed Sok recalls. He participates in IAVI's Neutralizing Antibody Consortium and has seen neutralizing antibodies developed and isolated in both humans and animal models, but there was something special about what was happening in cows (see *Stumbling on Greatness*, page 9). "Seeing that against one virus, and then seeing it span across multiple viruses…" He trailed off. "We've been trying to work on this forever. This is the first time we've seen that it actually did work. It's exciting."

Sok and Smider immunized four cows—Holsteins (two steers, two heifers) at Texas A&M—with the BG505 SOSIP HIV Env glycoprotein, an engineered immunogen that maintains the trimeric structure of native HIV Env. All four cows developed immune responses and did so quickly. After 42 days, a longitudinal serum analysis for one cow shows 20 percent neutralization breadth against 117 cross-clade isolates. At 381 days, serum analysis for the same cow showed 96 percent neutralization breadth against the same 117 isolates. A single monoclonal antibody isolate from the cow neutralized 72 percent of the cross-clade range. It also showed the unusually long chain characteristic to bovine antibodies that drew the attention of the two researchers in the first place. One of the antibody's heavy chains reached 60 amino acids in length. A typical human antibody heavy chain reaches 17 or 18 amino acids. All four cows developed robust and reliable responses, Sok says.

"The hypothesis is that cows have these four stomachs full of bacteria," he says. "The thinking is that cows have these long antibodies to maintain that microbiome, which could be full of pathogens. That's a hypothesis. We haven't tested any of that."

Global media grazed contentedly for days on the cow study, but Sok and fellow observers in Paris are roping in expectations. The ease with which cows developed a broadly neutralizing antibody response is noteworthy, but it's just a starting point. If, however, it becomes possible to create long-chain antibodies in humans, that could be a stepping-stone to more effectively inducing broadly neutralizing antibodies against HIV.

Common cause with cancer research?

At the beginning of September the US Food and Drug Administration approved its first-ever gene therapy, a chimeric antigen receptor-based treatment for pediatric B-cell acute lymphoblastic leukemia. Carl June, a University of Pennsylvania cancer immunotherapist and one of the lead researchers in developing this "living drug" that will be marketed by Novartis under the name Kymriah, earlier this year gave an address in Seattle at the Conference on Retroviruses and Opportunistic Infections in which he both described this antigen receptor-based treatment, and called on the HIV research field to more closely explore the techniques which produce these chimeric antigens, or CAR-T cells. The overlap and potential benefit from commonalities in both cancer and HIV research became even more explicit in Paris, featured in a special day-and-a-half-long forum on cancer and HIV cures.

A CAR-T cell is engineered to bind to the protein CD-19 expressed on B cells. Acute lymphoblastic leukemia causes overproduction of B-cell lymphoblasts in bone marrow which then multiply, causing a corresponding dropoff in the production of healthy red and white functioning blood cells and platelets. The CAR-T works by killing those B cells that are malignant, while at the same time suppressing molecules that had previously allowed the cancer cells to evade detection. The immune system's existing T cells are also reprogrammed by the engineered CAR-T to go after the cancerous

cells. As the modified T cells kill indiscriminately, normal B-cell function is replaced by an antibody therapy of gammaglobulin injections.

June was stirring with his case in Seattle, saying advances in cancer immunotherapy and gene therapy will provide methods that can be adapted for HIV. This remains to be seen—there are several aspects about CAR-T technologies that may not be equally matched to the challenges posed by HIV. But cancer research as a whole, some of the leading lights in both fields said in Paris, maps over HIV more than enough that it is worth a more determined effort to find areas of collaboration and common ground.

"When you talk about draconian ways to modify a disease when you have a pretty simple way to do so—namely, if you have a sensitive virus like HIV and you can suppress it one pill a day forever and not worry about it—the question is, should you put resources into something like gene editing?" asked Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases at the US National Institutes of Health (NIH). "I think the answer is yes."

Fauci was part of a roundtable discussion in Paris on cancer and cure research. "You want to push to the point of proving a concept. Once you prove the concept, you try to simplify it so it is scalable," he says. About 36 million people in the world live with HIV. More than half of them have access to antiretroviral drugs. About 17 million, however, do not. "If you have an intervention that is not scalable, it is interesting, but it is not going to address the global epidemic," Fauci says. "We should not let that take away the importance of pursuing it. You never know whether you are going to be able to get it to scale. That's why the NIH supports this kind of research."

Sharon Lewin, an infectious disease physician and director of the Dougherty Institute at the University of Melbourne, Australia, is monitoring a select number of HIV-infected patients who are also burdened with cancers, a set of illnesses that appear ready to increasingly beset the HIV field as the HIV-infected continues to age. There are wholesale changes in how oncology researchers are pursuing immunotherapies and gene therapy, with more than 1,000 clinical trials underway pursuing checkpoint blockers, interferons, and the rebuilding of adaptive immunity, fields which all have either tangential or direct uses for HIV research.

Given the wide variety of cancer immunotherapy and gene therapy initiatives, Lewin expressed a widespread concern for the HIV world, which is the issue of toxicity. "We really worry about it in these interventions," she says. The tolerance for potentially toxic treatments is much different for a patient facing a terminal cancer diagnosis than one beginning a burdensome but much more manageable course of lifelong antiretroviral therapy (ART). She and Fauci, though, see a clear need for more collaboration between to the two fields. Fauci suggested HIV labs take on a young postdoc with cancer training if the opportunity arises. "When HIV started it was all virologists who were involved," he says. "One day we thought: 'maybe, we need some immunologists.' It's the same thing."

The University of California, San Francisco's (UCSF) Steve Deeks, a prominent researcher in the HIV cure field, was also in Paris, where he and UCSF colleague Timothy Henrich presented research on two HIV-infected individuals examining whether extremely early initiation of ART leads to temporary remission or even cure. The small-scale study showed HIV relapse despite starting treatment at one of the earliest stages possible of HIV infection. While the treatment did lead to nearly complete loss of detectable HIV in blood and tissue, it did not lead to remission without treatment—perhaps due to the persistence of the reservoir.

This was not the case for a South African girl. The University of Witwatersrand's Avy Violari and pediatrician Mark Cotton of Stellenbosch University presented a rare case of remission in a nine-year-old girl, who has had undetectable levels of HIV for the eight-and-a-half years since she stopped ART 40 weeks after being diagnosed with HIV at the age of one month.

This immediately made global headlines, as the South African girl is one of only three to report a long-lasting remission so far. Only one, the "Berlin Patient," Timothy Brown—who was in Paris for the IAS meeting—remains HIV free, and he underwent a grueling bone marrow transplant because of concurrent acute leukemia. The South African girl is remarkable in many ways, including her youth. Violari says they can only detect traces of provirus in the girl. "By studying this case, we hope we will one day understand how it's possible to stop treatment."

While many expressed delight over this report, other cases of remission reported to date ended with individuals needing to resume ART, most notably the Mississippi baby. While these lightning-in-a-bottle cases are rays of light and strike hope about the possibilities of an HIV cure, for now, in any case, they leave researchers with little more than wonder. ■

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

Stumbling on *Greatness*

By Kristen Jill Kresge

When you talk with Devin Sok, the 30-year-old director of antibody discovery and development at IAVI, you get the feeling you are speaking with someone much wiser and more experienced than his age suggests. Looking at his docket of projects or lengthy list of scientific publications might lead you to the same conclusion.

Sok came to The Scripps Research Institute (TSRI) in La Jolla, California, in 2008 to pursue his PhD in organic chemistry. He landed, somewhat serendipitously, in the laboratory of Dennis Burton, co-chair of the Department of Immunology and Microbiology at TSRI and scientific director of IAVI's Neutralizing Antibody Center.

For years, HIV researchers had only a handful of antibodies at their disposal that could neutralize a broad range of the many HIV isolates in circulation, so-called broadly neutralizing antibodies (bNAbs). Just as Sok joined Burton's lab, things changed dramatically. Burton's group and colleagues at IAVI had just published in *Science* on the isolation of a duo of much more broad and potent bNAbs that were isolated from an IAVI cohort of HIV-infected individuals. A research team at the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases (NIAID) also began identifying new bNAbs soon afterwards. The isolation of this new generation of bNAbs was followed by a feverish period of antibody discovery and characterization, setting off a new course in HIV vaccine development that continues today.

Now, with hundreds of bNAbs to work with, several of which have been shown to block infection in animal models, research in this area is booming. These bNAbs are providing vital clues that can be exploited for vaccine design. Clinical trials are also testing whether direct administration of one of these antibodies can prevent HIV infection in uninfected volunteers, what is referred to as passive administration.

Devin Sok

For Sok, the timing was superb. He quickly immersed himself in the world of these antibodies, which became the focus of his PhD work. It turns out that HIV was a natural fit for someone whose undergraduate chemistry work focused on sugars—the outer surface of HIV is one of the most heavily sugar-coated or glycosylated viruses identified. Sok is now actively supporting efforts to develop vaccine immunogens capable of inducing bNAbs, engineering these antibodies so they are more potent and last longer in the body, and working with new animal models. His latest publication showed that cows can very quickly develop bNAbs after immunization with an engineered HIV protein, garnering headlines and inspiring many puns; I won't milk the story for any further jokes. He is also using all of the knowledge and techniques amassed in studying HIV antibodies to see if there are other areas that can benefit from similar approaches.

In our recent interview, we talked about all of these projects and also what it is like being a young researcher in this challenging and dynamic field.

How did you come to Dennis Burton's laboratory and become involved in HIV immunology research?

Well, I started at Scripps for my PhD. As an undergrad I studied chemistry, specifically organic chemistry, with a focus on sugars, or glycans. I chose to go to Scripps to do organic chemistry, and I chose Scripps just because it was an interdisciplinary place in case I wanted to switch more into biology.

When I first started out I was doing some glycan chemistry and jumped around to a few labs and couldn't find something that I was really excited about. I was actually on the verge of leaving Scripps and moving to another institute because I couldn't find something that I wanted to do. I had everything in motion to make the jump and move

and this PI [principle investigator] who I was communicating with whom I was planning on moving to—he was based at Harvard in Boston—he recommended seeing one more person before I left Scripps. And so I decided to look up who else was available and found Dennis's lab's website primarily because of my interest in sugars and glycans. HIV envelope is a unique protein in nature in that half its molecular weight is covered in sugars, so I thought that was interesting. So I decided to meet with Dennis and talk to him a little bit about the science and see whether or not it would be a good fit. The meeting obviously went well. He had a lot of exciting projects and challenges and so I decided to try it out for a few months.

I joined Dennis's group when Laura Walker was still in the lab and this was when the first papers on the next generation of broad neutralizing antibodies were being published. I came in right as all that was coming out and so it ended up being a really exciting place to be and all the people in the lab are super smart. It was just completely out of what I was used to and had been exposed to at that point. It was just a really difficult challenge that seemed really fun.

Sounds like luck was on your side coming into the lab at such an exciting time.

Yeah, I know. It was crazy.

Nowadays it seems you are juggling many different projects in the lab, both related to those early discoveries of broadly neutralizing antibodies and beyond that. Can you walk through what some of your work involves now?

Because of my chemistry background I think about antibodies as just protein molecules, so this was an area I quickly became interested in. It is a scale of science that I could understand. So the bulk of my PhD was focused on these new broadly neutralizing antibodies for HIV and understanding how the antibodies work and the epitopes that they target, rather than focusing more on HIV itself. There is a whole lot of work that I did related to isolating new antibodies.

That has now evolved. Now there is less interest in trying to isolate new antibodies to HIV and more work that needs to be done to evaluate antibody responses to the different immunogens that are being developed at the Neutralizing Antibody Consortium [NAC], and so that's another big effort that I am focused on. One question I grapple with is how do we determine whether or not the immunogens that we are testing in different animal models are eliciting the right antibodies, and how do we get at those details? And through that process, I'm trying to expand more into more antibody discovery in other areas. Now that we have these tools that we developed for discovering antibodies for HIV, the question then is, how can we apply these tools to other disease areas? So that's another area I'm interested in pursuing. We just submitted a proposal to DFID [UK Department for International Development] to identify monoclonal antibodies to treat snakebite, which affects up to 5 million people in the world. The current therapies for snakebite are from the late 19th century and haven't really changed much. It is one of the areas where we can apply these technologies that we developed and have the potential to make a really big impact. I'm excited about that.

And then we have another project where we are trying to engineer HIV antibodies for different applications. We're, of course, also using these antibodies to understand the virus and to develop a vaccine against it. Simultaneously we are exploring ways to use the antibodies themselves for therapy or as a prophylactic, so we're trying to engineer and improve these antibodies, which is another area that I'm focused on.

Now that there are so many antibodies available to work with, and as they target various spots on the virus, what is the most promising avenue of research in your opinion toward designing a vaccine immunogen that could induce these?

That is a very good question. Multiple groups have taken different approaches to trying to elicit these antibodies by vaccination. The more we're exploring, the more we learn.

From my perspective, I feel that the germline-targeting approach is a very elegant approach, and I do think it has a lot of potential. I think the great thing about the germline-targeting approach is that it is ultimately very universal. You can apply that approach and that technique to any other disease area so I think there is a lot of potential there, not only for making a significant impact against HIV, but also elsewhere. But I still think we all would be happy if there was a magical Envelope trimer that someone identified that was able to elicit all HIV antibodies.

What other areas might benefit from a germline-targeting approach? Would it only be useful for viruses for which antibodies must be heavily mutated to be capable of broad neutralization as they are for HIV?

With the majority of infectious diseases or viruses we have, if we can create an inactivated version of that virus or if it's not very variable, that is it is rela-

tively conserved, then we can just put it into a person and they will develop protective antibodies and we don't have to worry about it.

But for viruses that are variable—for example influenza virus or hepatitis C or any other potential virus that might emerge that would be highly variable like HIV—these approaches can't be used, so in those cases a germline-targeting approach might be beneficial. Because ultimately what the germline-targeting approach is trying to do is to manipulate our immune system to elicit a very specific antibody response, instead of just having a bunch of random antibody responses. I think that has important utility for a lot of pathogens that are highly variable.

For example, if we want to create a universal flu vaccine, we've identified conserved epitopes on influenza and if we can redirect our immune response to just hit those conserved epitopes then we wouldn't have to take a shot every year to protect us against influenza. That's one example.

Is this something your lab is currently exploring?

Yes, I think there is general interest in tying these approaches with influenza and malaria. The main focus is on HIV, and then we will do whatever we can elsewhere.

One topic that seems to keep coming up is this idea of the glycan holes in HIV's surface and their role in vaccine development. As someone who specialized in glycan chemistry, how would you describe the importance of glycan holes in HIV Env and their utility in vaccine design?

I feel like it's one of two things: it's either going to be, to use the pun, a rabbit hole, where it would just be a distraction, or it will be useful in increasing the immunogenicity of conserved sites. So it could be, for example, like the glycan hole that was described for BG505 SOSIP, that it is in a region that isn't present on all the other viruses. So we can develop antibodies against that hole, but whether or not that's useful in the context of protecting against other viruses is really the question.

In other cases, if you can create a hole around these conserved epitopes defined by these broad neutralizing antibodies, the question is can you redirect immune responses against these conserved sites? I think we are still evaluating whether or not creating holes around these sites will improve antibody responses against them. They might be effective for some epitopes and not for others, so there's still a lot of exploratory work that we could do in this area.

And then, of course, we can't forget the cows. You recently published a study in *Nature* on the induction of broadly neutralizing antibodies in cows. Were you surprised by all the jokes and puns people can make about cows?

They were very funny … I loved it.

How did you first get involved with these experiments and what is their significance for HIV vaccine development?

As I mentioned before, I chose to come to Scripps to do my PhD because it is such an interdisciplinary place and there are so many different really good people working on a bunch of different areas. Cow antibodies happens to be something that a professor at Scripps was focused on. Through working with him, we knew that cows have these unique antibodies that have ultra-long loops of CDHR3. A lot of the broadly neutralizing antibodies against HIV that we've identified also have these long loops. After the discovery of the BG505 SOSIP trimer, it was tested as an immunogen in animal models, but it wasn't able to elicit broadly neutralizing antibodies. So the question was, is it the immunogen that isn't working or is it the fact that we just don't have the right antibodies? So we decided to test the BG505 trimer in cows that have these long loops to see if we would we get broad neutralizing antibodies. And the answer is yes.

I think, in a couple ways, this finding is important for vaccine design. First, I think in all cases in science and technology, we just need to make something work first, in any system, in any case, so that we can learn how it works and then we can figure out how to apply that to make it work in humans. In this case we tried immunizing guinea pigs, rabbits, and monkeys, but we weren't able to elicit any broadly neutralizing antibodies. For the first time we were able to do it in cows. By being able to show that we can do it by immunization in this animal model, we should be able to learn things that we can then apply to humans.

I think one of the specific things that this cow study was able to do was show us that we should focus on this concept of enriching for these long loops in humans because it should make it easier for us to elicit broad neutralizing antibodies by vaccination. So I think that becomes a specific thing that we can focus on and try to achieve.

Any ideas for how that could be accomplished?

I don't know, but that's something we can start really, really thinking about.

What do you think about the idea of an HIV vaccine trial in infants or adolescents because it seems they may be more likely to develop broadly neutralizing antibody responses than adults?

It is very interesting. I know that in South Africa there have been reports of children who are infected through mother-to-child transmission and in their adolescence have a higher likelihood of developing these antibodies and developing them fairly quickly. So I do think that's a new area that definitely needs to be explored to understand why that is. I think there are probably a few hypotheses to why that could be, but I think it's definitely going to be really exciting to look at.

Another area you mentioned working on is the use of these antibodies for prophylaxis. What are your thoughts about their role in prevention?

That's exactly what the proposal I'm currently working on is about. I think there is a lot of potential in the use of these antibodies for prophylaxis. At the International AIDS Society's Conference in Paris this year, Tony Fauci [head of NIAID] gave a talk on the idea of a prevention toolbox; that there's no one drug that can take care of everything and that we should have a list of options so that people could choose what they want to do.

In the case of these antibodies, I think they potentially only need to be administered monthly or even bi-monthly, and if we can engineer them in the right way, you might be able to give them once every six months. If that's the case then you solve a lot of issues with regards to compliance. So instead of having to take a pill every day, as you do with oral PrEP [pre-exposure prophylaxis], you just go in for one injection and it will last you for a long time. One of these antibodies, VRC01, is currently being tested for prophylaxis in the AMP trial and I think there is going to be a lot of things that we can learn from that clinical trial. I'm glad that it's happening. VRC01 is a very broad antibody. It covers a lot of viruses. But it's not the most potent antibody so I think there is a lot of potential for these new antibodies that are very potent to also be used for prophylaxes. The biggest hurdle with antibodies is going to be cost. But it really just comes down to the dose, which is affected by the potency. For VRC01 they are testing two different doses—30 mg/kg and 10 mg/kg. But if you have an antibody that is a hundred-fold more potent than VRC01, then you might be able to get away with only giving one mg/kg, or even less. If that's the case then the cost for manufacturing is really, really low. The more that we can improve the potency of these antibodies, the more likely it will be that they can actually be used for prevention. The benefits are very clear—being able to give the antibody once every six months would be a huge benefit for compliance.

Is engineering these antibodies for greater potency another area that is applicable to different diseases?

Definitely. Trying to engineer these antibodies for greater potency and then also engineering the antibodies so that they stay in your body longer, a longer half life, those are things that can be directly applied to any other disease area. I think that's the exciting part about being in HIV. You are working on things that are at the forefront of research that could be applied to some other diseases and have high potential for public health impact.

How would you describe your experiences as a young researcher in the HIV vaccine field, particularly working within the various networks that you are involved in?

It has been really exciting. I have been so lucky and so fortunate to have fallen into a good position, being in Dennis's lab and being connected with a really good network of researchers. I've learned a lot and I feel like my skill sets in science have been honed and nurtured by both NAC and Scripps investigators. I have been constantly learning new things, and so, as a young investigator, it's been the ideal experience.

It is a very fast-paced field, it takes a lot to keep up, a lot of hard work. But when you are working with people who are really good at what they do, it makes it fun.

I do wish that the opportunities that were given to me were accessible to more young investigators, and that there were more positions for young investigators to go into. I've been lucky to be able to continue the work that I do in different capacities through IAVI, but that's not necessarily open to other young investigators. And I do think the fight towards an HIV vaccine is going to be a long one, unless we have some dramatic breakthrough, so the investments in these young investigators are going to be really important to keep the momentum going in the future. I try to talk to everyone—funders and policymakers—about young investigators, what we can do to keep them involved, and have positions for them to go into, especially because funding is so difficult and will potentially be even more difficult in the future. ■

PrEParing to Prevent HIV

Kenya strikes out as a leader in offering a recently proven HIV prevention method to men who have sex with men and others at risk of contracting the virus.

By Mary Rushton

In May, the Kenyan government launched a nationwide program making pre-exposure prophylaxis or PrEP—the use of daily antiretroviral drugs (ARVs) to prevent HIV infection—available to 500,000 individuals over five years to reduce their risk of acquiring the virus.

The 84-page PrEP implementation plan, developed with the help of over a dozen national and international partners, is the country's latest weapon against an epidemic that while waning, is still stubbornly persistent. Oral PrEP will be available in 28 of Kenya's 47 counties that account for 90 percent of the country's HIV/AIDS cases.

The East African country has also taken the unusual step of combining PrEP rollout with an unprecedented effort to make HIV self-testing kits available through public and private health facilities and select pharmacies for around US$8 each. The aim of the so-called "Be Sure" campaign is to try and remove common impediments, including stigma, inconvenience, concerns over confidentiality, and lack of transportation that discourage men who have sex with men (MSM), female sex workers (FSWs), and other individuals at elevated risk of contracting HIV from getting tested.

Kenya hopes to reduce the number of HIV infections among adults by an astounding 75 percent within two years, but to do so will require heavy-duty outreach and implementation of PrEP to anyone at substantial risk of contracting the virus, including those whose behaviors run counter to sodomy laws that date back to the British colonial era.

PrEP efficacy

The use of the ARV Truvada—a single pill combination of the ARVs tenofovir and emtricitabine—was first proven 44 percent effective at reducing HIV infection rates in a randomized, double-blinded placebo-controlled trial of 2,500 MSM and transgender women who have sex with men from the US, Brazil, Ecuador, Peru, South Africa, and Thailand (*N. Eng. J. Med.* **363**, 27, 2587, 2010). Two subsequent trials conducted in Europe, which were not placebo controlled, established Truvada's efficacy at 96 percent in preventing HIV infection in MSM and transgender women. Together, these trials led to the approval of oral PrEP by US and European regulatory authorities.

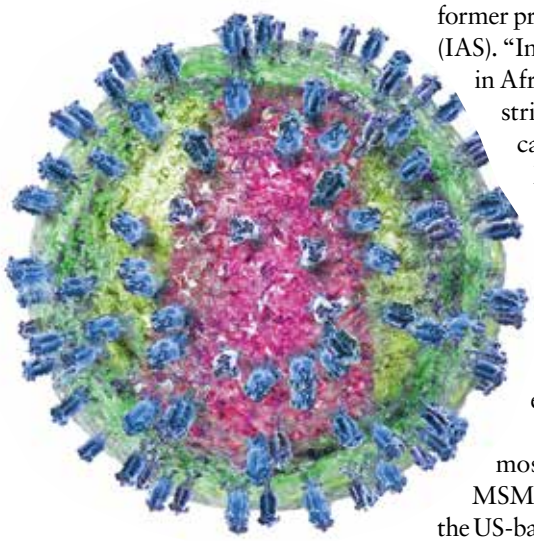
PrEP is now part of an array of HIV prevention options available in Kenya. Others include condoms, adult male circumcision, risk reduction counseling and testing, and treatment as prevention—the early initiation of ARVs to not only treat the virus, but also reduce the rate of viral transmission (see *Guidelines on Use of Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Kenya*, *NASCOP*, 2016 edition).

Kenya is not the first country to put in motion efforts to increase PrEP use. In December 2015, South Africa approved Truvada for use as PrEP by MSM, transgender persons, heterosexual men and women, adolescents, and injection-drug users (IDUs; *S. Afri. J. HIV Med.* **17**(1), Art. 455, 2016). Five months earlier, the US made Truvada part of its National AIDS Strategy for HIV prevention for MSM, transgender women, serodiscordant couples

(those in which one partner is HIV infected and the other isn't), and "others documented to be at elevated risk of acquiring HIV through sexual activity" (see *The National HIV/AIDS Strategy: Updated to 2020*, White House Office of National AIDS Policy, July 2015). France also began offering PrEP within its national health care system in January 2016.

What is surprising about Kenya's PrEP program is the level of engagement within the MSM community. Like prostitution and injecting drugs, homosexuality is considered illegal under the Kenyan Penal Code, punishable by up to 14 years in prison. Yet Kenyan authorities are remarkably forward thinking when it comes to recognizing the drivers of the HIV epidemic in their country and in implementing programs to help halt its spread.

"Kenya is really showing leadership here and that is encouraging," says Chris Beyrer, an epidemiology professor at Johns Hopkins University and former president of the International AIDS Society (IAS). "In 2013 we did a regional meeting on MSM in Africa that Kenya agreed to host. It was very striking that the national and local officials came. The physician who was heading the key populations program at the time for the Kenya Ministry of Health was very outspoken, saying that Kenya has a high burden of HIV and that they needed to do better and needed to consider PrEP. Most governments were not willing to say those kinds of things even if researchers were already saying that."



Even more than a decade ago, while most countries in Africa were overlooking MSM in assessing the impact of the epidemic, the US-based Population Council in New York surveyed the sexually transmitted infections (STIs) and HIV risk of MSM in Kenya with the blessing of Kenyan hospitals and research institutions. Recognition of stigmatized communities grew from there. In 2010, the government in partnership with the Joint United Nations Programme on HIV/AIDS (UNAIDS) hosted the first national symposium for key populations in Mombasa at risk for HIV/AIDS, including MSM. That same year the country's health secretary launched a website offering MSM sensitivity training for Kenyan health care workers.

This outreach with the MSM community has not always been well received, however. Researchers in Kenya have faced retribution. Seven years ago, angry mobs descended upon an HIV clinic in the coastal town of Mtwapa and attacked it for its involvement in MSM research. Then in 2014, police raided and arrested workers at a men's health and HIV/AIDS advocacy organization in Kisumu for illegally "practicing sexual orientation information" (*Nature* **509**, 274-275, May 15, 2014).

Still, Kenya stands apart from some of its neighbors. Uganda recently set in motion a Anti-Homosexuality Act that includes life sentences for adult consensual same-sex relationships (*In Brief, IAVI Report*, Vol. 18, No. 1, 2014), and last year Tanzania banned HIV/AIDS outreach projects aimed at gay men (*Washington Post*, Nov. 23, 2016). The many research partners working to implement Kenya's Ministry of Health and National AIDS and STI Control Programme have recognized that MSM are a key population and have demonstrated their willingness to work with diverse groups (*PloS One* **10**:e0137007, 2015). This level of engagement between healthcare workers and at-risk communities have carried over to the PrEP discussion.

An editorial published two years ago noted that in a continent decimated by AIDS, Kenya has been a leader in recognizing the health needs of stigmatized populations that feared legal authorities and had virtually no access to health services (*AIDS* **29**, (Suppl. 3) S195-S193, 2015). One of the editorial's authors is Eduard Sanders, a public health physician and epidemiologist who works with the Kenya Medical Research Institute-Wellcome Trust Research Programme (KWTRP). He says that although the country criminalizes homosexuality, its constitution entitles health care for all citizens. Sanders, who is a principal investigator of several observational studies involving mostly MSM and FSW in the Kilifi County, is receiving support from the Kenyan government to work with these at-risk communities. He established a long-running cohort of MSM and FSW in 2005 with support from IAVI and, to date, has tested more than 1,500 MSM, enrolling 950 in studies examining HIV incidence and disease progression.

Sanders' work in HIV began in Ethiopia in 1999, where he and several of his fellow scientists from Amsterdam were invited to set up a research laboratory in Addis Ababa to assist in the development of an AIDS vaccine. But it wasn't until he joined KWTRP in 2003, and helped to establish the District Hospital HIV Care and Research Programme in Kilifi, that he began working with the MSM community. Unlike in the US, where a vocal MSM community pushed to accelerate the development of ARVs at the dawn of the AIDS epidemic, the MSM population in Kenya, like those in other sub-Saharan countries, were largely suffering in silence. Enrolling MSM into cohort studies investigating the feasibility of an HIV vaccine,

which the clinical research facility was approved for in 2005, was unchartered territory.

Sanders says they began by dispatching individuals into areas where MSM engaged sex clients to do outreach. Gradually the cohort grew and today is arguably one of the best sources of information about MSM in all of sub-Saharan Africa. One of their initial studies, published just two years after the cohort started, showed HIV prevalence rates were 12.3 percent among men who have sex with men and women, and an astounding 43 percent among men who have sex with men exclusively, possibly due to an even higher rate of recent unprotected receptive anal intercourse (*AIDS* **21**, 18, 2513, 2007). Later, they conducted studies of acute HIV infection in MSM, looked at prevention and treatment of STIs, investigated predictors of HIV infection and the behavioral patterns of male sex workers who sell sex to other men, and evaluated the implementation of PrEP among MSM. "It is quite remarkable to have these cohorts in Africa, especially as Tanzania and Uganda have been much more aggressive toward MSM," says Sanders.

Robert Bailey, an epidemiologist at the University of Illinois School of Public Health who helped design Kenya's adult circumcision efforts and is now part of an effort to scale up PrEP use to 700 homosexual and bisexual men in Western Kenya says the country's PrEP policy really comes down to human rights. "The Kenyan Constitution protects human rights," says Bailey. "And a lot of the efforts by the Ministry of Health around PrEP for vulnerable people go under the umbrella that all Kenyans have universal human rights and providing services and access to health care is an essential part of that."

Indeed, Kenya's stated goal is to get to zero new HIV infections and do its part to help the United Nations reach its ambitious goal of ending AIDS by 2030.

But to that end, the country has a ways to go. While the latest incidence estimates from UNAIDS show that new HIV infections in Kenya dropped by 22 percent between 2012 and 2015, and the average HIV prevalence (5.9 percent) is half of what it was 20 years ago, there were still 78,000 new cases reported in 2015 and double-digit prevalence rates of 18 percent among MSM and IDUs, and 29 percent in sex workers. With 1.6 million people living with HIV, Kenya is still battling the spread of the virus.

PrEP's implementation challenges

Given these figures, Kenya seems a logical place to implement PrEP. But even in other countries where HIV rates are highest in specific populations, the uptake of PrEP is happening somewhat slowly. In the US, despite strong marketing in at-risk communities, only approximately 136,000 individuals have started PrEP since Truvada received approval for prevention in 2012, according to pharmaceutical company Gilead, which makes Truvada (*An Estimated 136,000 People Are on PrEP in the U.S.*, *POZ*, Aug. 18, 2017). Estimates suggest there are around 200,000 PrEP users worldwide. Without insurance, the cost for a year's supply of PrEP in the US is around $8,000-$12,000, so price may be one issue impeding PrEP use, but other factors are less clear and harder to characterize. A recent article in *The New York Times* by an African-American gay man who lost both of his parents to AIDS, illustrates how challenging it can be convincing individuals to take PrEP. In this case, skepticism of doctors, monogamy, and concerns that the PrEP pill might "weaken his body," convinced the writer to abandon PrEP after just one month (*My Struggle to Take Anti-HIV Medicine*, *NY Times*, Sept. 21, 2017).

In many settings it may be hard to convince healthy, uninfected individuals to swallow a pill every day, especially when it is an ARV ordinarily used to treat HIV infection. Numerous international clinical trials conducted in MSM, IDUs, high-risk heterosexual women, and serodiscordant couples have all found adherence to be the primary, and perhaps sole determinant, of PrEP efficacy. Yet there is no universal set of proven standards on how to convince people to start and faithfully use PrEP.

To make PrEP work in Kenya, the country will be seeking guidance from about a dozen ongoing demonstration projects and off-label studies, including five in Kenya, that have been examining the feasibility, cost-effectiveness, and acceptability of doling out daily oral PrEP to MSM, FSWs, and young women and adolescent girls (*Preparing for PrEP*, *IAVI Report*, Vol. 17, No. 3, 2013). Most of these projects are in the early stages or not yet started, but a few are already providing useful information. LVCT Health (formerly Liverpool VCT), a Kenyan non-profit that develops integrated HIV and reproductive health services for vulnerable populations, including MSM and sex workers, is leading a demonstration project that offers PrEP to at-risk individuals as part of a comprehensive HIV prevention package. They have noticed that support groups are an important resource in helping PrEP users remain adherent (*Support Groups a Driver to PrEP Rollout in Kenya*, PrEP Watch, June 2017). Groups of 10-15 people meet regularly to share their experiences and challenges with using PrEP, and while it's hardly a

12-step program, people do, apparently, prod one another to stick to their daily pill.

Another demonstration project is Partners PrEP, an open label study of just over a thousand serodiscordant couples in Uganda and Kenya that has been building on the findings from the Partners PrEP trial, a randomized double-blind Phase III study of 4,500 heterosexual men and women that found tenofovir reduced the risk of infection by 62 percent, and daily Truvada reduced HIV infection risk by 73 percent (*NEJM* **367**, 5, 399-410, 2012). The demonstration project found that a combination of PrEP and ARV therapy almost completely eliminated viral transmission in serodiscordant heterosexual couples. That data, presented two years ago at the Conference on Retroviruses and Opportunistic Infections, validated the idea of giving the HIV-negative partner PrEP as a "bridge" until or even after the infected partner begins full-scale ARV therapy.

KWTRP is also doing intensive outreach within MSM and FSW communities at their study sites in Mtwapa, Kilifi, and Malindi. Evanson Gichuru, a community liaison officer for IAVI's KWTRP HIV project, says the centers sponsor weekly engagement meetings with a dozen randomly selected HIV-uninfected participants from their cohort. The meetings cover a combination of prevention strategies. PrEP discussions typically begin with an animated video clip and end with an open discussion about its usefulness and its potential side effects and adherence barriers, as well as ways to deal with those barriers. Since the introduction of PrEP in July 2017, they have mobilized 169 MSM and 50 FSWs who are eligible for PrEP.

From this group, Kimani Makobu, a physician at KWTRP, will be taking the work a step further by creating a cohort of 40 MSM and 40 FSWs to more closely monitor PrEP uptake and adherence. The group will be broken down into sub-categories, including gay and bisexual men as well as transgender women, because behavioral surveys suggest there are differences in risk-taking behavior in these groups and therefore each group will likely need individualized PrEP adherence support. Makobu, who is doing his PhD research under Sanders, says one thing he has learned from these focus groups is that some MSM suspect they will use condoms less.

"Incidence is highest in MSM and FSW so they would potentially be the biggest beneficiaries of PrEP," says Makobu. "The caveat is that PrEP success is dependent upon users actually using it. If we are not able to motivate MSM and FSW to adhere to medication then the anticipated success may not be achieved."

Despite what researchers are learning from demonstration projects, it is still an open question whether large numbers of at-risk individuals in uncontrolled settings will embrace PrEP, or shun it for any of a variety of reasons. Mombo Ngua (a.k.a. Mantully), a sexual minority activist affiliated with the Sex Workers Outreach Programme (SWOP) in Nairobi, who likes to end his emails with *"If you hate gay marriages, blame the straight folks; they are the ones who keep having gay babies,"* points out that there is a lot of misinformation, some perhaps deliberate, being spread by MSM about PrEP.

"There are people who are saying that PrEP does not work and they should use it without a condom and if they turn positive they should sue the government," says Ngua. "They are telling people that it finishes sexual feeling and adds a tummy. They are saying if PrEP works, what's the use of condoms?" Ngua, who has been working with the MSM community for over a decade is trying to dispel these myths, and he has a very good argument. He has been taking PrEP for two years. "I think more education and sensitization around PrEP is needed in the MSM community," he says.

Finding ways to monitor PrEP users cost-effectively is also going to be a challenge in the long term, says Bailey. His research group in Kisumu, a county on the shores of Lake Victoria, is currently introducing PrEP to about 160 individuals from a long-standing cohort of 700 bisexual and homosexual men who they have been monitoring for years. The site hosts social events to engage the men—Monday movie night, coffee Wednesdays, fashion shows, and spiritual meetings—and uses peer educators to encourage adherence. The clinic also plans to monitor drug levels of PrEP participants to determine if it is being used consistently. But Bailey says the $50 per blood test will not be practical or cost-effective in a large-scale rollout, so the organizations charged with tracking these individuals will need to revert to behavioral methods of assessing adherence (for example, self-reporting or daily texts). As a result, "it's going to be necessary to have some demonstration projects measure what the sensitivity and specificity of the behavioral methods of adherence are," Bailey says.

Jhpiego, a global health non-profit and affiliate of Johns Hopkins University dedicated to improving the health of women and families in developing countries, is setting its sights on developing a model to scale-up PrEP in resource-strained countries

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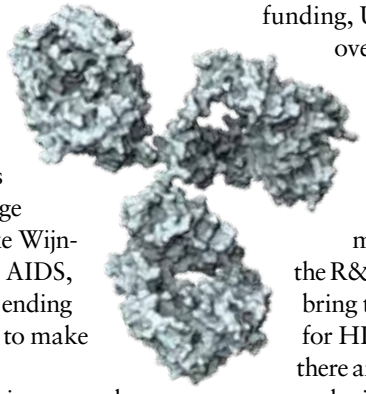
Spending Increases for HIV Vaccine Research, But Concern Rife for Future

In a tumultuous and conflict-ridden year when scientists have felt fraught enough to take to the streets and demonstrate, overall funding for a preventive HIV vaccine actually increased slightly over previous years, bringing it to the highest level in a decade according to the Resource Tracking for HIV Prevention Research and Development Working Group (RTWG).

Even so, the overall budget picture for HIV-related research and development is mixed. Global funding levels show signs of weakness with overall HIV prevention research and development investment dropping slightly from the year before, continuing a slow but steady downward trend. Major figures in the HIV research community, both in research and in policy roles, are expressing doubt and concern about future resources. Meanwhile, in Washington the White House moved to try and slash the budget for the US National Institutes of Health (NIH), the largest single source of HIV-related research funding, stirring opposition in the US Congress and setting up what will be a hard fight over the US federal budget in the coming weeks.



Worry about where future resources will come from furrowed many brows in Paris earlier this summer at the 9th International AIDS Society's Conference on HIV Science (IAS 2017; see story, page 4). "There's still a funding shortfall," says Marijke Wijnroks, interim director of the Global Fund to Fight AIDS, Tuberculosis and Malaria. "If we are serious about ending AIDS as a public health threat, we should be able to make the funding available to do it."

Since 2004, the RTWG has tracked trends in research and development investment for biomedical HIV prevention options, with the global advocacy group AVAC leading a group secretariat that includes IAVI and the Joint United Nations Programme on HIV/AIDS (UNAIDS).

The total funding for preventive HIV vaccines in 2016 came in at US$894 million, up from $859 million the year before. This was the largest gross investment since 2007's $961 million, the summer before the last global financial crisis hit. This year's boost in vaccine funding came mostly at the hands of the NIH, which invested at its highest level since 2000. This increase, according to the RTWG report, was due to the agency's support for the first HIV vaccine efficacy trial to begin in a decade—the HVTN 702 Phase III study in South Africa testing a modified version of the vaccine regimen that was tested in Thailand and showed a modest 31 percent efficacy.

Even as the funding for HIV vaccine R&D climbed by $34 million overall, public sector investment from European sources was the lowest since 2001, at $38.5 million. About $11 million of that is committed to two five-year programs aiming to test early stage vaccine candidates.

Overall investment in HIV prevention research and development efforts seem to be slowing, according to the RTWG report: funding fell to $1.17 billion, down $35 million from the year before. Other reports surfacing over the summer covering HIV efforts also paint a mixed picture. Funding levels from donor governments that provide bilateral programs and contributions for low- and middle-income countries to the Global Fund fell to $7.5 billion in 2015 from $8.6 billion in 2014, marking the first decrease in five years, according to a report from the Kaiser Family Foundation (KFF) and UNAIDS. Figures for 2016 are at $7 billion. "Donor government funding for HIV continues to be on the decline," KFF Vice President Jen Kates, director of Global Health and HIV Policy, said in a statement as the report came out. "Recent proposed cuts from the US, amidst other competing demands on donor budgets, will likely contribute to an ongoing climate of uncertainty around funding for HIV going forward."

The alarm caused by US President Donald Trump's original proposal for drastic decreases in the NIH budget were tempered over recent weeks as legislators made it clear they will resist deep retrenchment for the institute and other public health outlays. While administration officials called for a $5.8 billion to $7.5 billion cut in NIH funding, US Senate appropriations call instead for a $2 billion overall increase for the NIH, with increased contributions for Gavi, the Vaccine Alliance, PEPFAR, and the Global Fund. These numbers will fluctuate as the budget is hammered out, but for now the proposed cuts appear to lack congressional support.

Concerns remain, however, over sustained investment in HIV treatment and prevention programs and in the R&D needed to reach what for many is the ultimate goal, to bring the epidemic to an end. Not only are two clinical trials for HIV vaccine candidates progressing to advanced stages, there are long-acting antiretrovirals under study, a vaginal ring employing the antiretroviral dapivirine is under review by the European Medicines Agency, daily oral PrEP (pre-exposure prophylaxis) delivery is becoming more commonplace, investment in HIV cure research climbed in 2016 by $60 million, and more than half of the world's 36 million people living with HIV are on regular antiretroviral treatment. That last figure alone marks a startling jump from 15 years ago, says Michel Sidibé, executive director of UNAIDS, when the World Health Organization's "3X5" initiative—which aimed to get three million people living with HIV on antiretroviral treatment by 2005—seemed like a moon shot and, indeed, did not meet its goal on time. At the Paris conference health officials from Swaziland, once a place with the highest HIV prevalence in the world, were able to show that ramped-up treatment, testing, and adult male circumcision brought incidence down by 44 percent and that two-thirds of the country's infected population has fully suppressed virus.

All of this, leaders in the field say, points to the need for sustained investment. "Any cuts—*any cuts*—to funding jeopardizes our results," Sidibé declared to a crowded room in Paris. "We are breaking the backbone of this epidemic. It is a moment we should never, never let go. It is a moment for winning. It is not a moment for losing." —*Michael Dumiak*

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

Longer-acting HIV Prevention Methods: Take Two Antibodies and Call Me in Six Months?

"An ounce of prevention is worth a pound of cure," so Benjamin Franklin once said. Weighing the benefits of prevention in HIV suggests a few more ounces are needed. There are several ways to effectively protect against HIV infection: condoms, voluntary adult male circumcision, and daily oral pre-exposure prophylaxis (PrEP)—which entails giving antiretrovirals (ARV) to healthy, uninfected individuals. But what all of these methods except circumcision have in common is that they require the user to do exactly that, use them. And to do so consistently. This, researchers recognize, is not always what happens, even in clinical trials when volunteers receive frequent reminders about adherence and its importance. Demonstration studies of oral PrEP and clinical trials of an ARV-containing vaginal ring show that compliance is imperfect for a variety of reasons. Some individuals are reluctant to even begin using oral PrEP because it demands daily use to be effective (see *PrEParing to Prevent HIV*, page 13).

This is why researchers are focusing on developing longer-acting HIV prevention strategies, a topic discussed at a day-long meeting at The New York Academy of Sciences (NYAS) on September 22, just after the close of the United Nations General Assembly. While a vaccine that provides durable, high-level protection would be the ultimate long-acting HIV prevention modality, other strategies have the advantage of being closer to fruition. "Long-acting anti-HIV prophylactic agents are critical tools in our fight against the epidemic, and that must be developed within the next decade," says Emilio Emini, director of the HIV program at the Bill & Melinda Gates Foundation (BMGF), which co-presented the NYAS meeting.

Funders, advocates, and scientists who gathered at the NYAS meeting discussed the various prevention strategies under study, including long-acting ARVs for oral PrEP, vaginal rings containing ARVs, implantable devices capable of releasing ARVs or antibodies, or injections of antibodies that are engineered to last for longer periods. "We have never had as robust a pipeline for HIV prevention in clinical trials, let alone in early product development as well," says Mitchell Warren, executive director of AVAC, the HIV prevention advocacy group based in New York City.

The long-acting ARV that is the farthest along in development is the investigational drug cabotegravir (CAB LA), a long-acting injectable integrase strand transfer inhibitor. ViiV Healthcare, a company specializing in HIV that is owned by GlaxoSmithKline, Pfizer, and Shinogi Limited, is developing CAB LA for both HIV prevention and treatment. A Phase III efficacy trial of CAB LA for prevention (HPTN 083) is testing injections of CAB LA every two months head to head against placebo and daily, oral Truvada, made by pharmaceutical company Gilead, which is the current state-of-the-art PrEP drug. The trial started at the end of last year and will involve 4,500 volunteers. This is the first injectable PrEP drug to be evaluated in an efficacy trial.

Another ARV in development by Gilead for both treatment and prevention is known as GS-CA1. This experimental drug is a capsid inhibitor that prevents HIV's nuclear material from entering cells. Preclinical data on subcutaneous administration of this experimental ARV was presented earlier this year at the Conference on Retroviruses and Opportunistic Infections. The company is planning to test GS-CA1 in clinical trials by next year. Gilead is also testing F/TAF, a combination of emtricitabine and a derivative of the drug tenofovir—the two drugs that make up Truvada—known as tenofovir alafenamide to see whether this newer drug combo, which is already licensed for treatment, is also effective for PrEP. F/TAF has a much longer intracellular half life and the company is now comparing oral administration of F/TAF with Truvada in a PrEP trial known as the DISCOVER study. Another long-acting ARV slated for HIV prevention trials is MK-8591, an adenosine nuclease analog developed by Merck.

In addition to developing new compounds, researchers are also focusing on delivery systems that might be able to provide prolonged release of HIV drugs inside the body. These include using implantable devices similar to those used for hormonal contraception that either need to be removed surgically or that could biodegrade, or using self-assembled gels that act as long-acting injectables. The biotechnology company Intarcia Therapeutics, backed by a US$140 million grant from BMGF, is now developing an implantable drug-delivery pump for HIV based on one they already developed to treat type 2 diabetes.

> Long-acting anti-HIV prophylactic agents are critical tools in our fight against the epidemic, and that must be developed within the next decade.
> *-Emilio Emini*

Another approach is to use antibodies that can neutralize a broad swathe of the HIV variants in circulation, so-called broadly neutralizing antibodies (bNAbs), to prevent HIV. There is evidence that some of the recently isolated bNAbs can protect against infection in animal studies and there is already a Phase IIb efficacy study of one of these bNAbs (VRC01) underway: the Vaccine Research Center (VRC) at the National Institute of Allergy and Infectious Diseases (NIAID) is running the antibody-mediated prevention or AMP study involving 4,200 volunteers from seven countries. This is rapid progress given the first crop of new bNAbs was reported less than 10 years ago, says John Mascola, head of the VRC and a co-organizer of the NYAS meeting.

Results from the AMP study should come in 2019 or 2020 and will answer many preliminary questions about the role of bNAbs in prophylaxis, including whether they are feasible as a biologic and how much antibody is needed for protection.

Meanwhile, scientists are exploring introducing mutations into bNAbs to improve their staying power, thereby reducing the frequency of injections necessary to afford lasting and effective protec-

tion against HIV, while at the same time, improving their potency so a lower dose is needed. It is possible or even likely that a combination of bNAbs might be required so the lower the antibody dose, the less it will cost to manufacture the proteins on a large scale. Bruce Kerwin, vice president of drug product design at Just Biotherapeutics, says that to feasibly provide bNAbs for HIV prevention in sub-Saharan Africa the cost would need to be around $20 per gram of antibody. Right now the cost is more like $150 to $200 per gram, so researchers have a way to go. But studies suggest it might be possible to get there. "The potential to improve antibodies is quite remarkable," says Mascola.

Introducing a single mutation (known as the LS mutation) into VRC01 for example, increases the half life more than four-fold as compared to plain VRC01. This engineered antibody can even be administered subcutaneously rather than by intra-muscular injection and still maintain high levels for extended periods of time. The long-term goals is to administer the antibodies only every four to six months.

Another promising effort to create more broad and potent antibodies involves engineering existing bNAbs so that they recognize multiple epitopes on HIV, as recently reported by researchers from pharmaceutical company Sanofi, in collaboration with NIAID, Harvard Medical School, The Scripps Research Institute, and The Ragon Institute (*Science* 2017, doi: 10.1126/science.aan8630). These tri-specific antibodies neutralized more broadly than any single bNAb identified to date and also afforded complete protection against a mixture of hybrid HIV/simian immunodeficiency virus (SIV) challenge viruses in non-human primate studies. Clinical studies will determine how immunogenic these tri-specific antibodies will be in humans.

But even as research into these longer-acting prevention strategies progresses, there are still looming questions. One is how to sustain or even increase funding when so much of the current focus is on scaling up ARV treatment. There is also the larger question of what the individuals at highest risk of HIV infection, particularly in sub-Saharan Africa, will ultimately want or choose to use to protect themselves. Researchers are hopeful that answers to that question will come from implementation studies for existing or potential strategies, like the vaginal ring containing the experimental ARV dapivirine that was found to be 27 percent effective in protecting against HIV in two large clinical trials. Researchers at the International Partnership for Microbicides (IPM) and their partners are starting a trial next year in adolescent girls to see whether they prefer to use the ring or daily, oral PrEP. At the same time they are seeking licensure for the dapivirine ring from the European Medicines Agency, which allows them to apply for simultaneous pre-qualification by the World Health Organization. IPM also started a trial earlier this year testing a dapivirine ring that only needs to be swapped out every three months.

AVAC is now working on two implementation studies for oral PrEP, one funded by BMGF and the other by the United States Agency for International Development. Daily oral PrEP received approval from the US Food and Drug Administration in 2012 and there are now more than 200,000 PrEP users, which Warren says does not represent a failure in implementation, but more work is necessary as most of these PrEP users are in the US and Europe. Uptake in Africa is happening more slowly. "We don't fully know what people want," he says. "This is not just a product development conversation, it's a product delivery conversation. Just because we develop it doesn't make it so." Warren says that creating demand for new products is key, something that just seems to be starting in earnest for PrEP.

Warren suggests that determining how and by whom these existing or longer-acting prevention approaches in development will be used needs to be studied in large implementation studies, not the smaller ones done to date. "Let's be ready to spend tens of millions of dollars on product introduction," and do so earlier than what happened with oral PrEP, says Warren. "Asking questions three years after a product is registered is too late." —*Kristen Jill Kresge*

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through its Bridge To Scale project known as Jilinde. The Bill & Melinda Gates Foundation awarded Jhpiego $22.3 million over four years to reach 20,000 Kenyans most vulnerable to HIV infection, including adolescent girls and young women, FSWs, and MSM.

Daniel Were, oral PrEP director at Jhpiego-Kenya, says Jilinde, as part of a large technical working group spearheaded by the National AIDS and STI Control Programme (NASCOP), helped develop the framework for implementing oral daily PrEP, created training manuals and toolkits for providers and PrEP users, and will be conducting mathematical modeling in the third year of implementation to determine how much PrEP coverage is required to reduce infections in each risk group.

Jilinde, which means protect yourself in Swahili, already enrolled around 2,600 individuals at 10 different sites, but is encountering retention problems, possibly because people did not fully understand that the pills needed to be taken every day in order to work. "Many people are enrolling in the program but then quickly dropping and we're trying to understand why this is happening," says Were.

He says some reasons include an unwillingness to take a pill every day, or a preference for other HIV prevention options such as condoms. "Others enroll and drop out because of social stigma from their peers and surrounding community that labels them to be HIV positive because the medicine used for PrEP is similar to what is used for HIV treatment," Were says.

To address these issues, Jhpiego is adding more health care workers to provide counseling on all prevention choices upon enrollment and is bolstering their messaging around adherence.

So is Kenya ready for PrEP? Beyrer says Kenya has made tremendous strides but there are still challenges ahead. "Remember, when you look across the landscape things often look better in the larger urban areas. When you get out into more rural areas with smaller populations, you encounter much more traditional values and things can get really tough." ■

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

Upcoming HIV-Related Meetings

OCTOBER 2017

10th National Conference of AIDS Society of India (ASICON 2017)
October 6-8; Hyderabad, India
More information: asi-asicon.com/index.php

19th Annual International Meeting of the Institute of Human Virology (IHV 2017)
October 23-26; Baltimore, MD
More information: www.ihv.org/ihvmeeting

DECEMBER 2017

Biomedical HIV Prevention Summit
December 4-5; New Orleans, LA
More information: www.biomedicalhivsummit.org

19th International Conference on AIDS and STIs in Africa (ICASA)
December 4-9; Abidjan, Côte D'Ivoire
More information: icasa2017cotedivoire.org

8th Edition: HIV Persistence During Therapy
December 12-15; Miami, FL
More information: www.hiv-persistence.com

JANUARY 2018

20th Bangkok International Symposium on HIV Medicine
January 17-19; Bangkok, Thailand
More information: www.hivnat.org/bangkoksymposium

MARCH 2018

HIV & Women 2018
March 2-3; Boston, MA
More information: www.virology-education.com/event/upcoming/international-workshop-hiv-women

CROI 2018
March 4-7; Boston, MA
More information: www.croiconference.org/

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