

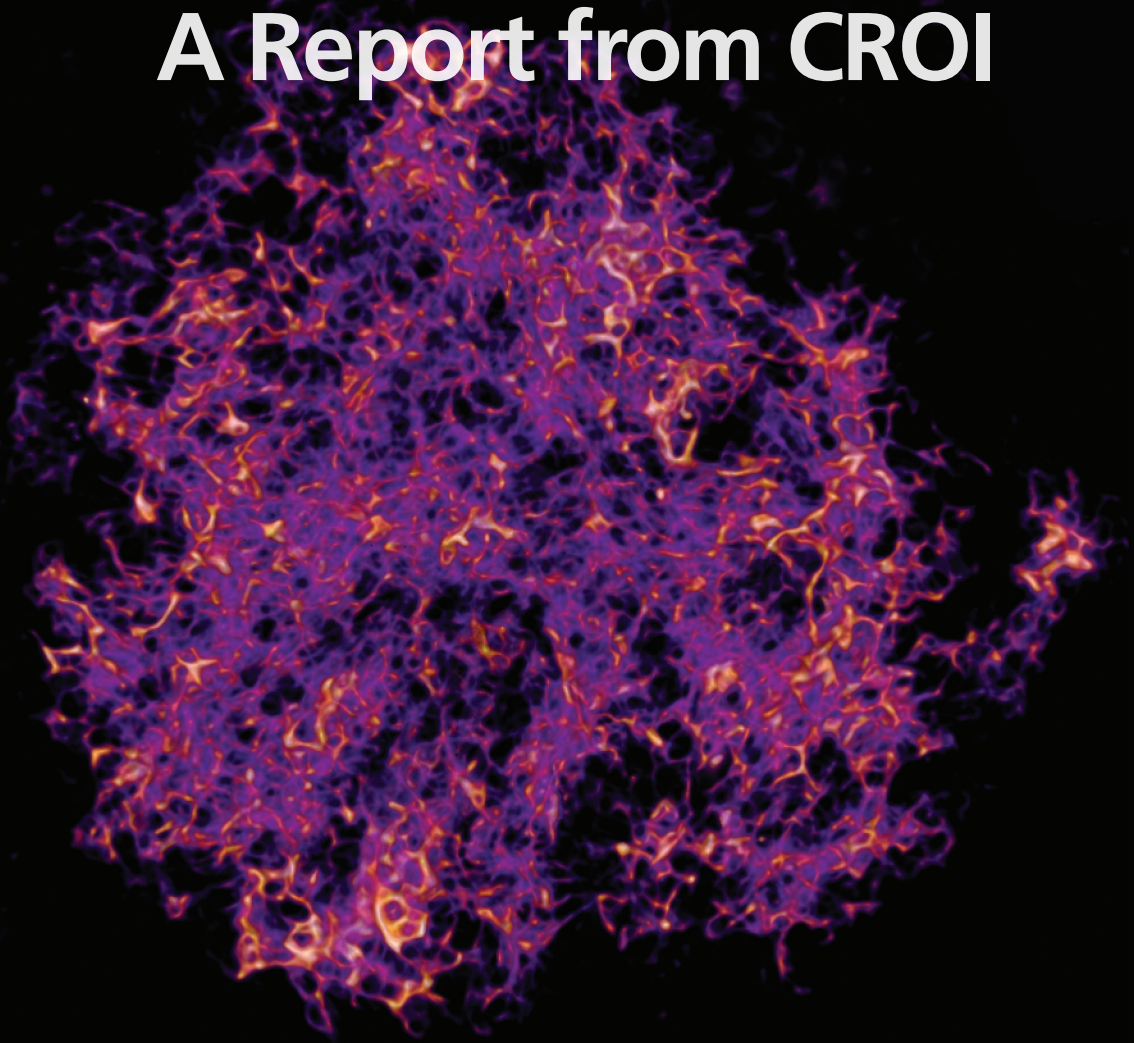
VOLUME 20, ISSUE 1

# IAVIReport

The Publication on AIDS Vaccine Research

WWW.IAVIREPORT.ORG | VOLUME 20, ISSUE 1 | 2016

## Long-acting Prevention: A Report from CROI



**Plus: William Snow on the future of the Enterprise;  
Wayne Koff departs IAVI**

## EDITOR'S LETTER

It was 20 years ago this summer that the first issue of *IAVI Report* was published. That was the same year that IAVI was founded as a product development partnership with an aim to expedite development of an HIV vaccine that was relevant in the parts of the world that were most affected by HIV/AIDS.

In *IAVI Report's* inaugural issue, Margaret Johnston, the then scientific director of IAVI, outlined the reasons why an HIV vaccine is scientifically possible. She concluded the list by saying this: "A slight but real sense of optimism is beginning to emerge in the effort to develop an AIDS vaccine." What is striking about this is that this captures precisely the sentiment that exists in vaccine research today. After many setbacks and discouraging results, researchers have gained a tremendous amount of knowledge about how the virus interacts with the immune system and how to design better HIV vaccine candidates.

It is also striking that in this issue we bid farewell to the person who replaced Johnston 17 years ago. Wayne Koff, who is only the second person in IAVI's history to lead the research and development effort, left his full-time role as Chief Science Officer at IAVI in March to take on a new role as President of the Human Vaccines Project. We pay tribute to Koff and his role in shaping HIV vaccine science, including establishing the Neutralizing Antibody Consortium, overseeing the Protocol studies that led to the isolation of scores of new broadly neutralizing antibodies against HIV, and the implementation of first-rate clinical research centers in Africa and India that are poised to contribute to the development of an HIV vaccine (see page 14).

In this issue we also discuss the future of HIV vaccine development and the Global HIV Vaccine Enterprise with Bill Snow, executive director of the Enterprise and a long-time vaccine advocate (see page 4).

Finally, we bring you a full report on the latest news in HIV prevention from this year's Conference on Retroviruses and Opportunistic Infections (CROI), which took place in February in Boston. Results from efficacy studies of a vaginal ring containing an experimental antiretroviral were reported and discussed extensively at CROI, as well as updates on the uptake of oral pre-exposure prophylaxis and emerging data on long-active antiretrovirals that may have both therapeutic and preventive roles in the future (see page 8).

Now, we ask for your opinion. As *IAVI Report* kicks off its 20th year, we'd like to ask our loyal readers to provide some feedback on the publication and its value so we can ensure it continues to meet the needs of our audience. To do so, please take a very brief survey online at: [www.surveymonkey.com/r/IAVIRreport](http://www.surveymonkey.com/r/IAVIRreport). We hope you will take the time to share your opinions with us.

– KRISTEN JILL KRESGE



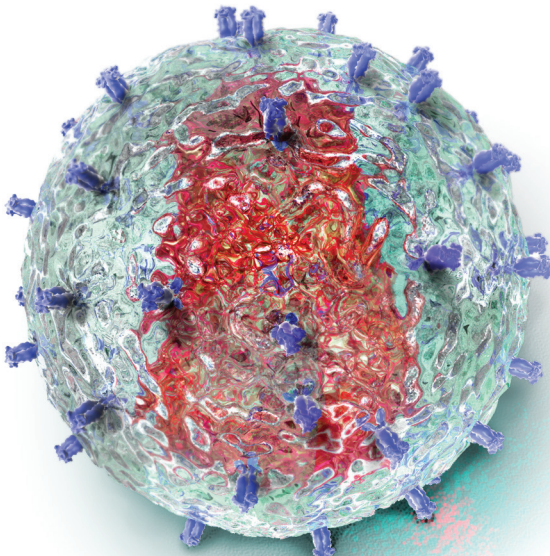
All rights reserved ©2016

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](http://www.iavi.org).

**04** **The View from the Mothership**  
Global HIV Vaccine Enterprise Director William Snow reflects on the past and ponders the future course for the organization, and the field of HIV vaccine research overall.

**08** **HIV Field's Current Contours Show in Boston**  
HIV prevention was the top story at CROI 2016, but issues of adherence and uptake still loom large in the battle to stop HIV's spread.

**14** **In Brief**  
Chief Science Officer of IAVI departs to lead Human Vaccines Project



# IAVIReport

**SENIOR PRODUCTION MANAGER**  
Nicole Sender

**MANAGING EDITOR**  
Kristen Jill Kresge

**CONTRIBUTING WRITERS**  
Michael Dumiak  
Mary Rushton

**FREE SUBSCRIPTIONS:**

To obtain a FREE subscription to *IAVI Report*, change your contact details, or receive multiple copies of *IAVI Report* to distribute and/or use in your programs, go to [www.iavireport.org](http://www.iavireport.org) and click on the Subscribe link.

For more information, go to:  
**[www.iavireport.org](http://www.iavireport.org)**

Comments/Questions?  
Email us at [iavireport@iavi.org](mailto:iavireport@iavi.org)

**[ ON THE COVER ]**

A 3D reconstruction of a follicular dendritic cell cluster *in situ* in a mouse spleen follicle, this image shows a network for cell migration, and a site that retains antigens. That this clustered dendritic cell lattice forms a network at all is notable. The follicular dendritic cell expresses the chemoattractant ligand for cells expressing the CXCR5 gene. This is essential in B and T cell migration. T-follicular helper cells migrate through the network site and are targeted by HIV. Such networks normally take up immune complexes and are vital for B cell and T-follicular helper cell activation. Researchers think it would be impossible for a cell to navigate this network and not contact antigen. Virus is not retained with a passive mechanism, which supports the idea that as viral particles are taken up like immune complexes, these networks can form a viral reservoir.

*Image courtesy of Michael Carroll, head of graduate program in Immunology, Harvard Medical School; produced by Balthasar Heesters, Dept. of Microbiology and Immunobiology, Harvard Medical School.*

# THE VIEW FROM *the Mothership*

Global HIV Vaccine Enterprise Director William Snow reflects on the past and ponders the future course for the organization, and the field of HIV vaccine research overall.

By Mary Rushton

Fifteen years into the AIDS pandemic, the world got a triple-dose of good news. Highly active antiretroviral therapy (HAART)—the combination of drugs to treat HIV infection—was incredibly effective. It rescued millions of HIV-infected people from the brink of death. The success with HIV treatment continues today with newer classes of drugs and drug combinations that are highly effective and less burdensome than the earliest therapies.

The search for a safe and effective vaccine is not so easy. HIV is a complex virus that outruns and outmaneuvers the immune response and presents a great challenge to vaccine developers. Almost all of the vaccine candidates tested to date have failed. The only trial to show any protection against HIV was the RV144 trial in Thailand and the regimen tested in this trial was only modestly effective (31.2%).

No candidate thus far has been capable of inducing antibodies against most circulating HIV strains, the so-called broadly neutralizing antibodies (bNAbs) that most researchers think would be necessary for an ideal vaccine. But scientists have been making remarkable progress toward developing antibody-based vaccine candidates. Hundreds of bNAbs have been identified and this, along with the recent stabilization of the notoriously shape-shifting HIV Envelope protein, are fueling vaccine design and development efforts. Meanwhile, scientists are building on what they learned from the RV144 trial and are developing modified candidates to test in future efficacy trials.

Amidst all of this, the Global HIV Vaccine Enterprise, headquartered in New York City and led by long-time AIDS vaccine advocate William Snow,

is trying to accelerate the pace of research, primarily through increasing dialogue and facilitating collaborations among the major players in the field. The Enterprise doesn't fund research, sponsor trials, or develop candidates, rather it troubleshoots issues and provides forums for the field to reach consensus on critical issues. The Enterprise's Timely Topics in HIV Vaccine Research, launched in 2012, regularly convenes expert panels to analyze and respond to unresolved questions that encroach upon vaccine development. The series kicked off with a session on the ethics of pediatric clinical trials (*Science* 300, 2036, 2003). Another recent topic was therapeutic vaccines, which figure prominently in the emerging field of HIV cure research. Lately, innovation and product development issues are at the forefront. A boot camp held last year by the Enterprise for vaccine researchers and product development experts looked at different ways to incorporate a more industrial-like approach in the vaccine discovery process (see *In Brief, IAVI Report*, Vol. 19, No. 4).

The Enterprise's Secretariat also meets regularly with funders and industry leaders and organizes the bi-annual HIV Research for Prevention (HIVR4P) meeting, which replaced the annual AIDS Vaccine meeting that ended in 2013. HIVR4P is the only meeting focusing solely on HIV prevention—the next one will occur this October in Chicago.

Like HIV vaccine researchers themselves, the Enterprise has struggled over the years. Before Snow took the helm as director in 2012, there were questions about how the organization could stay focused and remain relevant (see *The Enterprise Changes Course, IAVI Report*, Sep.-Oct. 2011). The Enterprise was conceived in 2003 by an alliance of orga-



William Snow

nizations that wanted to speed up the search for an HIV vaccine through mutual coordination, collaboration, and the sharing of knowledge (*Science* 530, 2036, 2003). This lofty premise gave way to six working groups that developed roadmaps and recommendations for the field and an interim Enterprise Secretariat, led by José Esparza, was established and housed at the Bill & Melinda Gates Foundation. Esparza at the time served as the Gates Foundation's Senior Advisor on HIV Vaccines.

Some were critical then that the Enterprise was primarily led by the Gates Foundation. The Enterprise's Board of Directors also had a hard time finding a permanent director to lead the Secretariat. There were doubts whether the Enterprise would be able to meet the challenge of its first Scientific Strategic Plan, published in 2005 (*Nature Medicine* 16, 981, 2010), that called for a doubling of research dollars and unprecedented coordination among independent researchers to allow intellectual property and data to flow freely.



Then in 2007, Alan Bernstein, the founding president of the Canadian Institutes of Health Research, became the Enterprise's first director. He led the organization from 2007-2011 and during this time many still questioned the role of the Enterprise.

In 2009, the New York City-based HIV prevention advocacy organization AVAC, which was co-founded by Snow, published a report that was critical of the Enterprise. In the report, *Piecing Together the HIV Prevention Puzzle*, the advocacy organization questioned whether the Enterprise still has the "influence to accelerate and activate conversations between funders and scientists that will lead to swift action in critical directions." A year later, and just weeks shy of the publication of the Enterprise's second Scientific Strategic Plan (*Nature Medicine* 16, 981, 2010), AVAC once again took a critical look at the Enterprise's role. In AVAC's 2010 Report, *Turning the Page*, the organization said it was the job of the Enterprise secretariat to hold donors, scientists, and organizations accountable for matching their work to the priorities outlined in the Enterprise's Strategic Plan. "Whether this will happen is, to be frank, an open question," the AVAC report noted.

Nelson Michael, director of the US Military HIV Research Program and a member of the Enterprise's Board of Directors, said following Bernstein's departure in 2011 there was a serious discussion about whether the Enterprise should even exist. "There was a very strong voice within this relatively small board that maybe we had done the experiment, that it had failed, and that it was

time to move on," Michael recalls. "The view was that the Enterprise, for better or for worse, had become expensive and was not particularly well connected with its primary mission."

But the Enterprise found its footing with Snow, a self-proclaimed gadfly with enormous credibility in the field. Snow's passion for ending the epidemic is matched only by his willingness to ask tough questions without apology. Though not a scientist, his roots in AIDS vaccine research run deeper than many. In what he calls a "personal journey," Snow's involvement in the famous activist group ACT-UP and with community advisory boards for clinical trials led him to co-found AVAC in 1995. He also sits on the AIDS Vaccine Research Subcommittee of the US National Institute of Allergy and Infectious Diseases (NIAID), and the US National Institutes of Health's (NIH) Vaccine Research Center Scientific Advisory Working Group. Snow also served on the Enterprise's original council and as treasurer of its board when it received its first round of funding.

Michael believes that were it not for Snow's appointment as director of the Enterprise Secretariat in 2012, the Enterprise would have been disbanded. "He worked in partnership with the board and the funders to carve out why the Enterprise should exist," says Michael. "And for a guy without formal scientific training, he really has an intuitive understanding of the disease and the epidemic, from scientific to psychosocial. At meetings we have attended he'd often say, 'If we were to ask this question and get this answer, how would it really help us to move the ball forward to make a vaccine for HIV?' He was masterful at that."

But Esparza worries that the Enterprise and the field of AIDS vaccine research in general is still losing momentum. "The Enterprise is an example of the 'big science' approach that 10 years ago we thought would result in an HIV vaccine," recalls Esparza, one of the early framers of the Enterprise and now the president of the Baltimore-based Global Virus Network, an international coalition comprised of virologists from more than 20 countries. "My major concern now is that the field of HIV vaccines does not seem to have the necessary sense of urgency. Basically, the HIV vaccine people are making themselves irrelevant for the current global HIV prevention effort. That is sad because we are convinced that without a vaccine the HIV epidemic will not be controlled, not even in the US."

But there is no question that the pace of discovery has picked up in recent years. The world in

which the Enterprise is operating is much different from when the concept was launched in 2003, and so is the organization itself. *IAVI Report* recently spoke with Snow about the early days of the Enterprise, where it is heading, and his views on the current HIV prevention landscape.

### Why did you take on the responsibility of running the Enterprise?

I saw it as a golden opportunity to try to do some of the things that I always thought ought to be, and could be done. I had always played the role of the gadfly, so this was almost like it was meant to be. I think the partners knew they needed someone who knew the field, who got along well with people, had the history and the background, and who could promote the principles and ideals of the Enterprise. I had never run a non-profit organization before or been a senior manager of one, but I am proud to have been representing the Enterprise for this period of time. It really is a collaboration of organizations that don't necessarily have to collaborate with each other and it is our job to facilitate that.

### How did you first become involved with the Enterprise?

AVAC was one of the signatories of the original article proposing the creation of a Global HIV Vaccine Enterprise (*Science* 300, 2036, 2003). At the time, Chris Collins was the executive director of AVAC, and he was the person who signed on to the article and went to the original retreat. After that I was asked to join the board of the Enterprise as it was being formed.

### Were you always a supporter of the Enterprise concept?

Yes. I thought that there was a need for more organization, high-level participation, and strategic thinking, so it sounded like an incredible opportunity from the beginning. And the individuals who signed on to that and stuck with it through the formation of the Enterprise were exactly the right people to lead that effort—top leaders in the field with the ability to influence change.

### Weren't there some who wanted the Enterprise modeled after the Human Genome Project?

Yes, there was a lot of talk about that when I was on the steering committee, but it turned out that that [Human Genome Project] was really more of an engineering, heavy lifting, big numbers kind of thing. I think of the Enterprise as more ambitious, really, and less certain.

### Was there much disagreement at first on the role of the Enterprise?

The initial proposal [described in 2003] proposed creating centers of excellence. But, early on, people began to realize that was unrealistic. So the idea evolved to be a more virtual network. The ultimate intention was to create a Scientific Strategic Plan for the field. That was done before the Enterprise Board started looking for a director. The strategic plan really laid the foundation for the NIH to create CHAVI [The Center for HIV/AIDS Vaccine Immunology] and for the Gates Foundation to create the CAVD [Collaboration for AIDS Vaccine Discovery].

### Who was involved in shaping the Enterprise in the early days?

Rick Klausner of the Gates Foundation and Larry Corey of the HIV Vaccine Trials Network were the lead authors of that first article in *Science*. They and a lot of other heavy hitters in the field got together for the meetings. The people who took this idea and really fleshed it out were at the Gates Foundation. Helene Gayle, who was running the Foundation's HIV program, hired José Esparza from the Joint United Nations Programme on HIV/AIDS (UNAIDS.) The Enterprise was one of Jose's major efforts when he first arrived and it remained dear to his heart throughout the whole process. He put his heart and soul and brain into forming it with a huge amount of support from Siobhan Malone.

### What do you consider to be the Enterprise's biggest accomplishment?

I think there is no question that its biggest accomplishment was getting people to work together. To this day its greatest impact has been just changing the way scientists and funders work among themselves. Basically, the funders got the idea early on to create mechanisms and make funds available for investigators and institutions to work together for the common good.

### What were the biggest obstacles to all this change?

There was a fair amount of resistance to the notion of giving large amounts of money to big collaborations. That was a real change from the model where people were getting their own funding and working independently at their institution or with a few close collaborators. I think for people working in HIV vaccines, and also for the funders, it was really a new way of doing things. And it took a while for that concept to prove itself. Also, during this time, NIAID opened its Vaccine Research

Center, so there were big tectonic shifts on how we were working. And like any shift, there was a lot of adjustment over what I would say was a period of six to seven years. Let me also say that there was the issue of shared samples, shared data, and confidentiality agreements. That added a whole lot of infrastructure to each consortia and required a lot of heavy lifting.

### **Did this slow down the pace of research?**

No, it really spurred people on. Once these groups got together they were just all over it. All of a sudden there were people from different institutions talking to each other, there was data coming in from a variety of different directions, and scientists were meeting frequently. It was, I think, a very positive experience for them.

### **Were vaccine advocates pleased with the Enterprise's work in the early days?**

Every year AVAC was pushing the Enterprise to move faster and to do more. The Enterprise didn't show much in the way of accomplishments after that first Scientific Strategic Plan. It took a lot of time to get the organization going and an equal amount of time to get the collaborations started. During that time, the project spun off from the Gates Foundation, a director was hired, and the Secretariat was moved to New York and staffed.

### **What are the biggest achievements of this greater collaboration?**

Without a doubt the whole area of identifying a transmitted/founder virus [the virus that initially establishes an infection] was one of the first things that came out of this. It showed us that the notion of making a vaccine was going to require more understanding of infection and understanding of the immune system's reaction to HIV rather than just using a vaccine platform that had worked for something else. Any vaccine should work against transmissible viruses. If only one or a few invaders infiltrate your system, they're the ones to repel and destroy.

### **What impact did the RV144 results have on the Enterprise?**

It was a major surprise for the Enterprise. They had just drafted a second Strategic Plan—the ink was drying and then RV144 happened, and the [vaccine] search turned on a dime to follow up on the results. The Enterprise's board met to figure out how to make the Enterprise more flexible and contribute to this effort rather than focus on a strategic

plan. The notion was that there were more discrete areas that you could work on in real time. I think that the effect on the Enterprise was very much reactive and prompted it to change direction.

### **What's come out of the Timely Topics events?**

Certainly, the focus we have had on industry has been important and valuable. People are realizing more and more that there are good reasons why industry isn't involved extensively in HIV vaccine research, and good reasons why some of the things they know and techniques that they use are important to the field, so the field is going to have to learn to access them another way. In the end, however, industry's knowledge is still going to be essential to making a deployable vaccine. There is no easy way around this because the only organization, outside of product development companies, that ever developed its own vaccines used to be the Army.

### **What's in store for the Enterprise going forward?**

In the near future, we are looking at doing more work in Africa, where we're trying to help set up a virtual network for African scientists. We're focusing a bit more on the clinical side, and we're also looking a little bit more at animal models. I believe we've proven our worth, but remember, the Enterprise is the collective of organizations and their achievements. Longer term, we want to stay current, which means anticipating the needs of the field. We can't be US-centric. Our focus will always be strategic rather than strictly scientific, and the prospects for a rich product pipeline have never been better. Everything an Enterprise partner accomplishes is, to some degree, an achievement for the field at large and for the Enterprise ideal.

### **Where is the field of AIDS vaccines headed?**

I think there is no question that we are on a path where we will get answers to certain questions in the foreseeable future that will be hugely important. That will help us to narrow down the directions we want to go in and help us to better understand what is going on with neutralizing antibodies and the RV144 model. Also, some new approaches and platforms may be transformative. The biggest handicap has always been how long it takes to do certain things—to get animal studies done, to get human endpoints and samples, etc. The field is really paying attention and trying to speed up the iterative process and I think that it is going to bear fruit. ■

---

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

# HIV Field's *Current Contours* Show in Boston

HIV prevention was the top story at CROI 2016, but issues of adherence and uptake still loom large in the battle to stop HIV's spread.

By Michael Dumiak

Last summer more than 2,500 women across the sub-Saharan nations of Malawi, South Africa, Uganda, and Zimbabwe completed their participation in a three-year clinical trial of a monthly vaginal ring containing an experimental antiretroviral (ARV) known as dapivirine (DPV). It was the larger of two simultaneous efficacy studies of vaginal rings as pre-exposure prophylaxis, or PrEP—the use of ARVs in healthy individuals to ward off HIV infection.

Researchers gathered for this year's Conference on Retroviruses and Opportunistic Infections (CROI), held Feb. 21-26 in Boston, heard firsthand the results of these two efficacy studies. Overall, the rings were 27 percent to 31 percent effective in reducing the incidence of HIV infection in women ages 18 to 45. The broader implications of this and other HIV prevention strategies set the tone at this year's CROI. Behavioral issues still loom large and researchers discussed how to reach younger, more vulnerable people with HIV prophylaxis, including daily oral PrEP, which so far shows much higher efficacy than the ring.

Meanwhile some of the newer ARVs in development may offer another option for both treating and preventing HIV infection.

## Aspiring to protection

The DPV ring was tested simultaneously in two placebo-controlled efficacy trials: A Study to Prevent Infection with a Ring for Extended Use, or ASPIRE trial (MTN-020), and what's called The Ring Study. ASPIRE, led by the National Institutes of Health (NIH)-funded Microbicide

Trials Network, is the larger trial with 2,629 volunteers enrolled at 15 study sites: nine in South Africa, three in Zimbabwe, two in Malawi, and one in Uganda. This trial took place from August 2012 to June of 2015. The Ring Study was led by the International Partnership for Microbicides (IPM) and involved 1,959 women volunteers in South Africa and Uganda. The budget for each trial was approximately US\$72 million.

DPV-containing vaginal ring development dates back to 2002 with the founding of IPM, which launched in order to develop antiretroviral-based microbicides for prophylaxis in mother-to-child transmission and to prevent sexual transmission between adults as well.

The ring is itself, which has been used for contraception, is essentially a silicone 'o,' which contains 25 milligrams of DPV, a non-nucleoside reverse transcriptase inhibitor never licensed for treatment. The ring is designed to slowly release drug over one month of use. IPM holds a global dapivirine license from Janssen R&D Ireland, one of the Janssen Pharmaceutical companies of Johnson & Johnson, which originally developed the drug as the independent biotechnology company Tibotec.

Volunteers in both trials were counseled to use the ring continuously and return each month for collection of the spent device, to obtain a fresh one, to be tested for pregnancy, HIV, and other sexually transmitted diseases, and to receive HIV prevention and risk-reduction counseling. Follow-up was for a minimum of one year.

Results from ASPIRE and The Ring Study differed only slightly in their overall protection rates,



with ASPIRE showing an overall 27 percent reduction in HIV infection and The Ring Study showing a reduction of 31 percent. But the trials showed vastly differing rates of protection when looked at more closely and analyzed by age. In ASPIRE, women aged 18 to 21 showed no overall reduction in HIV risk, whereas in The Ring Study it was only 15 percent. Among older women, there was a 56 percent reduction in risk for women ages 22 to 26, and a 51 percent reduction among women ages 27 to 45. The Ring Study showed 37 percent efficacy in women older than 21.

The main reason the protective effect varied so greatly was adherence. Adherence was significantly lower among women in the 18 to 21 age group. “We really wanted those numbers to be higher. We were disappointed, too, originally,” says Annlene Nel, IPM’s Paarl, South Africa-based chief medical officer. Even so, the researchers behind the studies say the results are compelling enough to pursue licensure of the DPV ring.

To receive regulatory approval, the group needed two pivotal trials showing statistically significant efficacy. “We’ve got that,” says Nel. “It is modest efficacy. We know that, very much so. But look at the burden of disease in the communities where we are conducting this trial. It is significant. If you can prevent a third of women from contracting HIV, over 10 years you prevent thousands of women from becoming HIV positive. Long term you can really change the incidence. It would be a huge difference coming down from 8 percent to 4 percent.”

The ring has many supporters in the HIV community, many of whom expressed their support in Boston. But some there also questioned the ring’s very clearly reduced effectiveness in younger women and the overarching problem with adherence. Development of the ring itself comes directly from the effort to improve adherence—insert the ring and forget about it. But adherence is still an issue.

Nel and other researchers suspect non-adherence had to do with volunteers being leery about the safety and efficacy of the product. “There may also be rumors in the community. A negative influence really spreads. And when there’s a change of partner, there’s a fear component where they will not disclose and then they might just remove the ring.”

Sheena McCormack, a clinical epidemiologist at the Medical Research Council Clinical Trials Unit at the University College of London, says the rings are a new beast altogether, and there are issues around vaginal practices that may influence

their use. “Women do like to wash after sex. It’s possible they take the ring out to do that. It might be something that doesn’t fit with their culture, doing that with the ring in,” she says.

## Finding the best drug

One critique of the overall ring results is that the protective effect was lowest in the young, sexually active women who are at great risk of HIV infection. Another is that the existing alternative, oral PrEP with the drug Truvada (a combination of the ARVs tenofovir and emtricitabine), is between 92 and 99 percent effective in preventing HIV infection when used consistently. Some wonder what accounts for this gap in efficacy.

“I have some questions around the drug. Would we have seen a different result if it had been a tenofovir ring or another drug that once released stays in the genital tract a little bit longer?” McCormack asks. She is co-principal investigator of the Microbicides Development Program and was chief investigator for the PROUD trial, which studied the use of oral PrEP in men who have sex with men.

Dapivirine and tenofovir are very different drugs, McCormack says. Oral PrEP acts systemically, so it takes longer to get into genital tissues; a vaginal ring releases a smaller amount of drug locally so there are high levels in the genital tissues but lower drug levels elsewhere. It’s altogether hard to differentiate which is more effective, given all the behavioral factors affecting use.

“It is clear that oral tenofovir, when used daily, has a higher level of efficacy,” says Robin Shattock, an immunologist and mucosal infection expert at the Imperial College of London. “That’s really when you are taking it every day.” Still, Shattock, who is researching combination prevention approaches, including ARV-based gels or rings as well as the use of broadly neutralizing monoclonal antibodies, is optimistic about the dapivirine ring’s chances. “When the ring was being designed, they could have put more drug into the ring. I think more drug probably would have given higher efficacy in women that used it,” he says. “That can be improved.”

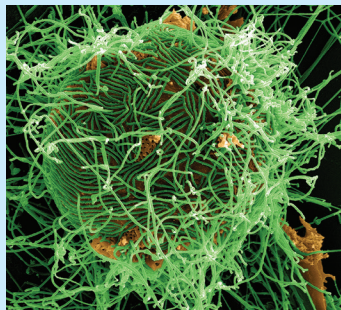
A combination of drugs may also provide better protection. Shattock says combining the ring with a contraceptive, as IPM plans to do, would be a no-brainer. “Women may then be using it for the convenience of contraception, and to have a contraceptive ring that also provides some level of protection against HIV may be more appealing than thinking, ‘I’m at risk and need to have something that will stop me from getting HIV.’”

 **As we enter the third decade of *IAVI Report*, we would like to ask you for your feedback. Please take our brief survey at [www.surveymonkey.com/r/IAVIReport](http://www.surveymonkey.com/r/IAVIReport).**

## A coda for Ebola

For the better part of 18 months, the world's largest Ebola outbreak to date raged through the western African nations of Liberia, Sierra Leone, and Guinea. It devastated villages and families, set the world on edge, and prompted a desperate global health response, heroic in the moment and in some cases criticized afterward for being sluggish. During all this, three vaccine candidates emerged into public view and went through quickly organized clinical trials. Safety and efficacy data emerged last fall (see *When Ebola Returns, Will the World be Ready?*, IAVI Report, Issue 4, 2015) and the trials continue to yield valuable information, as presented in February at the Conference on Retroviruses and Opportunistic Infections (CROI).

Researchers shared Phase II clinical trials results for the two leading vaccine candidates tested during the 2014-2016 outbreak. The first, a vesicular stomatitis virus-vectored replication-competent vaccine (rVSV-ZEBOV) from Merck and the Public Health Agency of Canada, was tested in Guinea and Sierra Leone. The other was a chimpanzee adenovirus-vectored DNA vaccine (ChAd3-EBO-Z) from GlaxoSmithKline and the National Institutes of Health, which was tested in Liberia. Also discussed at CROI was the Ebola treatment ZMapp, a triple monoclonal antibody cocktail tested in all three nations. The Merck and GSK candidates came under the collaborative umbrella representing dozens of international and local agencies in what's called PREVAIL: PREVAIL I is the effort covering the two vaccine candidates, PREVAIL II covered the ZMapp treatment effort, and PREVAIL III is an ongoing effort to gauge Ebola's longer-term impact on survivors of the virus.



Ebola virus particles (green) budding from a chronically infected VERO E6 cell. Image courtesy of the National Institute of Allergy and Infectious Diseases

Fatorma Bolay, director of the Liberian Institute for Biomedical Research, pointed out that both vaccine candidates are well tolerated and immunogenic, as has been reported previously. But further analysis of the data is now bringing other aspects into focus: for instance, the trial shows that six percent of volunteers entered the study with detectable levels of Ebola antibodies, suggesting they had been infected with the virus before but had no known history of the disease. The candidates also seemed to induce antibodies at different rates. The ChAd3 candidate produced immune responses in week one in 13 percent of volunteers, the VSV in nine percent, and the placebo in six percent. But by the end of one month, 87 percent of ChAd3-vaccinated individuals developed an antibody response, while 94 percent of VSV-

vaccinated individuals did, and only seven percent of placebo recipients had Ebola antibodies.

Meanwhile three studies of thousands of Ebola survivors are ongoing. Early data from these efforts provide evidence for a possible syndrome that develops in Ebola survivors, signs that Ebola can cause unrecognized and asymptomatic infection, and growing confirmation of the potential of Ebola to be transmitted through sexual transmission. "There are still many gaps in our knowledge of Ebola," says Gene Richardson, a Stanford field researcher. Bolay and Mosoka Fallah, of the Liberian health ministry, also reported that in the PREVAIL vaccine volunteer group totaling 1,500, 5.2 percent were HIV infected, which is unexpectedly high, according to the National Institute of Allergy and Infectious Diseases. The reported HIV incidence rate in the country overall is 1.9 percent, according to Bolay. This raises questions about whether the incidence is just much higher among younger people or if the estimated incidence doesn't reflect the actual size of the HIV epidemic in these west African countries. —M.D.

For any of the PrEP regimens, adherence is the key to efficacy. "For these things to work, people need to use them," Shattock says.

Bruce Walker, an immunologist and director of the Ragon Institute of Massachusetts General Hospital, the Massachusetts Institute of Technology (MIT), and Harvard, says tools need to be independent of behavior. "We need things that are going to work in women at the most vulnerable periods of their lives. The fact the ring didn't really work in women before age 25 is a disappointing finding. I'm less optimistic about that being part of a solution for HIV infection," he says. "The more you can take behavior out of the equation, the more successful these interventions are going to be."

Three of the 15 clinics in the ASPIRE trial were located in Zimbabwe, serving 678 of the study volunteers. Nyaradzo Mgodli of the University of Zimbabwe served as clinical researcher directing the study. "In Zimbabwe we have a saying, home is a woman. We want to take care of women because this is how you make steps in promoting public health. I'm happy about the results," Mgodli says.

She thinks that in Zimbabwe a ring has a better shot of being used, even given the adherence questions. "Most young women in Zimbabwe are unemployed. Some of them have secondary education. They are homemakers, they take care of their family and extended family," Mgodli says. "Any day they may be asked to go to rural areas to look after a sick relative, or attend a funeral, or go to a church conference." Mgodli recalls the VOICE trial that tested oral PrEP in sub-Saharan Africa. "The volunteers used to say they would forget sometimes to take their tablets. They want something which is less user-dependent, so I think this will be good."

IPM is pushing ahead with an open-label, follow-on study of Ring Study volunteers, and is also in discussions for a similar open-label study for ASPIRE participants. Open-label studies may positively influence adherence, according to the University of Washington's Jared Baeten, who led the ASPIRE study. Baeten says what is important now is to understand who are the populations that would use a pill, and who are the populations who would not use a pill but might use a ring. Meanwhile, the group is compiling data for a submission dossier which, if things go as planned, should be delivered to the European Medical Association and regional southern African regulators either by the end of this year or in the first quarter of 2017. The funders—the Bill & Melinda Gates Foundation, UK's Depart-

ment for International Development, and other European nations—appear to support this plan.

Response to the ring results stands in marked contrast to the disappointment over the RV144 vaccine trials which showed that a combination of two vaccine candidates reduced HIV infection rates among volunteers by 31 percent. Shattock says the overall gloomy reaction to the RV144 trial and the apparent enthusiasm for the DPV ring, despite similar overall efficacy rates, is due to the science.

“It’s an important first step and there are some obvious steps to take to improve it,” Shattock says of the ring. There are many other possible drugs that can be explored, and most importantly, researchers understand how they work. Human behavior is more complicated, but the science is not such a hard issue as it is with vaccines. “The contrast with the Thai trial is that to this day I don’t think anyone really understands what the mechanistic correlates are,” Shattock says. “You have lots of immune correlates that reduce risk of infection, but we don’t know the mechanism. So to know where to go next takes guesswork.”

## Getting word out on PrEP

Given the imprimatur of top health officials and its well-established efficacy, one would think oral PrEP would be a settled issue. But getting at-risk individuals to actually use it is very much a work in progress.

Gilead first launched Truvada for the treatment of HIV-infected adults in the US in August 2004. Based on results from the iPrEx and Partners PrEP clinical trials testing the drug for HIV prevention, the US Food and Drug Administration approved Truvada in 2012 as the first oral PrEP drug. That same year the World Health Organization recommended daily oral PrEP use for serodiscordant couples and also noted the scientific consensus emerging that PrEP reduces the risk of sexual acquisition and transmission of HIV regardless of population or setting. The institution later recommended oral PrEP for all high-risk individuals.

Since then, however, uptake is slower than expected. By the summer of 2014, Johns Hopkins University HIV epidemiologist Chris Beyrer was telling the *Guardian* that Truvada, to that point, was a “boutique intervention.” This was partly due to cost in the US, where it carried a price tag of between \$8,000 and \$14,000 a year, although Gilead was offering subsidies for those without private insurance. Daily adherence was also being seen as an impediment. These factors were at play especially in minority and poor communities.

The US Centers for Disease Control and Prevention (CDC) estimates 185,000 new HIV infections in the US could be prevented by expanding testing, treatment, and, notably, oral PrEP.

In Chicago and London, efforts are underway to address the lag in PrEP uptake. Chicago’s PrEP effort, as outlined by Jim Pickett of the AIDS Foundation Chicago, involves a social and promotional campaign launched in February. Pickett and Chicago health officials were able to enlist volunteer help from a global advertising agency to create a professionally-designed, data-driven marketing, social media, and publicity campaign for PrEP in Chicago.

Pickett says that in 2015 the number of new HIV infections reported in Chicago dipped under 1,000 for the first time since the epidemic began, with 973 new cases occurring in 2014. That’s about half of the peak number reported in 2001. But there are disparities: half of new cases are among black people, and of the women who do contract the virus, most of them are black. Three of four new infections are among gay or bisexual men in Chicago; half of this number are black men and another 25 percent are latino.

A CDC study shows 77 percent awareness of oral PrEP in Chicago, but further surveying shows of those aware, only 14 percent had obtained subscriptions. Of those surveyed who were aware of PrEP but did not have a prescription, half reported having unprotected anal intercourse. “We’re missing the boat,” Pickett says. For his crew in Chicago, time will tell how effective PrEP marketing can be. A second wave of the campaign launches this summer.

Elsewhere, researchers, clinicians, and advocates are also beginning to think about how to incorporate oral PrEP in order to reduce incidence of HIV among the subgroups of individuals at highest risk of infection. In the last decade HIV infections have risen across Europe by 33 percent among men who have sex with men, while falling 61 percent among heterosexuals from countries with generalized HIV epidemics and declining by 36 percent among those injecting drugs. In Europe there’s a new urgency for early diagnosis of HIV and other sexually transmitted infections. Since McCormack and her colleagues reported in 2015 on the PROUD study showing up to 85 percent effectiveness for Truvada, some 6,000 new HIV infections have been diagnosed in the UK. “Over half of them have been seen previously in the clinic and could have been offered PrEP,” McCormack said during her CROI presentation. “PrEP has to be part of the vision for the future.”

McCormack says a small clinic on Dean Street in the Soho neighborhood of London called Dean Street Express, which offers faster, more self-directed testing for HIV and other sexually transmitted infections, may be a natural place to promote PrEP. Dean Street Express neither looks nor feels like a clinic. An aid sets up a client with swabs. The client goes into the screening room, where a digital presentation on the mirror explains how to do the testing. The samples go into a container, which goes into a pneumatic tube. Test results are delivered in six hours by text message.

The UK National Health Service (NHS) is in the process of considering Truvada for listing, which would make PrEP free for UK residents. It is becoming a heated debate, though.

### Cutting half life in half

Another realm of prevention research discussed at CROI centers on the hundreds of broadly neutralizing antibodies (bNAbs) researchers have isolated from HIV-infected indi-

viduals in recent years. These antibodies, which can effectively neutralize a broad swath of HIV isolates, are the types that vaccine researchers ideally wish to induce through immunization.

In the meantime, researchers including John Mascola, director of the National Institute of Allergy and Infectious Diseases' Vaccine Research Center, want to determine whether directly injecting these antibodies into people may be able to block HIV infection, an approach referred to as passive administration. To optimize the antibodies for this purpose, researchers are attempting to improve the potency and half-life of these antibodies so that less antibody is necessary and it stays around for a longer time. "The consideration for using the antibodies for prevention has been that we may be able to test them on an interval of about every two months," Mascola said.

Two antibodies targeting the CD4 binding site (VRC01 and 3BNC117) are already in Phase I passive administration studies. Michel Nussenzweig and colleagues at Rockefeller University have started Phase I studies with the antibody 10-1074; Mascola expects studies with PGT121 to begin within the next year. These two antibodies target different vulnerability sites on the virus. Other antibodies, including PGDM1400, CAP256-VRC26, and 10e8, will probably take a year to 18 months to get into the clinic. Within the next couple years, Mascola says, antibodies targeting four major sites on the virus are likely to be in passive-administration studies.

He reported that in Phase I trials VRC01 lingered at titers of up to 10 micrograms per ml in serum for about two months. The question now is whether that concentration of antibody is sufficient to prevent HIV infection. A Phase IIb study, the Antibody-Mediated Prevention (AMP) Study, opened enrollment this month under the umbrella of both the HIV Prevention and Vaccine Trial Networks. "Can a passively infused antibody prevent HIV in humans?" Mascola asked. "That's what needs to be studied and answered." AMP will be a placebo-controlled study of VRC01 administered every two months in 2,700 men who have sex with men and transgendered people in North and South America, and 1,500 women in sub-Saharan Africa. The aim is to associate the level of antibody in a volunteer's plasma with the level of protection and therefore define the optimum dosage.

"If that level turns out to be fairly reasonable, a therapeutic range that we might expect, it translates into the possibility of giving an anti-

## Complex and persistent

Each HIV particle may be alike, but Melbourne immunologist Sharon Lewin's coming to conclude that every HIV infection persists in its own way.

"We're hearing a lot more about the complexity of how and where HIV persists," Lewin says, sitting for a minute in one of the huge halls of the John Hynes Convention Center at the recently held Conference on Retroviruses and Opportunistic Infections (CROI). "The initial dogma was that there was a long-lived resting pool of cells where HIV persisted indefinitely. We're seeing now that there's no one way that HIV persists. It probably persists differently in different immune cells in tissue and blood."

This is the central question for those pursuing an HIV cure: in order to rid a person of HIV, researchers need to understand exactly how the virus gets into specific cells, why it stays there, and how to flush it out. They'll need to flush it out because all indications are that if antiretroviral treatment stops, it's only a matter of time before this latent reservoir of HIV-infected cells causes viral rebound. "There's not one flavor of latency. We're trying to dig it out: in naïve T-cells, T-follicular helper cells, in proliferating T-cells. They all look very different," Lewin says.

Her lab at the University of Melbourne is able to mimic, *in vivo*, what she says is one of the latest wrinkles in persistence. Emory's Nitasha Kumar, a researcher formerly in Lewin's group, presented results at CROI demonstrating that latency can be established in non-proliferating and proliferating cells. Lewin says the implication is that virus persists not just in non-dividing cells, but also in cells that can proliferate. The virally infected proliferating T-cells divide, and make new infected T-cells. "The virus is intact, yet it doesn't destroy the cell, which challenges a long held dogma in the field," Lewin says. Many researchers believed if a virus was intact, then proliferation would activate the virus and therefore kill the cell. As it turns out, Lewin says, it appears that latency can be established in proliferating cells *in vitro* and that these cells are long lived. So if researchers are only looking for latency in long-lived resting cells, they may be missing another reservoir of the virus. —M.D.

body subcutaneously,” Mascola says. Muscle itself could, potentially, be lured into secreting antibody for weeks or months at a time, providing medium-to-long-term protection. “Knowledge of protection in a human setting would tell us something about neutralizing antibody levels and what a vaccine might need to elicit in order to protect.”

Mascola says there are many reasons to pursue passive administration: there’s a reasonable chance it will work, that because the antibodies are human antibodies they are likely to be well-tolerated, that a single shot could potentially deliver long-term protection, and that clinical efficacy would propel this approach into mainstream use. The ultimate goal, he says, is a subcutaneous injectable antibody that could be given every three to four months and safely and effectively protect high-risk individuals from HIV infection. “That’s where the field is trying to go,” Mascola says.

To do so, any eventual product needs to meet specific targets: it will need to cover 98 to 99 percent of all HIV strains, which may require a combination of bNAbs, cost about as much as ARV-based PrEP, and be given subcutaneously every three to four months. These elements, Mascola says, are already achievable in the lab. The bNAb N6 neutralizes more broadly than VRC01, only missing three percent of viruses as opposed to VRC01’s 13 percent, and is much more potent. Other antibodies can be engineered in order to boost their potency, and combining antibodies, at least in the lab, shows it is possible to gain 100 percent coverage and account for the diversity of HIV.

There is also reason to be optimistic about efforts to improve the half-life of the antibodies. Mascola uses an example from AstraZeneca subsidiary Medimmune, which is investigating a monoclonal antibody called motavizumab (the company had pursued it for respiratory syncytial virus infection unsuccessfully, but continues to work with it). A 2012 trial of mutated motavizumab, motavizumab-YTE, extended the half-life of the antibody for up to six months at 10 micrograms per ml of serum. “That’s a remarkable feature one would hope to take advantage of for prevention studies,” he says.

The VRC scientists introduced mutations into VRC01 to improve its half-life and are now testing the modified antibody in a Phase I trial. “We will know soon if we can take the half-life from about two months of therapeutic range out to four, five, or six months.”

## Long-lasting inhibition

Extending the half-life of ARVs also looks more promising. Jay Grobler, director of infectious disease biology at pharmaceutical company Merck, presented data at CROI on a long-acting, experimental nucleoside reverse transcriptase inhibitor known as MK-8591, which the company licensed from Japanese company Yamasa. Grobler said the drug has the potential for once-weekly oral administration as well as much longer-acting parenteral administration that could persist for up to a year. The drug is being explored for both HIV treatment and prophylaxis.

Grobler reported results from Phase I pharmacokinetic studies of MK-8591, which he says showed the drug had an even greater intracellular persistence and antiviral activity than was observed in *in vitro* studies and in rhesus macaques. Following a single oral 50 milligram-per-kilogram dose, Merck researchers saw a very rapid uptake of the molecule, with high concentrations reached in blood within an hour. Concentrations stayed over 10 micrograms per ml for more than a week; the absorbed drug has a half-life in monkeys of more than 50 hours.

In the Phase I dosing study, volunteers received varying doses of MK-8591 (10, 30, and 100 milligrams) once a week for three weeks. “At that 10-milligram dose we’ve already exceeded the target drug concentration with the SIV monkey model,” he says. “One week after dosing, the trough concentrations exceeds that target twofold.” Doses of up to 400 mg were well tolerated.

Merck considers the molecule ideal for low-dose parenteral formulations, either by injection or patch, which release effective drug levels for up to 180 days. There is potential for the long-acting ARV to even provide coverage for up to a year’s time. Either way, this type of treatment would greatly reduce the burden of therapy. As prophylaxis, it could potentially eliminate the reliance on behavior, which has proven problematic even with the monthly rings.

David Margolis, director of drug development at ViiV, the HIV joint venture between GlaxoSmithKline and Pfizer, has been overseeing another long-acting HIV therapeutic—in this case, combining the ARVs cabotegravir, an integrase inhibitor, with rilpivirine, a non-nucleoside reverse transcriptase inhibitor. Both were developed as once-daily pills. But in the LATTE program (*Lancet Inf. Dis.* 10, 1145-55, 2015), for which Margolis in Boston presented the second round of study results, researchers are testing the

*Continued on page 15*

# In BRIEF

## Chief Science Officer of IAVI departs to lead Human Vaccines Project

After nearly 17 years at the helm of the research and development program at the International AIDS Vaccine Initiative (IAVI), Wayne Koff left his full-time role as Chief Science Officer at the organization in March to assume a new role as President of the Human Vaccines Project (HVP). This recently formed non-profit venture is focused on rational design of vaccines against a variety of challenging pathogens.

Koff's work with HIV began in 1985 in academia. The virus, and stopping its spread through vaccination, became a thread that has run throughout his career in government, industry, and the non-profit sector. Koff joined IAVI in 1999, three years after the organization was founded, and is only the second person to head its research and development department. Margaret Johnston was the organization's founding Vice President of Scientific Affairs.

Koff recalls that time in IAVI's history as an exciting one. "At the beginning IAVI had the enthusiasm, naivety, and the energy of being a brand-new idea," he says. "We were on a ramp-up phase for a number of years. As the funding increased, the opportunity increased." IAVI's founder Seth Berkley, who served as chief executive officer until 2011, brought Koff on board to lead the organization's growing interest in research and development. Dennis Burton, scientific director of IAVI's Neutralizing Antibody Center and an immunologist at The Scripps Research Institute (TSRI) in La Jolla, California, recalls the combination of Berkley's leadership and Koff's innovative nature as a potent one. "I think those two complimented each other greatly. Seth was very charismatic and inspirational and Wayne was a visionary with the science," says Burton. "The two of them together were a formidable force."

During his tenure at IAVI, Koff oversaw several initiatives that opened the door for researchers to pursue many of the vaccine strategies that are being explored today. One of these initiatives was creating the Neutralizing Antibody Consortium (NAC) in 2002. The NAC was created to address what Koff saw as a fundamental challenge to HIV vaccine research: the elicitation of antibodies that could neutralize a broad swath of HIV isolates, so-called broadly neutralizing antibodies (bNAbs). But at that time, this was not the common view among researchers. "Wayne was visionary in his thinking about the Neutralizing Antibody

Consortium. He saw neutralizing antibodies as the future of HIV vaccines at a time when virtually everyone was looking to T cells," recalls Burton. That has since changed. Burton, who just

returned from the recent Keystone Symposium on HIV vaccines, says two thirds to three quarters of the vaccine presentations at the conference were on antibodies.

"When Wayne started the NAC it was about 10 percent," according to Burton.

The NAC began with six or seven investigators focused on different aspects of neutralizing antibody research and then expanded from there. At its largest, the consortium brought together as many as 26 investigators to work collaboratively on eliciting bNAbs against HIV.

Burton also views establishment of the IAVI Neutralizing Antibody Center in 2009 by IAVI and TSRI as another coup that has greatly influenced the current shape of the science. "Wayne was the real driver of this. He really steered IAVI into

supporting this," recalls Burton.

After its establishment at the Scripps campus in La Jolla, the Neutralizing Antibody Center was able to recruit top talent, including researchers William Schief, Pascal Pognard, and Richard Wyatt. "I had the ability to identify and hire people who were a lot smarter than I was and that helped create an R&D team that really contributed to the field," reflects Koff. Burton agrees and says that these hires "accelerated great progress."

Koff can also be credited with innovative epidemiology studies that are continuing to guide vaccine design efforts today. Koff is responsible for driving IAVI's Protocol studies, which helped researchers gain a better understanding of HIV disease among African cohorts as well as the immune responses that develop in response to infection, and also allowed researchers to identify the types of bNAbs that researchers surmised would be vital to vaccine-induced protection. During one of the Protocol studies, researchers collected samples from thousands of HIV-infected volunteers in Africa, India, Australia, Thailand, the UK, and the US. These samples are proving to be a treasure trove for vaccine researchers. In partnership with biotech companies, IAVI and its partners in the NAC were able to isolate dozens of very potent and broadly neutralizing antibodies from these samples. Identification of these antibodies then led to identification of multiple



targets on the virus that were not identified previously. Burton calls the collection of these samples “absolutely crucial to the vaccine field.” The antibodies isolated from these volunteers and the viral epitopes they target, are now the basis of much of the HIV vaccine design and development efforts taking place in labs around the world (see image at right). “The knowledge that has been gained on the HIV Envelope on the molecular level and the knowledge that has been gained with the antibodies is like an inflection point in the field,” says Koff. “We know so much more now.”

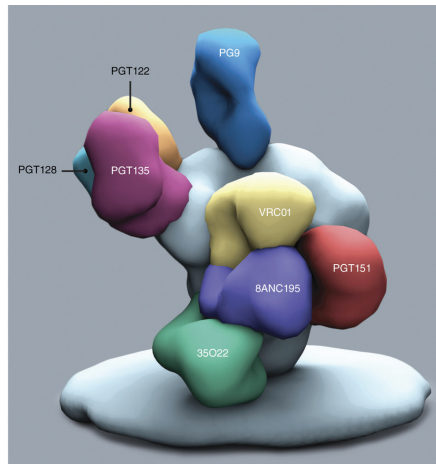
Burton also credits Koff and IAVI with being able to create partnerships with biotechnology companies to advance antibody discovery efforts. “Those interactions led to what many people do today but was all started through the ability of IAVI to move quickly on its feet and interact with these biotech companies. Wayne really orchestrated a lot of that,” adds Burton.

Other contributions include Koff’s oversight of a team that established the Human Immunology Laboratory (HIL) at the Imperial College of Science, Technology, and Medicine in London, and the development of a network of clinical research centers in East and Southern Africa that performed some of the first HIV vaccine trials on the continent. Jill Gilmour, executive director for human immunology at IAVI and principal investigator of the HIL, can enumerate Koff’s contributions and attributes, as well as his unwavering commitment to AIDS vaccine research. “On a personal level I know Wayne believes deeply in the mission,” says

Gilmour. “Wayne has scientifically, and otherwise, challenged himself, IAVI, and the field to tackle major road blocks and to do the right thing and not just what is on trend.” This was particularly true with the establishment of the clinical research centers in Africa. “This challenged the accepted norm and broke through barriers,” recalls Gilmour. “It helped ensure vaccines are tested rapidly in relevant populations and these expert Phase I/II centers now provide access to unique cohorts and samples that are driving vaccine innovation.”

Koff will no doubt be employing similar innovative ideas at the HVP. This non-profit organization started from an idea hatched together with vaccine veterans Stanley Plotkin of the University of Pennsylvania and Ian Gust of the University of Melbourne. The project involves deciphering the human immunome—creating a detailed map of the genes and proteins associated with the human immune response to vaccine antigens—through a series of clinical research studies. This will, in turn, help elucidate the rules of protective immunity and thereby fuel the rational design of vaccine candidates against HIV, influenza, cancer, dengue, and other infectious pathogens.

At the human vaccines project Koff says he’s “right in the middle of the excitement of a new idea,” much like when he joined IAVI. He remains confident that a vaccine against HIV will be developed, eventually. “This is a virus that has found a number of methods of immune evasion, but it is still a virus. It can be blocked and controlled. These are solvable problems.” —*Kristen Jill Kresge*



This image is an electron microscopic reconstruction of the HIV envelope glycoprotein trimer with some of the newly identified antibodies that target different sites of vulnerability on the trimer shown in different colors. These antibodies and the epitopes they target are helping guide vaccine design and discovery efforts. Image courtesy of Dennis Burton at The Scripps Research Institute.

**Continued from page 13**

combination as an injectable, long-acting HIV treatment.

LATTE2, a 32-week study aimed at establishing safety and efficacy of the combination and to set a dosing schedule for future trials, involved 286 volunteers randomized to receive gluteal shots of the ARVs either every four weeks or every eight weeks. A third group took oral cabotegravir and rilpivirine daily.

The trial volunteers had suppressed viral loads of less than 50 copies per ml prior to the injection of the ARVs. Maintenance of virologic success was steady over 32 weeks, Margolis said: by the end of the study, 95 percent of those receiving injections every eight weeks, 94 percent of those getting shots every

four weeks, and 91 percent of those on oral dosing met virological success, which was an undetectable viral load under 50 copies per ml of blood. Volunteer satisfaction was higher for the injection than the oral dosing: 90 versus 71 percent reported satisfaction. The next step, Margolis says, is a 48-week dose-selection for upcoming Phase III trials.

The long-acting cabotegravir/rilpivirine combination outlined by Margolis could be a “game changer” for treatment and prevention once implemented, according to Steve Deeks, a clinician at the University of California at San Francisco who specializes in HIV inflammation. “The CROI data confirm what most of us expected to see with these regimens.

This is an important, but not a particularly new story,” he says. MK-8591, however, could be in Deeks’ view an even more exciting approach to treatment and prevention. “It is potent and can be formulated for very long-acting delivery methods, due to the limited amount of drug needed to block HIV,” the San Francisco clinician says. “In contrast to the cabotegravir-related data at CROI, this data was a complete surprise and quite novel. I find it amazing that 10 mg of a drug could have such a potent and sustained effect.” ■

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

# Upcoming HIV-Related Meetings



## APRIL 2016

### *HIV & Hepatitis in the Americas*

April 28-30; Mexico City, Mexico

More information: [www.hivhepamericas.org](http://www.hivhepamericas.org)

## MAY 2016

### *10th International Workshop on HIV Treatment, Pathogenesis and Prevention Research in Resource-Limited Settings*

May 3-6; Cameroon

More information: [www.virology-education.com/event/upcoming/10th-interest](http://www.virology-education.com/event/upcoming/10th-interest)

### *Asia Pacific AIDS & Co-infections Conference 2016*

May 17-19; Hong Kong

More information: [www.virology-education.com/event/upcoming/apacc2016](http://www.virology-education.com/event/upcoming/apacc2016)

### *Cold Spring Harbor Laboratory: Retroviruses*

May 23-28; Cold Spring Harbor, New York

More information: [meetings.cshl.edu/meetings.aspx?meet=RETRO&year=16](http://meetings.cshl.edu/meetings.aspx?meet=RETRO&year=16)

### *International Conference on HIV & Emerging Infectious Diseases*

May 25-27; Marseille, France

More information: <http://www.isheid.com>

## JUNE 2016

### *12th International Workshop on Co-infection – HIV & Hepatitis*

June 2-3; Berlin, Germany

More information: [www.virology-education.com/event/upcoming/12th-co-infection-workshop-2016](http://www.virology-education.com/event/upcoming/12th-co-infection-workshop-2016)

## JULY 2015

### *21st International AIDS Conference*

July 18-22; Durban, South Africa

More information: [www.ias2016.org](http://www.ias2016.org)

## OCTOBER 2016

### *HIVR4P: HIV Research for Prevention*

October 17-20; Chicago, Illinois

More information: [www.hivr4p.org](http://www.hivr4p.org)

For a full list of meetings and their descriptions, go to [www.iavireport.org/meetings](http://www.iavireport.org/meetings).