

VOLUME 21, ISSUE 4

# IAVI Report

The Publication on AIDS Vaccine Research

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**Pediatric HIV  
Vaccine Trials**

**A Conversation with  
Thomas Hope**

**Drug-Resistant  
HIV on the Rise**

## EDITOR'S LETTER

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Nine years ago this month, we launched the redesigned *IAVI Report*. It was a major overhaul, introducing a new format, more varied content, and featuring our first full-color cover image. Ever since, we've collected and featured an array of images related to HIV on our cover. They are both striking and scientifically relevant as they are helping researchers understand more precisely how the virus behaves.

The image that graced that first cover is still one of my favorites. It showed an HIV-infected dendritic cell in the process of forming a virologic synapse, through which it would transfer HIV to a CD4<sup>+</sup> T cell. Even though it obviously depicts a static moment in time, it feels active. The CD4<sup>+</sup> T cell is being lured by a virus-infected cell, the synapse shown in a smear of red that seems to foretell the cell's future destruction.

That cover was provided courtesy of Thomas Hope, professor of cell and molecular biology at the Feinberg School of Medicine at Northwestern University. His lab continues to churn out alluring images of HIV's interactions and we are thrilled to feature another one of his group's images on this issue's cover. This one reminds me of an undersea landscape and is yet another example of how science makes great art. We also have an interview with Hope in this issue in which he discusses his team's contributions to the development of a long-acting HIV prevention strategy meant to bridge the gap until a future vaccine should become available (see page 9).

In a related story, a new writer to *IAVI Report*, Max Dorfman, profiles Marianne W. Mureithi, who apprenticed in Hope's laboratory in Chicago and is now a chief research scientist at the Kenya AIDS Vaccine Initiative. Mureithi is one of many young African researchers who have returned home after studies abroad to contribute to ending the epidemic that has cost them so much personally (see page 19).

In another feature, we provide an update on a topic the HIV vaccine field is currently grappling with—the possibility of conducting a vaccine trial in a pediatric population (see page 4). The issue is not a new one but recent scientific findings, both in humans and animals, are causing researchers and funders to consider this possibility with renewed urgency. We also delve into the growing threat of antiretroviral resistance in developing countries and how this is raising concerns among public health experts about the fragility of the AIDS response and the need for improved prevention (see page 14). This is undoubtedly an issue that will warrant consideration from Peter Sands, the newly appointed executive director of the Global Fund to Fight AIDS, Tuberculosis and Malaria (see page 18).

Finally, as this year draws to a close, our team at *IAVI Report* would like to wish all of you a healthy, peaceful, and joyous new year. Year after year we are inspired and amazed by the innovative science we get to write about, the personal motivation that drives scientists and advocates toward an HIV vaccine, and the extraordinary commitment of those working tirelessly to end AIDS.

– KRISTEN JILL KRESGE



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

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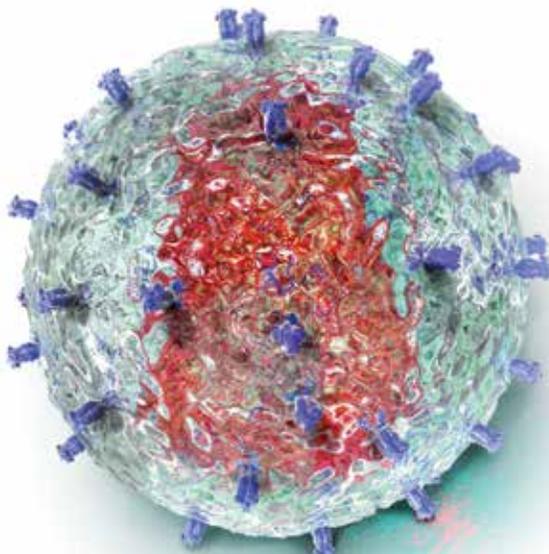
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# IAVIReport

## ASSOCIATE DIRECTOR

Nicole Sender

## MANAGING EDITOR

Kristen Jill Kresge

## CONTRIBUTING WRITERS

Max Dorfman

Michael Dumiak

Mary Rushton

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Email us at [iavireport@iavi.org](mailto:iavireport@iavi.org)

## [ ON THE COVER ]

Image shows a transverse section of crypts located in the rhesus macaque rectum 48 hours after rectal challenge with single round simian immunodeficiency virus-based dual-reporter expressing Luciferase and mCherry. The epithelial cells (green) forming the crypts are visualized by staining for the E-cadherin in adherens junctions, and the transduced (infected) cells are revealed by their expression of mCherry fluorescent protein (red). Nuclei (blue) are revealed by staining with DAPI. Panel image acquired on a DeltaVision deconvolution microscope.

*Image provided by Danijela Maric and Thomas J. Hope, Northwestern University.*

# Do Pediatric Vaccines STAND A BETTER CHANCE of Protecting Against HIV?

A committee asks age-old questions about immunity as they set out to look at how the delicate and complex immune systems of infants and young children might help inform AIDS vaccine development.

By Mary Rushton

In the decades-long search for a safe and effective AIDS vaccine, scientists have developed and tested dozens of different candidates, involving many different strategies. So far these efforts have been met with limited success. In 2009, results from the RV144 trial in Thailand showed a modest 31.2 percent efficacy against a prime-boost candidate that many AIDS researchers thought had a slim chance of working at all (see *Special Report: Thai Trial Results, IAVI Report*, Sep. 1, 2009). But the vaccine candidates—a canarypox vector-based ALVAC-HIV in combination with a genetically engineered version of gp120—tested in 16,000 individuals at risk for HIV, did not meet the criteria to warrant licensure. No other candidates have demonstrated any efficacy at all.

There are many reasons why it is so difficult to develop a highly effective and durable AIDS vaccine that could confer immunity against the vast numbers of circulating strains of the virus. One is that scientists have not yet been able to successfully design a vaccine capable of inducing broadly neutralizing antibodies (bNAbs) against HIV's many diverse strains because our immune systems are generally outmatched by the virus. The field also suffers from the limitations of animal models that do not perfectly mimic what occurs in humans following HIV exposure.

There are other reasons for sure, but it is an open debate whether one of those reasons is that

researchers are focusing too exclusively on developing and testing vaccine candidates for, and in, adults, rather than exploring ways to study the evolving and maturing immune responses in younger individuals. That was one of the questions that percolated in September when the AIDS Vaccine Research Subcommittee (AVRS), an advisory panel that provides advice and makes recommendations to leaders at the US National Institute of Allergy and Infectious Diseases (NIAID), devoted a whole day to the topic of pediatric HIV vaccine development.

Mary Marovich, director of the AIDS Vaccine Research Program at NIAID, says the discussion at AVRS was sparked in part by recent human and animal data, including compelling evidence that HIV-infected infants generate bNAbs faster than HIV-infected adults (*Nat. Med.* 20, 665, 2014).

“I was trying to be provocative with our experts... to push them to begin to think about whether we are in a situation where we could look at using and testing existing immunogens, as long as they are safe in adults, in an early life immunization strategy,” says Marovich.

The International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT), supported by NIAID, and the US National Institute of Child Health and Human Development have done early stage HIV vaccine trials in much younger volunteers. And a group of NIAID-

funded scientists led by investigators from the Duke University Human Vaccine Institute have been studying neonatal immunity in nonhuman primates vaccinated with HIV vaccine candidates for the past several years, as have researchers at the University of California at Davis.

But the AVRS wants to take this idea further. The September meeting spurred promises from the committee to form a working group populated by representatives from child health groups and HIV vaccine networks. Marovich says the working group, which she expects to be organized by January, will examine the immunization landscape over the next 18 months and determine which, if any, of the immunogens that have already proven to be safe in adults could reasonably be tested in children, and if so what would be the appropriate age to immunize.

“The AVRS meeting was about whether we should develop a research agenda in this area. The working group will be more about how to do this and who is going to do it,” says Marovich. “While we are not actively discussing doing pediatric efficacy trials now, we can do Phase I safety studies and the bridging studies once we have a signal in adults.”

Just what immunogens might be tested in Phase I pediatric HIV vaccine trials, however, remains an open question. Currently, there are only two HIV vaccine efficacy trials in progress. One, a Phase IIb test-of-concept study known as HVTN 702, is evaluating a prime-boost regimen that is based on the one used in the RV144 trial. The study is enrolling 5,400 high-risk men and women in South Africa. Last month another Phase IIb study began in South Africa testing a prime-boost regimen developed by the Ragon Institute of Massachusetts General Hospital, the Massachusetts Institute of Technology, and Harvard, advanced to clinical trials by Johnson & Johnson’s Janssen Pharmaceutical Companies, the Bill & Melinda Gates Foundation, and NIAID. The trial’s organizers plan to include four other countries in southern Africa pending regulatory approvals. The study, known as Imbokodo (the Zulu word for rock, part of a South African proverb that refers to the strength of women and their importance in the community), is evaluating an adenovirus serotype 26 (Ad26) viral vector vaccine candidate containing four mosaic antigens engineered to provide optimal coverage against all circulating HIV variants, in combination with a clade C gp120 vaccine candidate.

There are many other scheduled or ongoing Phase I and II studies of vaccine regimens or antibody-mediated prophylaxis, including a study in HIV-exposed infants that will test whether bNAbs administered by injection are protective. Infants and toddlers are also a major focus of HIV cure research, given some of the recent findings that show very early initiation of antiretroviral (ARV) therapy in HIV-infected infants can result in undetectable virus levels for a period of years.

But to date, there have been no efficacy trials for HIV vaccine candidates conducted in infants or children, and the majority of safety and immunogenicity trials of preventive vaccine candidates developed so far have also been done in people 18 years of age or older. This is partly because HIV is primarily transmitted sexually or by sharing needles with an HIV-infected person. But Marovich questions whether researchers should consider vaccinating earlier. “Does it make sense to keep testing vaccines in adults after their sexual debut or to lower the age range to establish protection before they are exposed or during high-risk times like breast feeding?” she asks.

As Marovich points out, despite the overwhelming success of preventing mother-to-child transmission (PMTCT) of HIV, children are still vulnerable to the virus during the breast-feeding period. PMTCT is credited with helping to prevent 1.6 million new infections since 1995, a 2016 Joint United Nations Programme on HIV/AIDS (UNAIDS) report says. Cases of perinatal HIV transmission have declined by more than 90 percent in the US, according to the US Centers for Disease Control and Prevention (CDC), and there are 60 percent fewer children being newly infected in sub-Saharan Africa since 2009. Yet there are still thousands of children acquiring HIV from their mothers. A recent UNAIDS report estimates that every year 110,000 children are being newly infected with HIV in 21 sub-Saharan countries, with more than half of these infections occurring during the breast-feeding period. “In areas where the epidemic is still raging on, there has been good efforts and success in preventing mother-to-child transmission, but there are still gaps,” says Marovich. “There are still approximately 200,000 infants [worldwide] that are infected each year with HIV because they are born to infected mothers. For whatever reason, they were late presenters [to care], or adherence to ARVs post-birth was poor, or it happened through breast feeding. So it is still an issue globally.”

## Past studies

Early on, before the dawn of ARV-based PMTCT, researchers were interested in testing vaccines to see if they could protect infants from the virus. In the early 1990s, a dose-escalation vaccine study led by New York University was conducted in 126 HIV-uninfected infants born to HIV-infected mothers in the US. The infants received four doses of recombinant HIV gp120 vaccine candidates developed by either VaxGen in partnership with Genentech, or Chiron, now part of Novartis, to see whether these HIV antigens were immunogenic. One regimen involved giving a dose at birth and then at one, three, and five months of age, while another more accelerated regimen started with a dose at birth, and then others at two weeks, two months, and five months of age (*J. Infect. Dis.* **181**, 890, 2000).

At the end of the study, immune responses were detected in over half the infants after the second dose and those responses persisted for 104 weeks, with stronger responses observed in infants given the accelerated regimen. But three years after this study, two Phase III trials in men who have sex with men (MSM) and injection drug users testing the VaxGen recombinant gp120 candidate failed to demonstrate any efficacy (*J. Infect Dis.* **192**, 974, 2005). This brought an abrupt end to any discussions about studying the regimen further in infants.

Plans to test another HIV vaccine candidate in breast-fed infants were also abandoned after the candidate failed to prevent HIV infection in adults. A collaboration between the Elizabeth Glaser Pediatric AIDS Foundation, IMPAACT, the HIV Vaccine Trials Network (HVTN), and Merck was planning to test the company's ade-

novirus serotype 5 (Ad5) vaccine candidate in the breast-fed infants of HIV-infected mothers in sub-Saharan Africa, but the trial was shelved after the Phase IIb test-of-concept STEP trial in MSM and high-risk heterosexual women evaluating the same vaccine candidate was stopped early for futility (see *A STEP Back?*, *IAVI Report*, Vol. 11, No. 5, 2007).

More recently, a small randomized, placebo-controlled trial known as HPTN 027 found that ALVAC-HIV vCP1521, one of the vaccine candidates used in the RV144 trial, was safe, well tolerated, and immunogenic in infants born to HIV-infected mothers in Uganda (*J. Acquir. Immune Def. Syd.* **65**, 68, 2014). Another Phase I/II study known as PedVacc 002 was conducted in Kenya to determine the safety and immunogenicity of a Modified Vaccinia Ankara (MVA) viral vector-based vaccine candidate in infants born to HIV-infected mothers. The single, low dose was delivered intramuscularly to healthy, four-month-old infants. The study demonstrated that the vaccine was safe but not immunogenic (*Vaccine* **32**, 5801, 2014).

## Why immunize earlier?

Most preventive vaccines are administered to infants and young children, largely before age two, because the developing immune systems of young children are more vulnerable to infection with life-threatening viruses. The sooner children are vaccinated, the less likely they are to be affected by the diseases the vaccines protect against. And when vaccine coverage is high enough, as is the case with many childhood immunizations, it can help eliminate virus transmission almost entirely.

To accomplish this though, the immune responses to childhood vaccinations must be strong and durable enough to be protective for long periods of time, which is something that has eluded HIV vaccine researchers so far.

It is possible, however, that immune responses to HIV antigens may be stronger in infants than adults, which is one reason the AVRS is discussing the topic of infant trials. Barton Haynes, director of the Human Vaccine Institute at Duke University, says that while some aspects of the neonatal immune system are immature and slower to respond, it is clear that in response to candidate HIV vaccines, infant immune systems respond as well or even better than adults.

Julie Overbaugh, a researcher at the Fred Hutchinson Cancer Research Center who has

## Relax and make antibodies

A recent study in mice led by scientists at the University of Colorado School of Medicine showed that a process that protects the body from autoimmune diseases also prevents the immune system from generating antibodies that can neutralize HIV. After being immunized with HIV Envelope protein, followed by the adjuvant alum, transgenic mice expressing symptoms similar to lupus, an autoimmune disease, mounted neutralizing antibodies against HIV (*J. Exp. Med.* **214**(8), 2283, 2017).

The researchers repeated the experiment in normal, healthy mice with a drug that impairs immunological tolerance—the mechanism that prevents the generation of auto-reactive antibodies that trigger diseases like lupus—and found that these animals started to produce antibodies with weak neutralization against HIV. When alum was added, the mice produced potent broadly neutralizing antibodies (bNAbs) that were able to neutralize a range of HIV strains. The findings raise the question whether transiently relaxing immunological tolerance, without triggering detrimental autoimmune reactions, could be a reasonable strategy for eliciting HIV-specific bNAbs through vaccination. —MR

studied the mechanisms of HIV transmission and pathogenesis extensively, says there is still a ways to go in understanding why this is the case. “We know surprisingly little about the differences in the way infants develop antibody responses compared to adults and need to know this to understand the best way forward.”

Recent studies from her lab detail the speed at which an infant mounts both neutralizing and binding antibody responses. Three years ago, Overbaugh published the first findings showing that some HIV-infected infants can rapidly mount a broad neutralizing antibody response to the virus, sometimes within the first year of life (*Nat. Med.* 20, 655, 2014), unlike the minority (10-20 percent) of adults who take two to three years on average to develop bNAbs following infection.

In collaboration with scientists in Kenya, Overbaugh’s lab tested the ability of serum from 28 HIV-infected infants enrolled in the Nairobi breast-feeding trial to see if it could neutralize a panel of viruses. Serum samples from more than 70 percent of the infants were able to neutralize one or more viruses from a different clade than the virus with which they were infected, in some instances within just 12 months after acquiring HIV. Serum from seven infants neutralized viruses across all four clades.

Building on these findings, Overbaugh’s team next isolated 10 neutralizing antibodies exhibiting low levels of somatic hypermutation (SHM) from an infant at around a year post-infection, including one bNAb with cross-clade neutralization capabilities that targeted the glycan-dependent N332 supersite on HIV’s Envelope (Env) protein that some bNAbs isolated from adults also favor. The low levels of SHM that the infant’s neutralizing antibodies exhibited suggest that neutralization breadth can occur without the much more extensive level of SHM that is evident in all adult antibodies isolated to date (*Cell* 166 (1), 77, 2016).

Work led by Duke University researchers indicates that neonatal immunization may also be helpful in skewing antibody responses to subdominant HIV epitopes. Six years ago, a study led by Haynes’ lab determined that the initial antibody responses that arise in HIV-infected people within 14 days of infection, and which target HIV Env’s gp41 protein, demonstrated cross-reactivity between gp41 and the gut flora. The hypothesis was that the early response to gp41 was really a secondary response triggered

by a pre-existing pool of memory B cells interacting with bacteria living in the gut (*J. Exp. Med.* 208: 2237, 2011; *Cell Host Microbe* 16, 215, 2014). Next his group studied samples from vaccinees in the Phase II and IIb HVTN 505 trials of a DNA/rAd5 vaccine candidate that contained Env gp41. This analysis showed dominance of the vaccine-induced antibody repertoire to gp41 with antibodies that cross-reacted with intestinal microbiome antigens (*Science* 349: aab1253-1, 2017). They went on to isolate gp41-microbiome cross reactive antibodies before vaccination, demonstrating microbiome-reactive B cells are expanded by HIV Env vaccination. Because intestinal microbiota shape the B-cell repertoire from birth, the researchers concluded that neonatal immunization with HIV envelope antigens may be able to imprint the B-cell repertoire to respond to antigenic sites on HIV Env that may otherwise be subdominant or disfavored, such as the broadly neutralizing antibody epitopes on HIV Env.

More recently Haynes’s group tested the same DNA/rAd5 vaccine regimen in neonatal rhesus macaques that was tested in the HVTN 505 trial, which was halted after failing to demonstrate efficacy in 2,504 MSM and transgendered women who have sex with men at 21 sites in 19 US cities (see *Large AIDS Vaccine Trial Shudders to a Halt*, *IAVI Report* blog, April 26, 2013). One of the objectives of the study was to see if gp41 immunodominance could be avoided by immunizing neonatal rhesus macaques during the early stages of microbial colonization (*J. Virol.* 91 21, 2017). They found that colonization of neonatal macaques occurred within the first week of life, and immunization of the animals during this time also induced a dominant gp41, microbiome cross-reactive antibody response, indicating that early vaccination could not overcome gp41 dominant responses.

Yet a retrospective study led by Sallie Permar and Genevieve Fouda, also with the Duke Human Vaccine Institute, found that infants were able to mount robust, durable Env-specific IgG responses, including anti-V1/V2 IgG responses, following vaccination with a recombinant gp120 vaccine candidate coupled with the adjuvant MF59, a potent oil-in-water emulsion made of squalene found in sharks and plants (*J. Infect. Dis.* 211(4), 508, 2015). This study assessed the binding and functional antibody responses in HIV-exposed vaccinated infants from historical samples collected as part of the Pediatric AIDS

Clinical Trials Group 230 and 326 protocols, which were conducted in the US during the 1990s. While the study conducted by Permar's group did not establish whether Env vaccination of infants would have been equally or more effective than HIV Env vaccination of adults, it did show they were capable of mounting robust antibody responses, including against the V1/V2 epitope that was an immune correlate of risk in the RV144 trial. They also tested samples from adults immunized with the same vaccine and found that the magnitude of the V1/V2-specific IgG response was higher in infants than in adults. (*J. Virol.* doi: 10.1128/JVI.01070-17).

Overbaugh says the idea of developing an AIDS vaccine for children is definitely worth thinking about, but added that there is still much to learn about how different types of immune responses are formed at this age in response to the virus. "In our study of breast-feeding infants we found that they developed broader and more potent antibodies rapidly [compared to adults], and a South African study found the same thing. So the interesting possibility that infants have an ability to make these antibodies quickly is, I think, incredibly important to study," she says. "This could mean that vaccinating infants is the way to early protection, but it could also be that what happens in an infant is fundamentally different, and shaped by the mother's antibodies passed on through breast milk."

Sharon Nachman, chairman of IMPAACT and professor of pediatrics at Stony Brook University School of Medicine who was present at the AVRS meeting, agrees that there are many open questions about testing HIV vaccine candidates in infants. "What do we know about infant immunity? What do we know about child responsiveness and what do we know about the vaccines themselves that will help inform the right vaccine and the right vehicle to put the vaccine in?" asks Nachman. "These are some of the key scientific questions that were the focus of the AVRS meeting."

### Clues from animal studies

Recent findings in animal studies also offer clues about early life immune responses to HIV and HIV vaccines. Inarguably, one of the biggest challenges in AIDS vaccine development has been finding immunogens that reliably induce bNAbs to HIV. But a recent study led by Devin Sok, Antibody Discovery and Development Director at IAVI, managed to do just that by immunizing

four calves (*Nature* 548, 108, 2017). When the animals were injected with a BG505 SOSIP trimer, all the calves developed bNAbs to HIV in their blood as rapidly as 35 to 50 days following two inoculations. This was a significant improvement from previous studies in rabbits in which the BG505 SOSIP trimer, while inducing neutralizing antibody responses against an autologous strain, was unable to induce bNAbs against the harder to neutralize Tier-2 viral strains.

What wasn't widely known, says Marovich, is that the cows were all six months old. Whether age was a factor in the robust response is unclear though. Sok has his doubts that it mattered that much. "I don't expect a difference between infant and adult cows because both have the same antibody repertoire," says Sok. "It's the antibody repertoire that's unique from other animals." But Marovich says a comparable study being done in adult cows could shed light on this question.

### Planning for a trial

"Given what we are learning about the babies' immune systems and their antibody responses to HIV, I think they are fully capable of responding to candidate vaccine immunizations," says Haynes. "It's perhaps useful to consider immunization of babies with an HIV vaccine candidate to try and understand in greater depth how babies respond."

Ultimately, Nachman thinks the way forward for AIDS vaccine development will need to be multi-pronged. "In any epidemic, thinking about one vaccination time-point is the least effective. In order for an epidemic to change course you have to target all ages at different times, and not necessarily with the same vaccine candidate."

She also thinks the surprise of RV144 is a good lesson for people to remember when deciding whether immunizing children is a path worth exploring. "If there is anything that RV144 has taught us it is that assumptions of how we think about vaccines are not always the right ones."

Yet Nachman also emphasizes ethical considerations of testing vaccine candidates in children. "You have to have good reasons to bring a vaccine into child," she says. "A region with a 40 percent acquisition rate of HIV would be a good place to do a vaccine study. It has to be a population of children where you can say it will do good and also do no harm." ■

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

# Hope for HIV *Prevention*

Implantable devices that can slowly and steadily release long-acting antiretrovirals into the body are one novel HIV prevention strategy now in development. Find out how a team of researchers at Northwestern University co-led by Thomas Hope is studying one such device.

By Kristen Jill Kresge

Ever since reading psychologist Barry Schwartz's book "The Paradox of Choice: Why More is Less," I came to believe that we are often crippled by the number of choices in daily life. Do I want the whitening toothpaste, or am I better off with the anti-plaque? Which of the 37 varieties of laundry detergent will actually work the best? That is just the beginning.

The proliferation of online shopping only seems to add to the confusion that endless choice creates. A simple search brings up dozens if not hundreds of possible options for any item you seek. And studies indicate that the more choices there are, the less likely you are to be happy with your decision. In fact, some studies even suggest the proliferation of choices may make people overall less happy than previous generations. There are plenty of TED talks on this topic, not to further overwhelm you with choices.

But in the world of HIV prevention research today, the prevailing argument is that people need more options. That is to say, researchers think offering more ways to protect against HIV infection will lead to more people actually using a preventive strategy that works for them. There are already a few choices: condoms, of course; adult voluntary male circumcision; and oral pre-exposure prophylaxis (PrEP, the use of HIV drugs to prevent HIV infection), which has been shown to be over 90 percent effective at preventing HIV infection when used consistently. But researchers say that the barriers are still too high to get many of the people who are at greatest risk

of contracting HIV to use any of these options consistently and correctly, which is, of course, the only way they are effective.

This is why researchers are moving ahead to apply for regulatory approval for the vaginal ring containing the antiretroviral (ARV) dapivirine, which was found to be 27 percent effective in pooled results from two large efficacy trials (see *HIV Field's Current Contours Show in Boston, IAVI Report*, Vol. 20, No. 1, 2016). It is also why they are investigating whether a regular injection of antibodies that can protect against many of the HIV isolates in circulation, so-called broadly neutralizing antibodies, can protect those who aren't willing or able to swallow a pill every day to stay HIV free. Another option is using long-acting ARVs that will be applicable not only for treatment but for prevention as well (see *Longer-acting HIV Prevention Methods: Take Two Antibodies and Call Me in Six Months?*, *IAVI Report*, Vol. 21, No. 3, 2017). These long-acting ARVs could be delivered orally, by injection, or via an implantable drug-delivery system that could self degrade or be replaced annually, similar to the implantable hormonal contraception devices that last for three to five years.

It is this type of implantable device for HIV prevention that is the focus of a US\$17.5 million grant awarded by the US National Institutes of Health to researchers at Northwestern University in Chicago. The five-year grant is funding the Sustained Long-Acting Protection Against HIV



Thomas Hope

program, involving 15 basic scientists and clinical investigators across 15 departments at the University's Feinberg School of Medicine, McCormick School of Engineering and Applied Science, and Kellogg School of Management.

One of the project's principal investigators is Thomas Hope, professor of cell and molecular biology at the Feinberg School of Medicine. The other is Patrick Kiser, associate professor in obstetrics and gynecology at the Feinberg School of Medicine and biomedical engineering at the McCormick School of Engineering.

Hope is a familiar face in HIV research and a rather colorful character. He often delivers presentations at conferences around the world clad in a Hawaiian shirt, and always with an air of joviality. But the work he and his group do is serious. Much of it involves understanding mucosal transmission of HIV and the critical events immediately following transmission that allow the virus to establish persistent infection. In addition to pushing forward the field's understanding of the important interplay between HIV and multiple cell types, this research generates stunning, gallery-worthy microscopic images of the virus within the mucosal environment where infection is first established following sexual transmission.

Hope's personality is perhaps most evident in the naming of Northwestern's program to develop an implantable drug delivery system. "A lot of these trials have inspiring names like ASPIRE, ASCENT, et cetera," he said recently at a meeting sponsored by the New York Academy of Sciences (NYAS). The program Hope co-leads is called the Sustained Long-Acting Protection Against HIV program, but it is the acronym that says it all. "We decided to take a more aggressive approach and call it SLAP HIV."

Hope spoke at the NYAS meeting about his team's efforts to develop an implantable device to deliver the investigational ARV cabotegravir, an integrase strand transfer inhibitor with potent antiviral activity that is being developed by ViiV Healthcare. Cabotegravir is one of the first drugs to be developed simultaneously for treatment and prevention. It is currently being tested as both an oral formulation and an injectable in a large prevention trial. And the goal of Hope's program is to advance an implantable cabotegravir delivery system to Phase I clinical trials by the end of the five-year grant period that began in 2015.

We spoke in detail about the program and its progress, and also the other projects he currently finds most promising.

### **Can you start by explaining the implantable drug delivery system that your group is developing as part of the SLAP HIV program?**

Basically, to make it you more or less compress the drug into a series of pellets and then you put the pellets inside of a membrane that is made from a polymer that is designed to let the drug leak out at a certain rate. You play around with the different polymers and you use the one that allows the drug to be released at the rate you need for protection.

It is interesting because you basically start with shelves of beakers with stir bars in them and you put the different prototypes of the implant in the beaker. Then you take a little bit of the liquid out and put a little liquid back in, kind of pretending the beaker is like a little system, and by doing this you can figure out how much of the drug is actually coming out. And then you make adjustments. Once you get close to the amount of drug being released every day that you want, then you move things over into, for instance, different animal studies.

### **And why work with cabotegravir?**

Even though there are many, many antiretrovirals, there are only a handful of them that can work for a long-term, sustained-release strategy because the drug needs to be very potent, and it needs to be cleared from the system slowly. Cabotegravir is one drug that that can be accomplished with. The others that might work, at least on paper, are the Gilead drug known as TAF [tenofovir alafenamide or Vemlidy; a drug approved by the US Food and Drug Administration for the treatment of chronic Hepatitis B virus infection] and the new Merck drug that they call MK-8591, or as I called it at the New York Academy of Sciences meeting, unobtainium, because they are not really sharing information about it with anybody. I thought they would be mad that I called it that, but they actually thought it was funny.

### **And then did they tell you all about the drug?**

Well, that's a different story, but the scientists from Merck did tell me they thought it was funny that I said that.

### **So you couldn't take any drug or combination of drugs and use a similar system to what you have developed?**

Well it is really about the drug's potency. The implant needs to be small enough that it is not obtrusive. If you had an implant that was the size

of a can of beer and you could put it under your skin somewhere, then you could use any drug. But the problem is the drug has to be very potent because the size of the device has to be small. You could probably only put hundreds of milligrams of drug in the little implantable device, and ideally, for an implant, you are looking for it to hold enough drug to last about a year in order for people to be willing to go through the surgery to insert the device. You can take a pill every day, but this is something entirely different. You have to have the device surgically inserted and then it has to be removed or replaced, and that is much more complicated than taking a pill. So for people to be willing to go through that, there has to be a real benefit. Therefore it really is potency of the drug that is the limiting step.

**If you were going to use a different long-acting antiretroviral, such as TAF, could you just change the polymer that controls the release and modify your device to work?**

Some technologies are readily adaptable to other drugs, but ours is very specific. Some people have devices that are more of a solid matrix with little holes drilled in it, but because ours is really just a tube of polymer and because each drug has different characteristics, the polymer that works best for TAF is not going to work for cabotegravir. There are other technologies that are being developed that are more universally applicable. For example there is one that is basically a metal tube that slowly pushes the drug out of one end, and so with something like that, you could use any number of different drugs because you are just pushing the drug out of a tube.

**Where are you now in the development and testing of your implantable in animal models and what are the plans for clinical development?**

Well, we are very anxious...the nature of this grant is that we are supposed to have a Phase I clinical trial completed by the end of the fifth year, or at least in the no-cost extension period, so we are trying to meet that. Right now we are transitioning from beakers into rabbits, and then into primates to see if the way these things seem to perform in these idealized systems within beakers translates to the living animal. Those studies are ongoing right now.

**Where does the device go in the body?**

That is a good question. It can kind of go anywhere but right now we are mostly thinking

of doing something similar to what is done for Norplant and other hormonal implants used for birth control. Those devices tend to go in the inner arm, around the lower biceps. And the logic for that, although we have not been able to find out explicitly why they decided to put it there, is that it is a place that is not going to be exposed to outside impacts, you know, like being in a car accident and hitting it hard against the inside of the car or any other sort of bumping into something. It is a little bit protected in that place. But there has also been some discussion of putting it in the buttocks or in the small of the back.

You want it to be someplace where there are not a lot of nerves and you are not going to notice it. But right now as we are doing our acceptability studies, we show examples of it being like the hormonal, sustained-release devices and so it is in that same spot on the inner arm.

**Is there also anything to be learned from the implantable insulin release systems that are used for treating diabetes?**

Insulin is a much bigger molecule than these antiretrovirals, so while I think some lessons can be learned, like how the body reacts to implants and that kind of stuff, the actual functions of the devices are going to be very different for a human protein versus a small molecule. These drugs are very small molecules.

**If you are trying to prevent against sexual transmission of HIV, how do you know how much of the drug needs to be in a person's system to protect against exposure? Will cabotegravir released by the implantable device have a different bioavailability than if swallowed in a pill form or administered by injection?**

So that's the idea behind the animal studies. It all comes down to the systemic drug levels. When you take a pill, depending on the drug, either all of it gets into your system, or with some drugs, not that much of it gets into your system. And so the bioavailability is dependent on the drug getting through your digestive tract to enter your system. We do not have that issue with the implants.

And so the idea is after—we have to do all the studies, of course—but after a certain period of time, days or weeks, the drug would be spread throughout the body. We know from studies of oral PrEP and some other things, that sometimes these drugs concentrate in one part of the body and

less in another part of the body, so that becomes important. You just have to have sufficient levels to provide protection, that is what it is all about.

**Could you theoretically develop this type of an implantable device to allow the broadly neutralizing antibodies to be released over time, or is it really specific for non-protein, small-molecule drugs?**

I do not think this technology with the membrane, where it releases the drug through the membrane, would ever work for broadly neutralizing antibodies. But people are developing technologies to accomplish this, it is just different kinds of technologies are required to make these things work.

**Is there any interest in developing an implantable device for HIV treatment, or just for prevention?**

You are absolutely right that this same exact device could be used for treatments, but in the grant program that is sponsoring this project, they were very explicit in saying you had to pick prevention or treatment, and because we have a lot more experience in prevention, we are focused on prevention. But the implant could easily be used for therapy.

**What role is the management school at Northwestern playing in this grant? Are they involved in figuring out whether people would want to use an implantable device and how to market it?**

So one of the things that the field is considering, and there is a lot of discussion about this, is how there have been all kinds of efforts to develop new products—vaginal rings, gels, et cetera—and then very often when it comes time to roll these new products out, the people that have to use them are not so excited about actually using a gel or a ring. Instead it is, “I would like this, but I don’t want it to be this way.”

So I think this program was set up really, very well. The first couple of years was a competition of different groups to see which one could develop a technology that made the most sense. And part of the decision process used to decide which of these technologies to advance into a Phase I clinical trial was going to be concerns about whether or not it would be used. If we have three technologies available that we can advance, and one of them people are excited about using for prevention, and the other two, they’re like, “I hate that idea,” then that would come into play. So the role of the School of Management has been in conducting acceptability studies.

Historically, as a hardcore scientist, I have not necessarily always been a big fan of this sort of work. But I am now convinced that it is of the highest level of importance. We need to start thinking about how we are going to get people to use these things and offer them the things that they are willing to use, otherwise we haven’t solved any problem.

Our number one guide in the management school, Bob Schieffer, is an expert in doing these kind of analyses. It starts with a focus group to get a sense of what people are thinking. Then you can turn that into hard science by doing something called a conjoint analysis and discrete choice analysis.

If you just tell somebody here are 10 things and say, “Which is your favorite one?” the responder might grab one, but then the next day they would grab a different one. And sometimes people don’t even know what they like or not. So instead of offering them—this is just one crude example—but instead of offering them 10 things to pick one from, you offer them the 10 different things two at a time. Then you can ask do you prefer this one or this one? This one or this one? This one or this one? And by doing this, some things become immediately apparent to analysts. One is that some people, like 15 percent of people, don’t know what they want so perhaps they can be excluded from the analysis. Then you can start to extract different information. Is their number one choice right next to their number two choice, or is their number one choice far superior to number two? These comparisons allow you to get this kind of information.

And then other choices are also very important. A good example is choosing between your favorite restaurant and your second favorite restaurant. The second favorite restaurant is across the street. Your first favorite is a 20-minute drive. You want to go to your favorite restaurant but it is raining, so you decide to go across the street. And then the next week the situation is different and you make a different choice. This example shows that the context of the things you have to consider when you make a big decision, or a small decision, are complicated and so you need to try to measure all of those things.

With the School of Management we’ve found a goldmine in my opinion. These people did this sort of work as a profession, they were successful and were able to retire, and now they are teaching the next generation by working in the School of

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We need to start thinking about how we are going to get people to use these things and offer them the things that they are willing to use, otherwise we haven’t solved any problem.

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Management. They can take those approaches and apply it to this very important area. Other people are of course doing this too, including the commercial firms that actually run the surveys.

I think that has been one of the several really neat things that have come out of this project that I was not anticipating.

### **Do people really need that many more choices when it comes to HIV prevention?**

People often cite birth control as an example, in part because it's sexually related, and in part because what actually works in getting people to use it more is having a choice of what method they want.

Back when there were very few choices, birth control was less successful. Now, there are all these different choices, even internationally, like rings, for example. Rings for birth control are much more popular in South America than anywhere else. In other parts of the world they aren't used at all. In the US, I think contraceptive rings make up less than 10 percent of the market, maybe eight percent. That is still enough for the companies to make money on it, but it is not the top choice.

What we really need for HIV prevention is to offer people options. The implant is an option for individuals that are not good at taking pills every day. Some people are good at taking pills every day, whether it is for blood pressure or anything else, and other people are not. And *bizarrely*, if you do not take the pill, it doesn't help you. From inside the bottle it can not do much.

### **What other areas of HIV prevention research are you involved in?**

Right now I think we have the best science ever happening in our lab, and one thing that I think is very relevant is that we are doing some work on injecting broadly neutralizing antibodies and learning neat things about how they distribute in the body. We inject them into a macaque and watch how they distribute. By doing this, we are learning all these new ways that antibodies get to mucosal sites and the brain that nobody knew about before.

Some other work that I am really excited about is that we are finding there are all these unique interactions between antibodies and mucins [glycoproteins] in mucus that can add to antibody function, and in some ways, even change the functions of the mucins.

We are excited about being able to contribute to HIV prevention.

### **So does that bode well for the antibody prophylaxis studies, perhaps?**

I am excited about those studies. I have to admit, a few years ago I was less enthusiastic, but the system has gotten so good at producing these antibodies at lower costs and modifying the antibody with certain mutations that make the antibody persist for a long time. I think some of that work that has been going on for a while is really coming together nicely.

### **Speaking of the interaction between antibodies and mucus, it reminds me of how your lab creates some of the most stunning images of the virus. I never knew mucus could be so beautiful!**

It is really fun to have these pictures of what we do because people can look at them and kind of get a sense of what is going on. Your average person can appreciate those pictures more than, say, a flow cytometry plot, or a bar graph, or something else abstract. With the pictures you can show them that the green dots are viruses and all of the sudden they can visualize what is going on. So it is a nice space to operate in.

### **Perhaps a gallery showing is in your future?**

We have thought about it and we have been involved with some of those. They had a show at the American Society of Cell Biology and they sold the pictures for charity. We gave them about 10 of our pictures and they used them all and they sold them all. So we do that a little bit. It's fun.

### **You are also training and collaborating with early career researchers in Kenya, one of whom we profile in this issue. What inspired you to establish those connections?**

I think it is very important, and we have to do these things. It helps establish contacts and collaborations because they have local knowledge that is important. They can help us to get highly relevant samples. We haven't progressed that far yet where we are worried about this, but if we make a vaccine, we want it to work in Africa, and in the US, and everywhere else, especially in places where there is more transmission occurring. And there are differences in these populations that we have to understand and address. So these kinds of international studies are really important in the long run. One of the things we are doing is just trying to compare mucosal environments between volunteers in the US and Nairobi, Kenya. We are also trying to transfer some of our technologies to Kenya, and one of the cool things is they just got a microscope like ours, so that is exciting. ■

# A Rise in Resistance

Half the world's people living with HIV are now on treatment. This is a tremendous accomplishment, but a rise in drug resistance is of increasing concern.

By Michael Dumiak

During his stops in dusty clinics in the KwaZulu-Natal hinterland and in inner city Durban, South Africa, the infectious disease physician Richard Lessells is used to seeing the difficulties that come with administering and maintaining an effective HIV treatment response. When the virus shows resistance to the drug regimens, Lessells says it becomes really complicated.

“In the clinics, I see that we are really struggling with maintaining quality of care,” he says. “It’s a very overstretched system.”

He and his colleagues at the South African Treatment and Resistance Network are no strangers to this issue. They wrote the book on it, in fact. The network’s *HIV & TB Drug Resistance & Clinical Management Case Book* that describes the challenges that clinicians face in managing complex forms of drug-resistant HIV is due to go into a second printing next year. Lessells is working on the new edition over the holidays. In the meantime, he keeps one of the last boxes of the original 2013 printing in the trunk of his car for distribution to health workers in the field. The cases addressed in the book describe how to manage patients when drug resistance occurs, and also how to prevent resistance with better treatment and care.

This summer the World Health Organization (WHO) put its heft and might behind addressing the growing problem of HIV drug resistance, which has frontline medical staff, policy strategists, and funders alike increasingly concerned. Last month, the WHO convened a brief meeting in Johannesburg to review surveillance and progress on the resistance issue. It was following up directly on the heels of a workshop

dedicated to HIV drug resistance that was held in Africa for the first time in its 20-plus years.

Precisely how widespread HIV drug resistance is and how much of a problem it will become is difficult to gauge. One certain thing is that it will greatly shape the overall response to the HIV epidemic. It can impact everything from how doctors prescribe therapies and treat patients, to how drugs are priced, as well as the drive and momentum for developing an HIV vaccine or other preventive strategies.

All this while there are still millions of people in need waiting to start treatment in the first place. “Half of the world’s population living with HIV, 19 million, are on therapy, and this is an extraordinary achievement. But we still have more than 17 million who have never started therapy, and a substantial proportion of the 19 million who have defaulted at one point or another and who need to be reintiated to therapy if they are going to benefit,” says Chris Beyrer, a Johns Hopkins University epidemiologist and former president of the International AIDS Society. “These [people] are in low-income countries where HIV is highly prevalent and who have had challenges with managing antiretroviral regimens in the past, or where in some cases they’ve had issues with stock-outs,” he says, referring to empty shelves in a pharmacy—supply-chain issues which can result in irregular adherence.

“It’s kind of a watershed time,” says Stanford’s Bob Shafer, an infectious disease researcher who has extensively catalogued HIV drug resistance. “Resistance has been going up.” Things may improve mightily in the next five years due to the introduction of the antiretroviral drug dolutegravir, an integrase inhibitor manufactured by GlaxoSmithKline,

but Shafer says it is too complex a problem to say the solution lies simply with new and better drugs.

Newer and better drugs are, however, poised to make a difference. A deal to introduce dolutegravir, an antiretroviral (ARV) that inhibits HIV's integration into host cells, at affordable prices is due to come into effect soon in lower- and middle-income countries. The Bill & Melinda Gates Foundation and the Clinton Health Access Initiative reached ceiling price agreements earlier this year with India-based generic drug manufacturers Mylan Laboratories and Aurobindo to offer dolutegravir, licensed from developer ViiV, at an average price of US\$75 a year per patient. Dolutegravir has been on the market for three years and is already used in fixed-dose combination therapies in wealthier nations under the brand name Tivicay.

Dolutegravir is set to debut in South Africa on a large scale by the middle of 2018. "That will be a game-changer," Beyrer says. But getting it out to clinics in South Africa, and in the 90-plus other countries the deal covers, is going to be no simple task. Lessells says it became apparent at the Johannesburg workshops that there are differing opinions on how dolutegravir should be rolled out; from some who favor a slow and methodical approach, to those in Botswana, for instance, who want to set a fast pace in uptake.

These questions are all important, sources say, because resistance is both an immediate public health care problem and a potential long-term threat. But there is no way to skirt the issue entirely. "Some levels of resistance are an inevitable phenomenon. As we scale up antiretroviral therapy, we will see some level of resistance as a consequence of the presence of the drugs. As drugs become more widely available, more resistance will be seen," says the WHO's Silvia Bertagnolio, a medical doctor and expert on HIV drug resistance. Researchers have kept tabs on HIV drug resistance for years. But between 2012 and 2017, Bertagnolio says, resistance levels to the most common frontline therapies in lower- and middle-income countries under surveillance started climbing over five percent. "Something happened."

A new regression and meta-regression analysis commissioned by the WHO from the University of London's Ravi Gupta and his colleagues sets pre-treatment drug resistance levels to non-nucleoside reverse transcriptase inhibitors (NNRTIs), the ARV class contained in the most common frontline regimens in lower- and middle-income countries, at 11 percent in southern Africa, 10.1 percent in eastern Africa, 7.2 percent in western and central Africa, and 9.4 percent in Latin America and the

## Why resistance develops

Mutations are one of Darwin's great engines and the reason why HIV develops resistance to the drugs used to keep it under control. The virus replicates at an extraordinary rate: in early infection, an HIV virus can double its population every 12-16 hours. The copies are not perfect, though. While it is replicating, the virus makes genetic errors of all kinds. While these mutations are chance mutations—there is no conscious intent on the part of a virus, as much as it might seem like there is—the ones that prove beneficial to the survival of the virus are selected for. Among the keepers are those that allow the virus to escape pressure from antiretroviral (ARV) treatment.

The problem of resistance to HIV, then, is as old as the response to the epidemic. It is, after all, what propelled researchers and clinicians toward developing and prescribing the ARV cocktails that turned the tide against the HIV epidemic in the mid 1990s in the US and Europe. When AZT, the first ARV, was introduced as a stand-alone therapy, the virus rapidly developed resistance to it. The viral loads, or the levels of virus in HIV-infected individuals, rebounded after being initially suppressed by the drug. The effort to overcome this AZT-resistant virus led researchers to develop drug combinations. It was a critical moment in the response to HIV when researchers first showed that an ARV cocktail made it much harder for the virus to mutate around the drugs, allowing viral loads of treated individuals to remain suppressed for longer periods of time.

Regimens were then improved and optimized over the years. "Drug resistance was always around the corner," says Bob Shafer, an infectious disease specialist at Stanford University who helps maintain the publicly accessible HIV Drug Resistance Database that collects data on how often mutations occur with and without therapy. "There were patients who developed viruses with resistance to every drug that was marketed and available." As new-generation drugs came along, however, resistance receded. It happened because these drugs have a higher genetic barrier to resistance: that is, the virus needs to contain a higher number of mutations to change enough to avoid the drug. Sometimes these mutations make the virus itself unstable.

There are now eight classes of HIV drugs: nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors (the NNRTIs), protease inhibitors, fusion inhibitors, entry inhibitors, integrase inhibitors (of which dolutegravir is most prominent), pharmacokinetic enhancers, and combinations of these in a single pill. Because of the quantity of ARVs now available and the variety of regimens that can be created, therapy failure has become much less common overall. In the US and Europe, even though transmission of HIV with drug-resistant mutations may still be common, most of those mutations are to the NNRTIs being superseded by the newer fixed-dosed combinations of drugs.

Mutations in the virus occur at the nucleotide level, which then results in a change in the amino acids that make up the viral protein, thereby changing its shape. Three nucleotides encode each amino acid. Most mutations in HIV are the result of a single nucleotide change, however, some are the results of multiple changes. In most cases an amino acid change leads to reduced binding or less stable binding between the drug and its target. If the resistance is to a protease inhibitor, the mutations are in protease. If it is to an integrase inhibitor, then integrase. Many small interactions are what leads to the connection between a drug and its target protein on the virus, and if even a few are disrupted, the binding between the two is not as effective.

Characterizing these mutations leads to names such as M184V, which affects tenofovir and zidovudine. The mutations are written in a coded nomenclature, with the capital letters signifying the amino acids—M for Methionine, and V for Valine, for example—and the number signifying the position of the amino acid that is changed. M184V is a single-amino acid substitution from wildtype Methionine (M) to Valine (V) at the point 184 amino acid of reverse transcriptase.

At this point, Shafer says, most of the common mutations have been painstakingly characterized and catalogued. A decade ago Shafer's team and a set of other labs were asked by the World Health Organization to compile a comprehensive list of drug resistance mutations to help facilitate surveillance. The full list ran to 93 mutations. Shafer does not expect to see many more now, having characterized the most common, but he does think the list should be updated to add a few integrase mutations, especially as integrase inhibitors are among the newest classes of drugs, with less known about resistance to them even as they are expanding in use. The assay company Monogram Biosciences also maintains an extensive database of about 150,000 correlations between HIV genotype and *in vitro* susceptibility to different ARVs. —MD

Caribbean. These figures are on the increase. The odds in certain populations for developing ARV-resistant virus are rising 23 percent a year in southern Africa, 17 percent in eastern Africa, 17 percent in western and central Africa, and 11 percent in both Asia and Latin America.

In recent years, 14 countries, including Cameroon, Namibia, South Africa, Zimbabwe, and Uganda, have conducted national surveillance of HIV drug resistance following statistical survey methods recommended by the WHO. Based on a systematic review of studies covering 56,000 patients in low- and middle-income countries, the prevalence of resistance to the kind of ARVs most used in these countries—the NNRTIs such as efavirenz and nevirapine whose availability and affordability transformed the nature of HIV treat-

ment—is currently increasing on an annual basis from 11 percent to 29 percent in frontline countries.

“These numbers are worrisome, and they reflect a real problem for real people,” Beyrer says. He and colleague Anton Pozniak recently penned a commentary arguing that the emergence of HIV drug resistance is a very real threat to the astounding gains made in getting people with HIV onto treatment, a signature achievement during the 30-year history of the epidemic (*N.Engl. J. Med.* 377, 1605, 2017).

### Alarming estimates

There are seven million people in South Africa infected with HIV, about 56 percent of whom are on ARV therapy. The most common first-line regimen for treatment in the region, as in most developing countries, consists of the NNRTIs efavirenz and nevirapine. Surveillance data cited by the WHO, as well as those tracked locally, show rates of resistance in the country climbing, says Gillian Hunt, a senior researcher at the South African National Institute for Communicable Diseases’ Centre for HIV and STIs. “The levels of resistance are really quite startling.”

Analysis of HIV drug resistance data led the WHO, the Global Fund to Fight AIDS, Tuberculosis and Malaria, and the US Centers for Disease Control to distribute an action plan last summer in Paris coinciding with the International AIDS Society’s annual meeting. The plan examines HIV drug resistance in what it breaks down into three types: acquired, transmitted, and pretreatment drug resistance. Acquired resistance is when the mutations develop within individuals on treatment. Transmitted resistance occurs when previously uninfected people are infected with an already drug-resistant virus. Pretreatment HIV drug resistance is used as something of a catch-all: it can be either transmitted, acquired, or both, and is detected in people who have never taken antiretrovirals and are just starting on them, or those who are restarting a first-line antiretroviral regimen after an interruption. This set includes, for example, pregnant women who have taken antiretrovirals to prevent transmission of HIV to their children, or people who are using antiretrovirals for pre-exposure prophylaxis (PrEP).

The action plan strongly emphasizes the figures for pretreatment HIV drug resistance. If these figures reach 10 percent or higher within a county’s population, the WHO now urgently recommends shying away from using NNRTIs in frontline regimens and substituting alternatives.

The plan highlights other figures, too: of 11 countries reporting pretreatment drug resistance

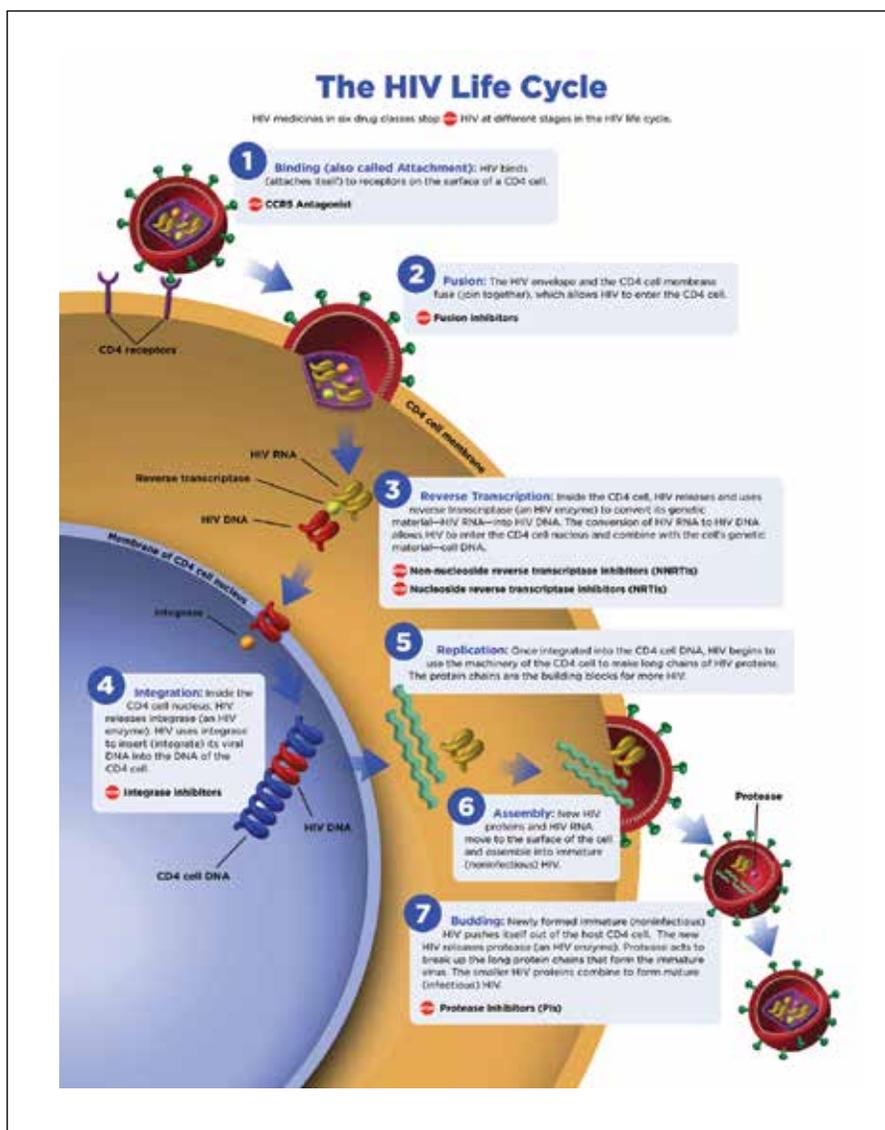


Image accessed from *AIDSinfo* Dec. 13, 2017.

data, six of them showed levels of 10 percent resistance or more to NNRTI regimens. Prevalence of acquired resistance to NNRTIs range from 4.3 percent to 16.7 percent in individuals on treatment for between one and two years, and from 4.2 percent to 28.3 percent for those on treatment longer than that. It is much higher for those on treatment with unsuppressed viral loads, with figures ranging from 47.3 percent in Zambia to 76 percent in Guatemala. For those with unsuppressed viral loads despite treatment for longer than three years, the prevalence of NNRTI resistance was above 80 percent.

“The human cost of HIV drug resistance cannot be underestimated,” the report warns. People with NNRTI resistance are less likely to achieve viral suppression, more likely to experience virological failure or to die, more likely to discontinue treatment, and more likely to acquire new drug resistance mutations.

Lessells and his colleagues are seeing this and putting it straight into the next edition of their casebook. “It’s more about second-line failure and complex third-line issues and the kind of things we’re seeing more of here,” he says, referring to the iterative failures of HIV drug regimens that can occur in individuals on therapy. Lessells expects issues even with the arrival of dolutegravir. People on therapy stop treatment often, and then return to try new drugs. If they are advised against it, they may go to a different clinic.

“We tell people, OK, you are going to be able to have a fairly normal quality of life and expectancy. But it will be a daily oral regimen for life,” says Beyrer. “That is a big ask.” Yet gaps in adherence to the daily drugs, for whatever reason, can allow the virus to more easily accrue the mutations that lessen the effect of therapy.

People living with HIV in wealthier countries of the world are routinely monitored and tested for drug resistance. But routine testing is expensive—it involves reading viral DNA contained in a blood sample and checking it against the list of drug mutations. Currently the South African HIV Clinicians Society recommends a test, not when a patient is first diagnosed, but when there is evidence that the first-line antiretroviral therapy regimen is failing. Even at that point the test is expensive for South Africa, at about \$350, which puts a burden on the health system. “With failure rates, we’re sitting at between 10 and 15 percent on an annual basis. That’s 300,000 genotypes a year. It’s just not doable,” says Hunt. “We’d love to be able to test everybody, but it’s not practically possible.”

Limited testing means resistance may not be detected quickly. “There are cases where people are resistant to NNRTIs and they are not being picked up. And time is going by,” says Beyrer. “There can be 12 months, 18 months, when you are taking drugs and it is not doing you any good, it is not affecting the virus, and mutations are ongoing.”

This is an issue even where health care systems are relatively stable and consistent. It is even more problematic where securing second or even third-line regimens is a challenge. “This is a developing world issue,” Hunt says, which is one reason she was quite pleased that the International Workshop on HIV Drug Resistance and Treatment, for the first time in its 26 years, was hosted in November in Johannesburg. Lessells was there, too, as he, Tulio de Olivera, and their colleagues work on distributing their case book to clinical health workers. Together with South Africa’s Technology Innovation Agency, they have also set up the KwaZulu-Natal Research and Innovation Sequencing Program (KRISP) to try to offer bioinformatics and genomics expertise, including sequencing and diagnostics, and to help build testing capabilities. There are also new testing kits and shotgun sequencing web-based applications that may well bring down costs of monitoring resistance in developing country populations.

Three years ago the Joint United Nations Programme on HIV/AIDS (UNAIDS) set a target of 2030 for ending AIDS as a threat to public health, framing the target squarely within the United Nations’ development agenda. A big part of the push comes from striving toward “90-90-90” goals: diagnosing 90 percent of all people with HIV, providing treatment to 90 percent of those diagnosed, and ensuring 90 percent of people on treatment achieve virological suppression by 2020 and maintaining those levels into the future. According to the WHO/Global Fund/Centers for Disease Control plan, if NNRTIs continue to be included in first-line antiretroviral therapy regimens, and the level of pre-treatment drug resistance to NNRTIs reaches above 10 percent overall in sub-Saharan Africa, that global target to end AIDS by 2030 will be missed.

Beyrer points out that, whether it is because of resistance or, more likely, a combination of many factors, a place like Malawi is getting close to reaching its 90-90-90 goals, yet is not seeing the epidemic diminish in terms of the number of new infections as quickly as expected. Anthony Fauci, director of the US National Institute of Allergy and Infectious Diseases, penned a commentary at the end of October tracing the different steps to meeting the 90-90-90 goals and end-

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## Prepping for resistance

“Our newest and most effective prevention tool, PrEP with daily oral tenofovir-emtricitabine, is also at risk from HIV drug resistance.” With this line in a recent commentary, Chris Beyrer from Johns Hopkins University stirred a lot of feedback and protest (*N.Engl. J. Med.* 377, 1605, 2017).

Oral pre-exposure prophylaxis (PrEP), the use of antiretrovirals to prevent HIV infection, is slowly making its way into communities as a highly effective HIV prevention option. As it does, there have been a few cases of HIV infection occurring while an individual is on PrEP. If that happens often enough, it could be another way people develop drug-resistant virus. But for now, researchers such as Gillian Hunt from the South African National Institute for Communicable Diseases’ Centre for HIV and STIs, does not see this as a big concern, even though PrEP is licensed in South Africa. “There aren’t huge numbers of people on PrEP,” she says, and the resistance profile is overall very good. “[But] one also doesn’t want to ignore it.”

Beyrer also says that while resistance developing as a result of PrEP use is a concern, it is not on the same level as his much greater concern about resistance to the non-nucleoside reverse transcriptase inhibitors that are the backbone of treatment in many developing countries. —MD

## Former Banker Looks to Boost Global Fund Resources as New Director

At a time when deft financial negotiations can seem almost as vital as basic research in providing access to lifesaving treatments and vaccines, Peter Sands may be a logical pick to head the Global Fund to Fight AIDS, Tuberculosis and Malaria. The former chief executive of Standard Chartered PLC, a global bank headquartered in London and involved in an unusually broad variety of financial businesses, comes into the job as a respected figure in both finance and public health.

“It’s an outstanding appointment,” says Ngaire Woods, founding dean of the Blavatnik School of Government at Oxford and an expert in global economic governance. Woods worked with Sands on a World Bank/Wellcome Trust project proposing ways for governments and development partners to finance and strengthen pandemic preparedness. She lauds his commitment to the effort. “He put in a huge amount of time, analysis, and writing. He’s low-key, listens extremely well, is a fantastic analyst, and a terrific communicator.”

Sands, a onetime non-executive director to the UK Ministry of Health, is slated to take the reins as executive director of the Global Fund in March. He will be taking charge of the world’s largest funder of anti-AIDS, tuberculosis, and malaria efforts. The Global Fund has distributed more than 795 million insecticide-treated bed nets in the fight against malaria, is supporting antiretroviral (ARV) treatment for nearly 10 million people living with HIV/AIDS, and has funneled more than US\$17 billion in paid pledges from international donor governments to public health initiatives.

Long the front-runner to take the leadership role at the Global Fund after Mark Dybul stepped down last May after a four-year term, Sands takes over from Marijke Wijnroks, who has been acting as interim executive director and has been on the IAVI Board of Directors since 2011.

There were some hiccups in the process of selecting the Global Fund’s new executive director. Even before Dybul left as planned when his contract expired, the Global Fund suspended and then re-set its search for a new leader because donors were unhappy with how the process was being managed. It was then reported that Sands had taken his name out of the running only to re-enter the race just days before being appointed (see Devex.com for more information). And *The Lancet* recently reported that Sands received near-universal backing but did not gain support from the US—apparently due to Standard Chartered bank’s business transactions with Iran (*Lancet* 390, 2338, 2017). The US is the top contributor to the Global Fund, with its \$13.2 billion pledged contributions (\$12 billion of which had been paid as of 2016) making

up 32.4 percent of the total pledges, according to Kaiser Family Foundation figures. This makes the relationship between the US and Global Fund a vital one for Sands to manage.

Ron Waldman, a global health professor at George Washington University who, among other things, once led the United States Agency for International Development preparedness unit for influenza and other pandemics, says the Global Fund is in a period of transition. “It was created to fill a void that the WHO [World Health Organization] allowed to develop, and as far as I can tell it did that. If we were starting from scratch and rebuilding the global

health architecture, would it still have that place? I’m not sure,” he says. “There has been substantial donor investment in it, so that might be called a success. Will replenishment continue? That will depend on a lot of factors including perceived need and, if the need is there, to a large extent on Mr. Sand’s ability to convince donors that the Global Fund remains a worthwhile investment. He should be good at that.”

The Global Fund is a player in the recent price support deal struck by the Bill & Melinda Gates Foundation and the Clinton Health Access Initiative to bring the integrase inhibitor dolutegravir to 90 low- and middle-income countries, where it is expected to have a big impact in not

just convenience and effectiveness but in beating back a worrisome threat of viral resistance to existing ARVs (see page 14).

In a statement provided by the Global Fund press spokesman, Sands describes his background in economics, finance, and management as relevant to the challenges facing the institution, including sustainability. His priorities, as laid out in a recent commentary, are to raise the ambition levels for the Global Fund and deploy greater resources (*Lancet* 389, 2086, 2017).

“The most powerful argument that the Global Fund can bring to donors is impact: millions of lives saved along with a massive economic burden lifted and significant economic development in communities that have been held back by these diseases,” Sands says in the press statement. “We need to continue to make the case of proven delivery: that donor’s resources are well spent and delivered. We also need to make the case of the escalating benefit of being able to eliminate and stamp out these diseases both in countries and in key populations. There are always going to be pressures on government budgets and competing priorities, but the Global Fund starts in a strong place. We have shown we can make a huge impact.” —*Michael Dumiak*

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



**Peter Sands**

## A New Wave of African Researchers at Work on HIV

Marianne W. Mureithi, lecturer and postdoctoral scientist at the University of Nairobi and chief research scientist at the Kenya AIDS Vaccine Initiative (KAVI), knew she wanted to be involved in the sciences, even from childhood. She recalls being fascinated by the human body, needing to know every organ's function and purpose. "When I was really young, I was fascinated by biology," Mureithi says. Yet it wasn't until the 1980s, when HIV/AIDS hit her home country of Kenya, that she understood she had a calling. She lost several family members and friends to the epidemic. "I wanted to know why HIV was affecting people in sub-Saharan Africa. It was killing families and no one could understand why." Even then she recognized that the lack of research centered in Africa would be a major detriment to solving HIV. So after receiving her PhD in Immunology & Microbiology at the University of Bristol in the UK, and pursuing her post-doctoral studies at Harvard University, Mureithi returned to Kenya with a plan to contribute however she could in defeating the virus.

Now she is part of a new wave of African researchers that is making steady progress in understanding HIV transmission in an effort to develop new and improved prevention strategies. She is also part of the surging movement to create sustainable, self-sufficient research in the areas hit hardest by AIDS. For Mureithi, her part in this movement is driven by both personal and intellectual concerns.

The HIV/AIDS epidemic is having particularly devastating effects among young women in Kenya. According to the latest data from the Joint United Nations Programme on HIV/AIDS, there is a significantly higher prevalence of HIV/AIDS among women aged 15-49 in Kenya than men of the same age—almost seven percent among

women, compared to around four percent for men. This high prevalence among women necessitates a focus on prevention, Mureithi says, which is why she became involved with KAVI.

There, Mureithi is studying mucosal transmission of HIV by analyzing tissue samples collected from hysterectomies performed on HIV-infected female volunteers. This work is being done in partnership with Thomas Hope, professor of cell and molecular biology at Northwestern University's Feinberg School of Medicine (see page 9),



Marianne W. Mureithi

who mentored her. Mucosal surfaces are the first point of entry for the virus during sexual transmission. Understanding the role proteins, known as mucins, and other components of the mucosal environment play in providing a barrier—or welcome mat—to HIV is critical to attempts to block the virus. By observing how the tissues of the uterus and cervix obtained from HIV-infected women reacted to the virus, Mureithi and her team can more clearly illuminate the mechanisms by which mucosal immune responses slow HIV, with the hope that understanding and eventually triggering these responses can create a pathway to vaccine development.

Now Mureithi and her team will be able to conduct this research with cutting-edge technology. The newest addition to her lab is a high-powered deconvolution microscope, the same one that Hope's lab is using in Chicago. It is one of the first of its kind in Kenya, and the region. It was provided through funding from the US Agency for International Development. This state of the art device allows Mureithi and colleagues to observe living cells, helping them understand in real time how HIV interacts with immune cells in various tissues. —Max Dorfman

Max Dorfman is a staff writer at IAVI based in New York City.

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ing the epidemic. He argues that with enough progress in prevention and treatment—using highly effective contemporary treatments and getting people at high risk of HIV infection to use PrEP—it is, theoretically, possible to get there (*J. Amer. Med. Assoc.* 318, 1535, 2017). "Ending the HIV/AIDS pandemic without a vaccine is possible," he wrote, "although it is unlikely." What would be the tipping point in finishing the epidemic is a vaccine, even one that is moderately effective.

"Before we didn't even have the tools," Fauci says. "Now we have treatment for the individual, treatment as prevention, and we have pre-exposure prophylaxis." Better implementation can go a long way to improving the situation. "But if you really want to end the epidemic," he says, "we need an extra tool. It doesn't have to

be a 98 percent [effective] vaccine. But you must prevent infections in a different way along with treatment as prevention and pre-exposure prophylaxis. A vaccine between 50 and 60 percent effective would be enough."

Recent research advances continue to provide hope there will be such a vaccine. "It is critical to continue to accelerate a robust research effort in that direction while aggressively scaling up the implementation of current treatment and prevention tools," he concluded in the commentary. "To do anything less would lead to failure, which for HIV is not an option." ■

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

# Upcoming HIV-Related Meetings



## JANUARY 2018

### *20th Bangkok International Symposium on HIV Medicine*

January 17-19; Bangkok, Thailand

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

### *Keystone Symposia: Emerging Technologies in Vaccine Discovery and Development*

January 28 - February 1; Banff, Alberta, Canada

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

### *Keystone Symposia: Progress and Pathways Toward an Effective HIV Vaccine*

January 28 - February 1; Banff, Alberta, Canada

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

## FEBRUARY 2018

### *Keystone Symposia: Antibodies as Drugs: Translating Molecules into Treatments*

February 25 - March 1; Whistler, British Columbia, Canada

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

## MARCH 2018

### *HIV & Women 2018*

March 2-3; Boston, MA

More information: [www.virology-education.com/event/upcoming/international-workshop-hiv-women](http://www.virology-education.com/event/upcoming/international-workshop-hiv-women)

### *CROI 2018*

March 4-7; Boston, MA

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

## APRIL 2018

### *Keystone Symposia: HIV and Co-infections: Pathogenesis, Inflammation and Persistence*

April 15-19; Whistler, British Columbia, Canada

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

### *HIV & Hepatitis in the Americas*

April 19-22; Mexico City, Mexico

More information: <http://hivhepamericas.org>

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