

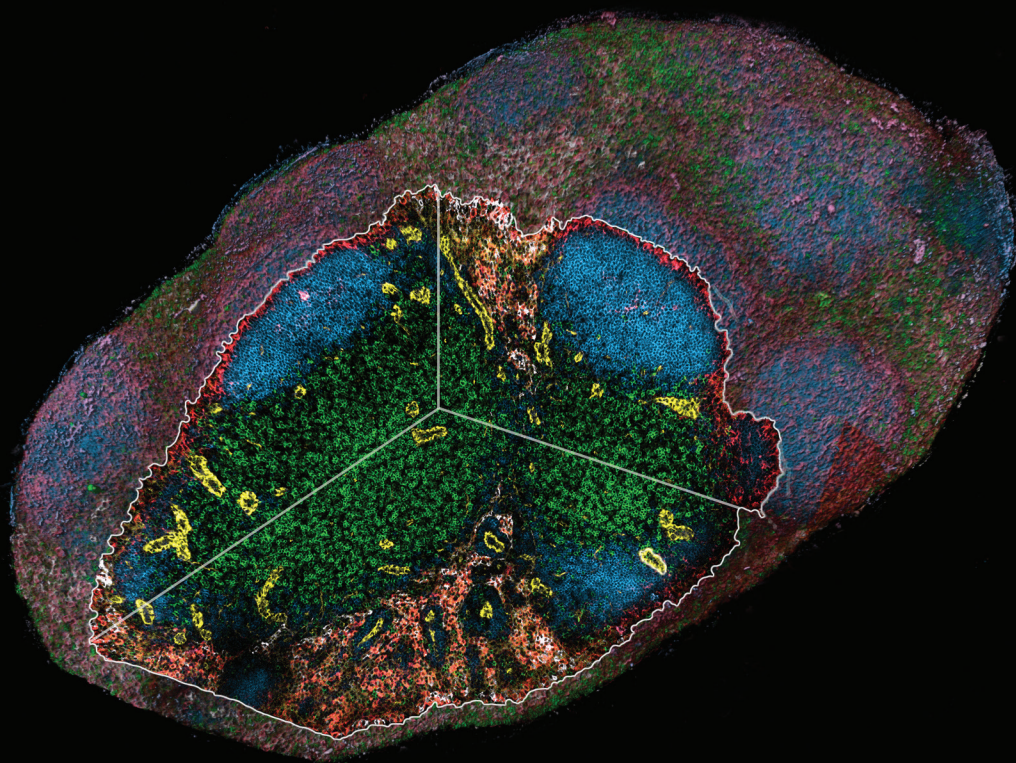
VOLUME 19, ISSUE 4

# IAVIReport

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## Françoise Barré-Sinoussi: an Incredible Career



**Plus: Updates on microbicides  
and Ebola vaccine development**

## EDITOR'S LETTER



I imagine there are many spectacular perks to being editor of a travel magazine. Trips to exotic destinations, stays in fancy hotels, those sorts of things. Well, one of the best parts of being editor of *IAVI Report* is sitting down with some of the greatest scientists and policymakers in the field and chatting with them about their lives, their work, and the disease that has in many cases been the central focus of their careers. Trust me, it's a big perk, and for this issue I had the opportunity to talk with one of the greats—Françoise Barré-Sinoussi.

She of course is a Nobel laureate for her role in discovering HIV and is one of the most outspoken advocates for cure research. It just so happens she retired recently and so we used the occasion of her hanging up her lab coat to talk about her inspirational career and her thoughts on treatment, cure, and vaccine research today (see page 10).

Also in this issue we review the latest developments in microbicide research. The microbicide field which was once beleaguered by seemingly multiple failed trials, is now eagerly awaiting the results from a pair of studies evaluating whether vaginal rings containing HIV-specific drugs can prevent HIV infection (see page 4). We also take an in-depth look at the status of the research and development of Ebola vaccines (see page 14). While 2014 was marred by the worst Ebola epidemic to date, this year there was great progress in the development of vaccine candidates designed to prevent another outbreak from escalating out of control, or ever occurring at all.

Together, these articles capture inspiration, hope, and progress. And we couldn't think of better sentiments to close out the year. We wish all of our readers a happy, healthy, and safe 2016!

– 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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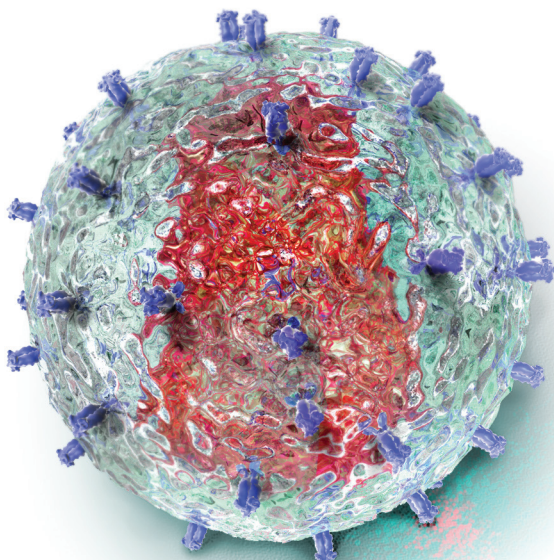
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### [ ON THE COVER ]

Ron Germain and his team at the National Institute of Allergy and Infectious Diseases' Laboratory of Systems Biology are producing three-dimensional images, such as this murine lymph node, using quantitative whole organ microscopy. First, the lymph node is stained. B cells are shown in blue and are located in peripheral B cell follicles; CD8<sup>+</sup> T cells are in green and are located in the central T-cell zone; blood vessels are in yellow; and macrophages are in red and are seen lining the follicles. Using clearing-enhanced 3D achieves high clarity while preserving all morphological and phenotypic cell characteristics. Researchers can then take high-resolution multi-parameter images of entire organs using confocal microscopy. Germain and colleagues want to combine this method with nucleic acid techniques that permit detection of integrated virus or detection of viral RNA to help identify the cells that are productively and latently infected with simian immunodeficiency virus (SIV) in nonhuman primates.

*Image courtesy of Michael Gerner and Ron Germain, Lymphocyte Biology Section, National Institute of Allergy and Infectious Diseases*

# Microbicide Development Hinges on New Products Administered in New Ways

Non-specific or antiretroviral-based vaginal gels failed to work but new formulations offer hope.

By Mary Rushton

Nearly a decade ago billionaire philanthropist Bill Gates, appearing before 20,000 people at the 16<sup>th</sup> International AIDS Conference, urged the world to accelerate the search for a microbicide. “This could mark a turning point in the epidemic, and we have to make it an urgent priority,” he said on the opening night of the biannual conference in Toronto.

The Bill & Melinda Gates Foundation had already given close to US\$2 billion to support HIV/AIDS projects and considered development of an AIDS vaccine its top priority. But with HIV incidence static, and the development of an effective vaccine several years away, Gates said microbicides along with oral antiviral drugs to prevent HIV transmission—a then still hypothetical strategy dubbed pre-exposure prophylaxis or PrEP—were necessary to help reduce the rate of HIV infections.

Gates wasn’t alone in sounding the call. Former US President Bill Clinton’s foundation was primarily focusing on helping to make antiretroviral (ARV) drugs affordable for millions of HIV-infected individuals in developing countries. But at the conference they too broadcasted the need for vaginal microbicides—defined then as gels or creams women applied to the vagina prior to intercourse to prevent sexual transmission of HIV.

How far the field of microbicides has progressed since then is a pipeline half-full, pipeline half-empty situation. Unlike the army of positive findings that led the US Centers for Disease Control and Prevention (CDC) and most recently the World Health Organization to recommend oral PrEP for all high-risk, HIV-uninfected individuals (see *New Global Goals and Guidelines Aim to Eliminate AIDS*, *IAVI Report*, Vol. 19, No. 3), the results from so-

called topical microbicide candidates have been largely disappointing thus far (see *PrEP Works*, *IAVI Report*, Vol. 19, No. 1). Only one trial of a topical vaginal microbicide to date showed any efficacy and follow-up studies have failed to confirm the candidate’s protective effect. The biggest reason: women don’t use it. Or as researchers say, there is poor adherence. While poor adherence has been a factor in some oral PrEP studies, the inability of volunteers to use a topical microbicide gel consistently—particularly high-risk young women in the setting of clinical trials—has essentially sidelined the development of topical microbicide gels.

Yet the microbicide pipeline remains quite robust with attention now focused on new formulations that are less user-dependent. Two pivotal Phase III trials are assessing the efficacy of a vaginal ring containing the ARV dapivirine (DPV) that slowly releases the experimental drug over one month, freeing women from having to apply the gel around sex to be protected. Intra-vaginal rings that simultaneously protect against infection with HIV and herpes simplex virus (HSV), while also preventing pregnancy, are also in development. And while vaginal gels may no longer be considered optimal, microbicide gels applied rectally are still being explored as a potential approach for use by both men and women who engage in anal intercourse. One candidate has just completed testing in a Phase II trial and additional studies are being planned.

Other new methods for delivering microbicides include vaginal films which can deliver multiple broadly neutralizing antibodies (bNAbs)—infection-fighting proteins that can neutralize most of the HIV isolates in circulation—or other

ARVs such as integrase inhibitors, which could provide several days of protection from HIV with a single application. “I’m really excited about all the new technologies,” says Sharon Hillier, a professor of medicine in the Department of Obstetrics, Gynecology and Reproductive Sciences at the University of Pittsburgh and principal investigator of the Microbicide Trials Network (MTN), a worldwide clinical trials network funded by the US National Institutes of Health.

The need for HIV prevention options is as important as ever, Hillier and others stress. According to the Joint United Nations Programme on HIV/AIDS’s 2014 Gap Report, nearly half of the 5,000 HIV cases reported daily across the globe occur in women and adolescent girls, despite the proven efficacy of oral PrEP. “You know, there are many methods of contraception and no one ever questions whether another one should come on the market because the need is huge,” says Zeda Rosenberg, the founding Chief Executive Officer of the International Partnership for Microbicides (IPM), a non-profit product-development partnership. “One would argue the need is going to be huge for HIV/AIDS for a very long time. Just look at the rate of new infections among women. Even with the roll-out of medical male circumcision and the rollout of treatment, in general it has not taken one ding. The number of new infections in women in sub-Saharan Africa remains alarmingly high.”

## An evolving pipeline

The field of microbicide research has been one of peaks and valleys. The earliest microbicide candidates—an assortment of spermicides, surfactants, HIV entry inhibitors, and acid buffer gels which keep vaginal pH at protective levels—all failed to protect against HIV. The reasons they didn’t work varied by candidate, and in some cases still aren’t entirely clear. Repeated use of the spermicide Nonoxynol-9 (N-9) and the entry inhibitor cellulose sulfate (CS) in microbicide trials were found to actually increase risk of HIV transmission because they disrupt the protective genital epithelial barrier, thereby making it easier for HIV particles to get across (see *Some Candidate Microbicides Can Damage Epithelia*, IAVI Report, Vol. 12, No. 2). Another microbicide candidate known as PRO 2000—a water-based topical gel composed of 0.5% of a synthetic polyanionic polymer designed to bind nonspecifically to viruses and bacteria—initially looked promising. Ultimately it was found ineffective in preventing HIV infection, most likely because the seminal plasma reduced the effective-

ness of PRO 2000, but also perhaps because the microbicide candidate reduced protective mucosal immune mediators (*Int. J. Infec. Dis.* 15, 10, e656, 2011). SAVVY, a surfactant microbicide gel, was also ineffective in preventing HIV infection and was associated with a higher incidence of reproductive adverse events (*Int. J. Infec. Dis.* 15, 10, e656, 2011).

In 2009, microbicide researchers thought they had a winner with a topical PrEP candidate containing a gel formulation of the antiretroviral tenofovir (TDF). The CAPRISA 004 trial, involving 889 high-risk South African women, showed the candidate reduced HIV incidence by 39 percent and HSV-2 acquisition by 51 percent when used in a coitally dependent manner. Volunteers were instructed to insert the applicator containing gel within 12 hours before sex and as soon as possible, but within 12 hours, after sex. They were also instructed not to exceed more than two doses in a 24-hour period (see *Microbicides Finally Gel, Securing Spotlight at the International AIDS Conference, IAVI Report*, Vol. 14, No. 4). Principal investigator and director of the Centre for the AIDS Programme of Research in South Africa (CAPRISA) Salim Abdool Karim, who presented the results at the International AIDS Society meeting in Vienna in 2009, said that with this level of efficacy, mathematical models indicated that the gel could prevent 1.3 million new HIV infections and over 800,000 deaths in South Africa alone. His presentation received a standing ovation, which even given the more positive news in HIV research of late is still a rare occurrence.

Not only were these results good news for the field of microbicides, they provided the first clinical evidence that PrEP, topical or otherwise, could be an effective strategy in blocking HIV. Researchers were ebullient. But two confirmatory trials proved disappointing. Neither the FACTS 001 study designed to evaluate the original CAPRISA 004 peri-coital approach in 2,059 high-risk women from South Africa, nor the Vaginal and Oral Interventions to Control the Epidemic (VOICE) trial involving 5,029 high-risk women that evaluated both oral and topical PrEP regimens at sites in South Africa, Zimbabwe, and Uganda, showed a reduction in HIV infections among women who used the TDF gel. In both trials poor adherence was the apparent reason that the approaches were not effective.

Based on returned vaginal applicators and a self-reported number of sex acts, investigators who led the FACTS 001 study determined that women used the TDF gel during just 50 to 60

percent of sex acts per month. And only 13 percent used it at least 80 percent of the time. A total of 123 HIV infections occurred during the three-year study, 61 in the microbicide arm and 62 in the placebo group. Analysis of HSV-2 incidence is still ongoing, according to CONRAD, the health research organization that sponsored the study.

The VOICE trial, conducted by the MTN, evaluated the effectiveness of both daily oral and daily topical TDF as well as daily oral Truvada—a combination pill containing TDF and the ARV emtricitabine (FTC)—and reached the same conclusion as FACTS 001. The gel arm was halted after an independent Data Safety Monitoring Board (DSMB) determined that the rate of new infections was the same (6 percent) in the microbicide and placebo arms during the course of a year. Investigators also halted the oral TDF arm after a separate DSMB said it would be unlikely this trial would be able to show that this strategy was effective. Investigators continued to evaluate oral Truvada until the end of the study, but ultimately found that ineffective as well (see *The VOICE Results, Loud and Clear: Adherence Matters*, IAVI Report Blog, March 4, 2013). Meanwhile, multiple others trials established the efficacy of orally administered TDF and FTC in preventing HIV infection among men who have sex with men (MSM), men and women in heterosexual serodiscordant couples in which one partner is HIV infected, and heterosexual men and women recruited individually rather than as a couple.

The VOICE and FACTS 001 trials showed, however, that there was a disconnect between what women were reporting and what they were actually doing with the gels and pills. Over the course of the study, women reported remarkably high adherence to PrEP and the counts of returned tablets and used gel applicators—another measure of adherence—seemed to support what the women were saying. But quarterly blood samples from a sub-group of randomly selected participants told a different story. Detectable levels of TDF were found in just 25 percent of samples from the microbicide group, 28 percent from the oral Truvada group, and 30 percent from the oral TDF group, suggesting poor adherence across the board. The lowest drug levels were found in those under age 25, the subgroup of women at greatest risk of contracting HIV, researchers noted. The results were consistent with FEM-PrEP, a Phase III study of oral Truvada conducted in 1,951 high-risk women in Africa that was also stopped for futility (see *PrEP Trial in Women*

*Halted Due to Doubts That It Could Show Efficacy*, IAVI Report, Vol. 15, No. 2).

This remarkably poor adherence had researchers puzzled. A VOICE sub-study led by study investigator Ariane van der Straten of RTI International in San Francisco, uncovered some troubling revelations last year. Her study suggested many of the women had strong reservations about daily PrEP and misconceptions about the study drugs and the dangers of research. Interviews with about 102 randomly selected women revealed that some of the women were afraid of the stigma associated with taking a daily ARV-based regimen used primarily by people already infected with HIV. Others thought the regimens would make them infertile or increase their risk of HIV infection. Some objected to the vaginal wetness created by the microbicide gel. “Some women indicated that the lack of real-time monitoring allowed them to mislead the staff and not take their products ... while several women minimized the consequences of their own behavior in the context of a large, blinded trial, counting on others for compliance,” the investigators of the sub-study analysis noted (*PLoS One*, doi: 10.1371/journal.pone.0089118, 2014).

Hillier said in retrospect some of the findings were not that unexpected. “Given the long-standing fears some women had about ARVs, the stigma surrounding the use of oral ARVs, and the fact that some women just didn’t like the wetness of the gels, it’s not necessarily surprising that they made those decisions. What is clear is that we need alternatives to oral daily tablets and vaginal gels.”

When publishing the final results of the VOICE trial this past February, researchers concluded that products that do not require daily use, including sustained delivery of antiretroviral agents from vaginal rings or injections, might be a better option for women (*NEJM* 372, 509, 2015).

## The ring cycle

Attention in the microbicide field is now focused on just those types of strategies. Researchers are eagerly awaiting the results from two pivotal Phase III studies testing a monthly vaginal ring containing 25 milligrams of DPV, the experimental ARV developed by Janssen Sciences Ireland UC (formerly Tibotec Pharmaceuticals). This drug was never approved or licensed as an HIV treatment because it isn’t absorbed well when administered orally. But DPV does build up well in vaginal tissue. In 2004, Tibotec granted IPM rights to develop DPV as a microbicide and they are now leading one of the efficacy trials of the

drug administered via a vaginal ring that slowly releases it over the course of a month. The Ring Study, as this trial is known, involves 1,959 women from South Africa and Uganda.

Investigators from the MTN are leading the other efficacy trial of a DPV vaginal ring. This trial, known as ASPIRE—an acronym for “A Study to Prevent Infection with a Ring for Extended Use”—involves 2,629 women at 15 clinical trial sites in Malawi, Uganda, South Africa, and Zimbabwe. The first efficacy results from these studies are expected in 2016, perhaps as early as the annual Conference on Retroviruses and Opportunistic Infections (CROI) in February. If the results are favorable, IPM plans to seek regulatory approval and licensure of the ring as soon as possible, says Rosenberg, adding that DPV would only be the start. There are many other ARVs and combinations of ARVs that could be delivered vaginally in this manner she says, mentioning integrase inhibitors, protease inhibitors, and the CCR5-inhibitor Maraviroc, among others.

The dapivirine ring is made of a flexible silicone material measuring 2 ¼ inches in diameter. It sits high up in the vagina. Rings have been used for hormonal contraception since 2001. But figuring out the correct concentration of drug to put in the ring for HIV prevention—enough to prevent HIV infection but at the same time minimizing systemic exposure—is a balancing act. Data presented last year at CROI by University of Pittsburgh researcher Beatrice Chen, study chair of the MTN-013/IPM 026 Phase I trial evaluating the safety, acceptability, and drug absorption qualities of a vaginal ring, found that a vaginal ring containing DPV blocked HIV infection of cervical tissue samples, but a ring containing the CCR5-inhibitor Maraviroc was not absorbed enough by vaginal tissues to be effective.

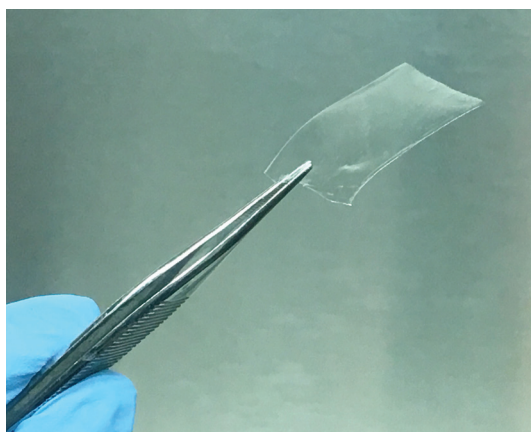
Because the bioavailability of DPV is higher in the vaginal compartment when delivered via a ring than when taken orally, less of the drug needs to be

used to be effective, says Thesla Palanee-Phillips, Director of Clinical Trials at the Wits Reproductive Health and HIV Institute in Johannesburg, South Africa, and protocol co-chair of ASPIRE.

“Studies have shown that the ring can deliver high concentrations of active drug to vaginal tissue for a month or longer with only trace amounts of the drug being absorbed elsewhere in the body,” says Palanee-Phillips. “What this means is that when used as a vaginal microbicide for the inhibition of vaginal transmission of HIV-1, much lower doses of DPV may be used than those used for a systemic, therapeutic indication.”

## Other modes of delivery

Vaginal rings are furthest along in the pipeline, but other delivery methods are also being developed.



**Vaginal film.** A monoclonal-antibody based microbicide formulated as a vaginally inserted film is one of several HIV prevention strategies under development for women. Image courtesy of Deborah Anderson at Boston University School of Medicine.

Another microbicide strategy involves delivering antibodies grown in tobacco plants using a vaginal film the size of a small Band-aid. This approach is now in early stage clinical testing in the US. The vaginal film, which contains the bNAb VRC01 and a second antibody that neutralizes HSV-1 and 2, is inserted manually into the vagina by the woman.

The trial will be conducted in multiple phases, beginning with a study involving single use of the films

in eight women to monitor safety and the release of the antibodies in the vagina. In this phase, the film will be placed by the doctor. In the second phase, 15 women will insert a new vaginal film every day for seven days, while a control group of 15 women will insert a placebo film daily.

To develop this approach, Deborah Anderson, a professor of obstetrics/gynecology and microbiology at Boston University School of Medicine who is leading the program, is working with scientists from San Diego-based Mapp Biopharmaceuticals—the maker of the ZMAPP experimental antibody therapy used to treat Ebola infection during the latest outbreak—and Kentucky Bioprocessing, which uses tobacco plants to express human monoclonal antibodies,

or “plantibodies” (see *Cape Town Connections, IAVI Report*, Vol. 18, No. 4). A previous study conducted in Europe tested the safety of vaginal use of a single HIV-specific “plantibody” in women and found no adverse side effects. Anderson says their program is the first one to use a formulated cocktail of antibodies. They are also considering adding more potent and broadly neutralizing HIV antibodies to the mix, including an anti-sperm antibody that could be used as a contraceptive. Anderson says the HIV-specific bNAbs being tested in the second generation version are ones that block both cell-associated and cell-free virus transmission.

Anderson’s collaborators at the Yerkes National Primate Center in Atlanta have also used a vaginal ring to release bNAbs in non-human primates. “The HIV antibodies were released at levels correlating with protection for over two weeks,” she said. “We’re hoping we can get one that releases in women out to a month, which will improve adherence.”

The field of rectal microbicides is also moving forward. Ian McGowan, a University of Pittsburgh professor of medicine who has been leading rectal microbicide trials at the MTN for years, says MSM are much less averse to using a rectal gel because the vast majority of them use lubricants anyway, making the product more acceptable. Some men have expressed concerns about having to use applicators to deliver the product, says McGowan. To put it bluntly, they would rather squeeze the gel on their fingers and apply it directly to the penis.

Whether this would deliver enough drug to the rectal mucosa is unknown, so the MTN has designed a microbicide study to find out. In the trial MSM will either insert the DPV gel into the rectum using an applicator or apply the gel with their finger. Samples of rectal tissue will be collected from volunteers to look for the presence of DPV and to see whether the rectal tissue can resist infection when the tissue biopsies are incubated with HIV *in vitro*.

The MTN has also completed a Phase II study of approximately 200 MSM and transgendered women in Peru, Thailand, South Africa, and the US that compared daily and peri-coital rectal use of a tenofovir gel with oral Truvada. Results are expected in 2016. McGowan said the group is still determining which product to test in a Phase III study. Whatever is decided the study design will be complicated by the success of oral PrEP. That’s because for ethical reasons, anyone enter-

ing an HIV prevention study in a country where PrEP is the standard of care must now be offered PrEP. “If [enrollees] use oral PrEP at the levels we want them to it becomes virtually impossible to develop another product,” says McGowan.

To determine the practicality of a Phase III rectal microbicide trial, MTN recently received approval to conduct a study involving MSM and transgendered women that will offer volunteers oral PrEP, but also randomize volunteers into a placebo-controlled study of a rectal gel containing an ARV, most likely DPV. “If everyone says, ‘great, thanks for the oral PrEP, love it, use it every day,’ that will answer one question about operational feasibility of a Phase III trial,” says McGowan.

## Tackling adherence

Regardless of which vaginal or rectal microbicides move forward and in which settings, adherence will remain an issue. Investigators have already incorporated some of the lessons learned from previous studies and adopted new methods of screening and monitoring volunteers.

The ASPIRE study devised social engagements and group meetings to help the volunteers be more open about any difficulties they have using the ring. Other events either included or were exclusively for male partners. Researchers also monitored adherence more regularly to gauge how things were going as the trial progressed. “Without compromising the blinded, placebo-controlled nature of the study, blood samples and used rings were tested routinely for drug availability. These data were pooled according to trial sites as well as the study overall so that challenges with use could be addressed as they became apparent,” said Palanee-Phillips.

Meanwhile FHI 360, which led the FEM-PrEP trial and has been involved in microbicide research for over two decades, was just awarded funding from the US Agency for International Development (USAID) to advance microbicide introduction, including the development of a community health clinic model that encourages the consistent and safe use of microbicides. A central theme of the CHARISMA project—which will be led by RTI and carried out in five African countries—is to counter harmful gender norms that interfere with microbicide or oral PrEP use, including partner violence. The idea is to set up an environment where PrEP can be used without the “taint of stigma” attached to it. “We have a lot of work to do to understand that dynamic,” acknowledges Tim Mastro, direc-

tor of Global Health, Population and Nutrition at FHI 360 and a longtime PrEP researcher.

FHI is leading a separate USAID-funded project called OPTIONS to develop a product delivery platform for current and future microbicide candidates as well as oral ARV-based HIV intervention.

“It is important that we continue to move forward,” says Mastro. “Science generates new evidence, which generates new questions. Look, the Pill came out nearly 60 years ago and we’re still looking for ways to improve contraception. We’ll be defining prevention options for decades to come so it is important to continue to make advances. There are still large issues related to adherence that need to be sorted out.”

## Funds are tight

Money is another challenge. Like many global health programs, funding for microbicide research is constrained. A report released earlier this year by the HIV Vaccines & Microbicides Resource Tracking Working Group found that global investment in microbicide research and development declined by US\$17 million last year, to \$193 million, and has been declining since 2012. The National Institutes of Health, which accounts for about 59 percent of microbicide research spending, reduced its support last year by about \$4 million, but the largest drop-off came from the Bill & Melinda Gates Foundation, which reduced funding from \$19.2 million to \$7.6 million.

Still other agencies stepped up their support. USAID boosted its support for microbicide and PrEP research significantly in recent years. Funding rose from \$35 million in 2011 to \$45 million in 2014, according to the HIV Vaccines & Microbicides Resource Tracking Working Group.

Future funding of microbicide research will likely hinge on the outcome of ASPIRE and The Ring Study. “If the dapivirine ring works, it opens up huge opportunities in product development, but if it doesn’t work we’ll need to find out why,” says Mitchell Warren, executive director of AVAC, the HIV prevention advocacy group based in New York City. “Perhaps we’ll find DPV was not the right drug or women just didn’t like the ring. It’s a remarkable but anxious time for those of us in advocacy.”

Sheryl Zwierski, director of the Prevention Sciences Program at the US National Institute of Allergy and Infectious Disease’s Division of AIDS, says interest in microbicide research has not been lost in the after-glow of oral PrEP or the push toward treatment as prevention. “Microbi-

cides are still a very important and key strategy,” she said. “If you think about it, what may be taken up by a gay man in Harlem might not be the same as for a woman in South Africa. Our philosophy is to go and try and provide different strategies.”

McGowan concurred. “I really believe we need a prevention tool box,” he says. “Some people will embrace gels, some will embrace pills, and some will want long-acting injections, so we do need to strive for diversity in prevention options.”

Long-acting, injectable ARVs are another strategy being investigated for both treatment and prevention. These drugs persist in the body for far longer than daily formulations, suggesting they may be a potential solution to the adherence problem. But because they linger in the body longer, the pharmacokinetics of the drugs need to be sorted out as well.

GSK744 and rilpivirine are two compounds being studied as long-acting PrEP products. A recent study found that a monthly injection of GSK744 protected monkeys against repeat intra-vaginal challenge with a simian/human immunodeficiency virus hybrid over an 11-week period (*Sci. Trans. Med.* 7, 270, 2015). Clinical trials are now being conducted in HIV-infected men and women to determine the correct dosages of both GSK744 and rilpivirine before studying the drugs in efficacy trials.

Another HIV prevention tool that also shows promise is the passive administration of bNAbs—delivering antibodies directly into the body via injection to prevent infection. A Phase I safety trial now underway in HIV-uninfected men and women is assessing different doses of the bNAb VRC01.

The variety of ARV and antibody-based strategies demonstrates how far the field has come in developing new HIV prevention strategies. But it has also blurred the lines between microbicides and PrEP, and even vaccines which also aim to induce bNAbs. This complicates how funding is tracked and raises questions about how products shown to be effective should be marketed and explained to a lay public that may not understand all these distinctions.

Warren says the most important questions ought to be what are the active drugs being used and how are they being delivered. “People do get caught up on all of this, but personally, for me, I think of it all as PrEP,” Warren says. ■

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

# AN INTERVIEW WITH *Françoise Barré-Sinoussi*

The Nobel laureate, former president of the International AIDS Society, and passionate advocate for HIV prevention, treatment, and cure research recently retired. But she is far from finished with her life's work.

By Kristen Jill Kresge

Françoise Barré-Sinoussi needs no introduction. There are a handful of individuals who have been involved in the HIV/AIDS pandemic since the very beginning and Barré-Sinoussi is one of them.

In 1981 when the US Centers for Disease Control and Prevention published the first reports of a deadly new illness that would eventually become known as AIDS, the causative agent was unknown. At the time, Barré-Sinoussi was working as a retrovirologist with her mentor Luc Montagnier at the Institut Pasteur in Paris, a non-profit research institute that she joined in the early 1970s even before earning her PhD in 1975. It was at the Institute Pasteur that she joined scientists who were trying to determine the cause of this mysterious new disease.

The rest, as they say, is history. In 1983, she and Montagnier identified a new retrovirus as the cause of AIDS. As Barré-Sinoussi recounts, this was the first time in her scientific career that experiments she and her colleagues conducted verified their hypothesis. In 2008, she and Montagnier were awarded the Nobel Prize in Physiology or Medicine for their role in discovering HIV. Not bad for your first proven hypothesis.

Since then Barré-Sinoussi's career has been shaped by the pandemic. She is a vocal advocate for HIV prevention and treatment. Most notably of late she has been a leading voice in the

push for HIV cure research. Always a realist, Barré-Sinoussi recognizes that a traditional, sterilizing cure may be a long shot because of the virus's uncanny ability to form reservoirs in various cells and tissues within the body. However, the possibility of achieving a sustained remis-

sion for HIV-infected individuals is something Barré-Sinoussi sees as an achievable goal. Her efforts were integral in establishing an agenda for cure research and she is a mainstay at annual meetings to address the latest findings in cure-related work. Barré-Sinoussi also served as president of the International AIDS Society (IAS) from 2012 to 2014.



At the end of August, Barré-Sinoussi, at age 68, retired from active research, which she notes was a requirement not a choice. Barré-Sinoussi has a ready and hearty laugh and remains humble despite her vast achievements. She is steadfast and passionate, a quality she thinks all scientists must possess to be successful. Otherwise, "it's just a job." Although she may be retired now, her calendar of engagements suggests otherwise, and she seems far from finished with her work.

Barré-Sinoussi spoke recently with Managing Editor Kristen Jill Kresge about her remarkable career, what it was like to be a woman HIV researcher in the early days, and her views on the state of vaccine and cure research today.

**Your involvement with HIV started with the discovery of the virus. When you reflect on that, what was it like at that time?**

The discovery of the virus was of course very exciting. As a scientist it was really wonderful because we were making a hypothesis and defining approaches to try to confirm this hypothesis. For me it was really the first time in my life that we were making an experiment to verify a hypothesis and the hypothesis was confirmed. So as a scientist it was really exciting. But as a human being, it was really awful. At that time, AIDS was really a tragedy. People were dying. They were young, dying of this new disease, and knowing as a scientist that it would probably take time, too much time for many of them to benefit from any treatment that science could deliver was really very, very stressful.

**How has your thinking about the virus changed since the earliest days? Did you initially think that the road to treating, preventing, or even curing HIV infection would be easier than it turned out to be?**

We were very naive in the early 1980s. After the discovery of the virus and the linking of the virus and the disease we thought that it could be very easy and very fast to develop treatment or even to develop a vaccine. We started to understand a little bit later on the complexity of the interaction between the virus and the different tissues and compartments in the body. Then we moved from a naive vision to a much more complex vision, which is the reality.

However, I think there was some rapid progress. First, in terms of development of diagnostic tests, which was a very important step. This quickly made it possible to prevent transmission of the virus by blood and blood derivatives. Secondly, AZT was introduced in 1985, so it was quite rapidly that the first inhibitor of reverse transcriptase was in clinics. Of course it was not sufficient and we had to wait until 1996 to see the first results of combination antiretroviral treatment, but I would say progress has been quite fast in terms of treatment. If we think about prevention, we still do not have a vaccine today; however, we have learned a lot over the years. We have also learned progressively that treatment is prevention.

**What role did activism play in accelerating HIV treatment?**

The role of activists has been really critical. The pressure they put on pharmaceutical compa-

nies, on governments, and on the decision makers has been really critical for making progress in the access to care and treatment. That was the first time I've seen such a movement to get the people affected by the disease access to what the scientists were delivering. This is a good lesson for other fields. I think we really need the same movement today for curing people that are infected with HIV.

**You've recently been one of the main scientists pushing the cure research agenda forward. Do you consider yourself an activist?**

Some people say that. It's difficult for me to know whether or not I am an activist. What I know for sure is that for me, it's unacceptable as a scientist to not be part of any movement for improving science and improving the delivery of tools for the benefit of people that are affected by a disease like HIV. Scientists have a role. It's their responsibility to apply pressure if the tools they develop cannot be accessed by the people who are affected by disease.

**What do you think the prospects are today for the development of a preventive HIV vaccine?**

Today I think we are going in the right direction. I would not have said that before the data of the Thai trial, RV144. But since 2010 there's been wonderful progress in terms of the data with the new broadly neutralizing antibodies and exciting data that suggest non-neutralizing antibodies may also be important for ADCC [antibody-dependent cellular cytotoxicity] activity. We also need to understand better the T-cell response that might be important for vaccines to induce. So I think it's really progressing in the right direction and the reason for that, in my opinion, is really because scientists are combining basic science together with pre-clinical and clinical research. We are really starting to see the results of that so I'm very positive today. I would not have been so positive before 2009.

**It's good we are doing the interview now then.**

(Laughs.)

**What are your thoughts on the prospects for therapeutic vaccines?**

Therapeutic vaccines are a critical issue for cure research. I cannot separate the two because probably therapeutic vaccines will be one of the components of a future cure strategy. There are

several promising approaches today. The wonderful data from Louis Picker using the CMV [cytomegalovirus] vector are really encouraging. There are also data using chimeric antigen receptors in order to improve T-cell responses and some other approaches based on immune therapy for cancer, which are also encouraging. I think we should go in both directions—preventive vaccines and therapeutic vaccines together.

**Do you think HIV vaccine research is fueling scientific discovery in other fields, such as cancer research or even more recently with Ebola? And in the case of Ebola has the experience working with HIV/AIDS on the ground influenced the response to this latest outbreak?**

I would say for cancer research today the opposite is really happening. It's really the data regarding immunotherapy in cancers that is driving new avenues for HIV cure science or HIV vaccine research, in my opinion, which is good. However, HIV research all together has certainly impacted other areas. With HCV [hepatitis C virus] treatment for example, the approach was based on the development of HIV antiretroviral treatment.

This is the reason I would like to push for more interaction between HIV and non-HIV researchers. This is the way to go if we want to have new creative ideas that can be useful for both HIV vaccine and cure research and other diseases.

You also mention Ebola. I remember when the Ebola outbreak was announced and the information we were getting at the time reminded me very much of the early years of HIV. Of course it is not the same virus and the disease outcome is not the same, but the reaction of the population in Africa really reminded me of what happened with HIV. They were afraid about contamination, the behavior of the police, and the behavior of doctors. We were in a very similar situation with HIV. And certainly the lesson that we learned from HIV is that the communities need to be involved in giving information and counseling to the populations. This is critical in terms of research for Ebola. And I know that some of my colleagues working on HIV stopped working on HIV to start clinical trials on Ebola. Some of my colleagues that were involved in social science studies of HIV/AIDS moved rapidly to start working on Ebola. So I think the lessons learned from HIV/AIDS are

very useful for other outbreaks like Ebola. HIV/AIDS can be used somewhat as a model. Not a perfect one, but it is useful.

**Considering some of the recent disappointments in cure research, including the famous case of the Mississippi baby who was thought to be cured after very early initiation of therapy but later experienced viral rebound, it seems that the goal of curing HIV may be even more difficult than anyone appreciated. Do you think a true HIV cure is possible?**

The view of cure research has changed for people outside the field. For those involved in the field of cure research I don't think the outlook has really changed because it's been for years that we are mentioning a sterilizing cure, or a functional cure or sustainable remission, personally a term that I prefer. We knew already that obtaining a sterilizing cure would be what I call on my slides, an impossible mission. Then I cross out impossible mission and put remission—that's possible. This is not something new. We have learned a lot from the Mississippi baby and the Boston patients. The viral rebound that occurred in these cases is just telling us that we don't have the right tools to measure the viral reservoir. This is very important. One of the priorities of cure research is really to develop new tools to quantify the reservoir.

Today, according to the technology and knowledge we have, a cure is still very difficult. However, maybe in the coming years we will have new strategies and new biomarkers, for example, to identify cells that carry the virus and we will be able to target those cells in different compartments of the body. We don't have that today but we cannot say whether in the next 10 years we will have such tools. You never know in science so it's impossible to say.

However, it's certainly more realistic to think about sustainable remission. We know that there are patients in the VISCONTI cohort that have been treated very early on—within 10 weeks after infection—and the vast majority of them after more than 10 years are still controlling the virus and are not on treatment anymore. They are what we can call a sustainable remission. So those people already exist.

Still, to achieve a functional cure on a large scale will take time and will certainly require a combination of approaches. We need to have better strategies. We need innovation and creativity.

We need a novel generation of scientists. We need to interact better with non-HIV researchers. It's critical today to have HIV cure researchers interact with scientists working in cancer. We also need to have public-private partnerships. This is very important if we want to accelerate cure research. This is a list of what we need and this could be achievable I'm sure. These are the aims of the IAS HIV cure project.

#### **Does either cure or vaccine research in your opinion need more funding?**

If you ask this question of a scientist they will always say 'of course.' We always need more money.

But when you work together in a consortium of researchers with different expertise, you spend less money. It's also one of the ways to not do—I'm sorry to say this—what has been done in the past for vaccine research. To be very empiric and try everything; all the vectors, all the constructs, without knowing where we were going. You spend a lot of money doing this and in the end you could have nothing. In my opinion, if you want to do more with less money, you can, if you are creative and work better with others.

#### **Do you think African nations could play a broader role in HIV research?**

I think it's critical to promote African leadership. This is critical because there is a link between the development of science in countries and economic development. So it's critical for the populations of those countries and it's critical for their economies. What I hope will happen in the future is to have more and more consortiums of the African countries working together with African leaders. The CAPRISA [Center for the AIDS Programme of Research in South Africa] program in South Africa is a good model, in my opinion, of strong leadership and training to strengthen the capacity of a new generation of researchers working together in South Africa today.

#### **So what convinced you that it was the right time to retire?**

I was obligated to retire. In France when we arrive at a certain age we have to retire. We have no choice. So that's the reason I had to retire. I do not have a lab anymore but it was time for the people working with me to be totally independent and to have their own laboratories and to

develop their own programs. I think it was the right time to do that. That does not mean of course that I am not doing anything anymore. I will continue to advocate for cure research for IAS. I will continue to be a member of different expert panels at an international level. I will continue to coordinate research programs in Southeast Asia, and particularly in Vietnam. So I think I'm going to be very busy as a volunteer.

#### **You are inarguably the most famous woman in HIV research. What was it like being a woman researcher in this field early on?**

For sure it was not easy. It was very difficult to be heard by the male researchers. For me there was also the fact that I was much younger then, of course, than I am now. When you are a young woman it is very difficult to get men to listen to you. However, even in the early '80s a lot of women were involved in HIV research so they really have been at the forefront.

#### **What advice would you give to young women who are just starting out in science?**

Science is really a passion. If they don't see it that way, it is just a job. If they are really motivated to become a scientist, not for themselves, not for their CV, not for making publications, not to be known, but really to do it for others, then it's the most beautiful work that you can do. When you are able to deliver tools to help those who suffer, this is really great. It is so wonderful to see people that I know still alive and happy to live. My advice is to be very persistent and the results, the success will happen. They have to be ready to overcome all the obstacles, and if they are persistent and motivated they will.

When I talk with women affected by the disease or with drug users, they are expecting so much from science. They believe in us so it's our duty to try to give our best to respond to their expectations.

#### **If you could go back 30 years in your career, is there anything you would have done differently?**

Maybe one thing. One thing I should have done but it's too late is spend several years working in a resource-limited setting. That's the only thing. The rest I think I would have done exactly the same. Nothing is perfect—you can always do better for sure. But at the end that's not so bad. ■

# WHEN EBOLA RETURNS, *Will the World be Ready?*

A year ago there were dire predictions as the worst Ebola outbreak in history spread through west Africa. There was no Ebola vaccine or approved treatments available. Should another outbreak occur, of Ebola or any other deadly pathogen, hopefully the story will unfold differently.

By Michael Dumiak

The world's worst outbreak of Ebola seems to have abated.

Sierra Leone was declared free of Ebola on Nov. 7, and as of Nov. 23, Guinea had no more Ebola patients and had started a six-week evaluation at the end of which it could also be deemed Ebola-free. Even so, despite being declared Ebola-free twice before (once in May and then again in September), three new cases of the disease were reported last month in Liberia.

After killing more than 11,000 people, the focus is shifting from how to extinguish the Ebola outbreak to learning from it. Close attention is still being paid to the virus in labs around the world and in the offices of the World Health Organization (WHO). Much of this attention is focused either on improving the response to the next epidemic or developing ways to prevent another outbreak of this scale from ever occurring in the first place.

There are now at least six Ebola vaccine candidates in clinical trials (see table). While data collected so far look promising, the environment in which these candidates are being studied and developed has changed quite a bit from a year ago when the epidemic in west Africa was raging. Vaccine developers, public agencies, and governments formed partnerships to rapidly accelerate the clinical development of these candidates. The entire searing experience of this outbreak is providing landmark and long-term lessons in how to respond to emerging pathogens and public health crises, how to quicken vaccine research and development, and even how vaccine vectors and formulations can inform efforts against endemic diseases like HIV, malaria, and tuberculosis.

## Stopping a frightening bug

The Ebola virus, part of the Filoviridae family, is a single-stranded RNA virus that was first identified near the Ebola River valley in the Democratic Republic of Congo, then Zaire, in 1976. It causes a highly lethal hemorrhagic fever syndrome in humans and nonhuman primates, with mortality rates ranging from 50 percent to 90 percent in the half-dozen outbreaks that have occurred in central and west Africa over the last three decades. The virus infects many different kinds of cells, including dendritic cells, endothelial cells, hepatocytes, epithelial cells, monocytes, and macrophages. It then moves through the lymph system into the liver, spleen, and adrenal glands, eventually leading to organ failure. All this occurs in just two to three weeks. After this time, complications of Ebola infection will either kill you, or because of an effective immune response, intensive medical treatment, or both, it won't.

Ebola is highly infectious: a single drop of blood can contain millions of viral copies. The virus gets into humans through mucous membranes, such as tear ducts or nasal passages, or breaks in the skin. The number of hazmat-suited healthcare workers who contracted the virus during the last outbreak shows it takes very little for it to make effective contact. But the virus is not airborne—it needs direct, fluid-to-fluid contact to spread. And because the virus runs its course in humans so quickly, symptomatic Ebola sufferers are less likely to spread the virus to large numbers of people.

What makes Ebola so scary is its high case fatality rate, says Vincent Racaniello, a Columbia University microbiologist, blogger, and host of the *This Week in Virology* podcast. Proper clinical care can

have a real impact on reducing mortality. Building clinics, employing epidemiological tracing of Ebola patients in viral hotspots, vigilant hygiene, stringent burial practices, effective quarantine, and heroic medical treatment are the factors which brought this latest outbreak from the nightmarish forecasts of a year ago to where it is now. In the future, though, a preventive vaccine, coupled with effective treatments, may also be available.

## The candidates

Of the at least a half-dozen preventive vaccine candidates in different stages of clinical trials, the two candidates furthest along in development are the products of recently formed partnerships among public research institutions and large private pharmaceutical manufacturers.

GlaxoSmithKline (GSK), the UK-headquartered pharmaceutical firm, is pursuing a candidate in collaboration with the US National Institute of Allergy and Infectious Diseases (NIAID) called ChAd3-ZEBOV. ChAd3-ZEBOV is a one-dose vaccine that uses a non-replicating, live-attenuated chimpanzee adenovirus serotype 3 (ChAd3) vector to express part of the Ebola glycoprotein, the major surface protein on the virus. This protein induces antibody and cellular immune responses, both of which are thought to be important for protection. Phase I safety trials showed no safety concerns and indicated that Ebola glycoprotein-specific antibodies were induced in all the volunteers. GSK is currently conducting a Phase II trial involving 3,000 adults and 600 children in western Africa, but not in the three countries most affected by the epidemic. ChAd3-ZEBOV was set to be part of a big Phase III trial in Liberia, potentially enrolling 27,000 volunteers, but plans were halted earlier this year as the outbreak ebbed.

Merck, meanwhile, has progressed rapidly with another candidate, rVSV-EBOV-GP, first developed by the Public Health Agency of Canada. The agency then licensed the vaccine for US\$205,000 to NewLink Genetics, an oncology and immunology biotech company in Iowa. As the wave of Ebola cases crested in November 2014, Merck bought the license from NewLink for \$30 million, with an additional \$20 million and potential royalties to come if the candidate passed efficacy trials and went into production (no royalties would come from purchases by low-income nations, but stockpiles for militaries and civilian populations of wealthier countries would appear to be included). The US Department of Health and Human Services' Office of the Assistant Secretary for Preparedness and Response contributed \$30 million to a wholly-

owned subsidiary of NewLink, BioProtection Systems Corp., to underwrite initial clinical trials. The contract has options to extend the agreement 10 months beyond the original 14 months with another \$41 million in funding. The rVSV-EBOV-GP candidate utilizes an attenuated, replication-competent Vesicular Stomatitis Virus vector that, like ChAd3, is genetically engineered to express a bit of the Ebola glycoprotein in order to provoke an immune response. This vaccine is currently in Phase II and III clinical trials in Liberia, Guinea, and Sierra Leone.

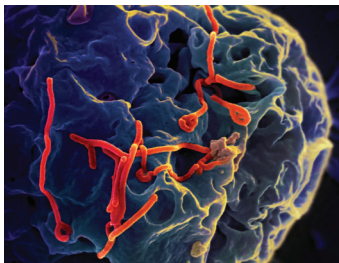
The way the Ebola crisis unfolded pressed vaccine development efforts to breakneck speeds, making it seem like these new vaccines appeared almost overnight. In fact, most of them had years of research behind them. Both ChAd3-ZEBOV and rVSV-EBOV-GP have their origins in turn-of-the-century biodefense research. Before the unprecedented 2014 Ebola outbreak gained traction, the National Institutes of Health (NIH) was already planning safety studies of the ChAd3 candidate to begin in March 2015.

Within a year the world has gone from having no volunteers in any clinical trial of an Ebola vaccine to more than 20 clinical trials on five continents ranging from Phase I through to efficacy, says Vasee Moorthy, team leader for vaccine development at the WHO. "It's all very novel."

The scale of the 2014 outbreak created an unprecedented sense of urgency. "There was a global focus on moving development very quickly," says Rip Ballou, GSK's vice president of clinical research and translational science. Vaccine manufacturers performed feats under extraordinary time pressure. GSK compressed the process of determining dosage from what normally would be a three-to-five-year timeframe into a matter of months.

Vaccine	Developer / Partnership	Phase reached
ChAd3-ZEBOV	GlaxoSmithKline / NIAID	Phase II / III
VSV-EBOV	Merck / NewLink / Public Health Agency of Canada	Phase III
Ad26-EBOV + MVA-EBOV	Johnson & Johnson / Bavarian Nordic	Phase I
Recombinant protein	Novavax	Phase I
JK-05 recombinant Ad5	Beijing Institute of Biotechnology / Tianjin CanSino Biotechnology	Phase I
Recombinant influenza	Russian Federal Ministry of Health	Phase I
SynCon DNA	Inovio	Phase I
VesiculoVax	Profectus / NIAID / CDC / US Dept. of Defense	Preclinical
DepoVax	Immunovaccine / NIH / NIAID	Preclinical

Ad: Adenovirus; MVA: modified vaccinia Ankara; NIAID: National Institute of Allergy and Infectious Diseases; CDC: US Centers for Disease Control and Prevention; NIH: National Institutes of Health Sources: *World Health Organization, BioSpace*



Ebola virus particles (red) budding from an African green monkey kidney epithelial cell. Image courtesy of the National Institute of Allergy and Infectious Diseases

### [ LEARNING FROM EBOLA ]

The World Health Organization engaged the Harvard Global Health Institute and the London School of Hygiene & Tropical Medicine to report on and recommend public health reforms in the wake of the 2014 Ebola epidemic. Their report, *Will Ebola Change the Game?* (*Lancet* 386, 857, 2015) concludes that the latest outbreak exposed systemic weaknesses in the international institutions responsible for protecting the public. The report outlines 10 recommendations it considers are "warranted and feasible."

This was possible because they did many studies simultaneously instead of sequentially. GSK started its original Phase I study, then two weeks later started another study in the UK that expanded the dose range, and then two weeks after that started a study in Mali with a parallel study in Lausanne, Switzerland, to collect additional safety data.

Ethics committees, which would normally take a week or two to evaluate a trial structure, were asked for responses in days if not overnight. Protocols for drug and vaccine testing are incredibly rigorous, detailed, and complex. Negotiating how to adapt them in order to respond to a crisis situation required flexibility on the part of vaccine manufacturers and regulators, Ballou says. It took a lot of good will between all parties. "That allows things to happen that normally do not at that pace."

But even with this incredible speed, some researchers were left about three-quarters of the way to the finish line before the number of Ebola cases dwindled, affecting their ability to conduct efficacy trials. For ChAd3-ZEBOV, dosage, safety, and tolerance data are in, but actual efficacy data are not. Ballou says GSK will supplement the data it has collected already with studies in nonhuman primates. The company is still about six or seven months away from submitting data to regulators in a bid to license its vaccine and is in ongoing discussions with US and European regulators about how best to do this. "We don't think they've taken a firm position on what data will be required. We would hope there is not a complete rethink about this," he says. Ballou is cheered in part because the GSK candidate has a similar method of action to Merck's, and for that candidate, efficacy data is available.

Merck's experimental rVSV-EBOV-GP vaccine candidate was tested in a trial involving 7,651 individuals in Guinea that was conducted earlier this year. This trial, known as the 'ring trial,' used the same kind of trial design used in the fight against smallpox. In this instance, 'rings' of close contacts to Ebola-infected individuals are vaccinated. Half the contacts in the rings are vaccinated immediately after a case is diagnosed; as a control, the other half is vaccinated three weeks later. The study was organized by the WHO. Both GSK and Merck got invitations to test their candidates, but GSK couldn't provide enough doses of its vaccine by the trial's start date.

An interim analysis of the trial was published in July (*Lancet* 386, 857, 2015). Swati Gupta, Merck's executive director for Public Health and Scientific Affairs, says the vaccine appears safe and vaccinated volunteers showed immune

responses to Ebola at three months and six months. Researchers are continuing to follow the volunteers. The study shows that in villages where Ebola outbreaks occurred, the vaccinated volunteers remained Ebola-free from a week to 10 days after injection. This translates to 100 percent protection in the interim results. "We're pretty excited," Gupta says. "We're pursuing licensure as aggressively as we possibly can."

### Partnering for progress

The rapid and dramatic progress in research and development of Ebola vaccine candidates was a direct result of public-private partnerships, some of which predate the Ebola outbreak, and some that were forged during the crisis. This did not happen in a particularly systematic way. GSK, for example, has its Ebola candidate now because in 2013 it bought Okairo, a Swiss vaccines firm that had developed interesting (and exclusive) technologies for stimulating CD8<sup>+</sup> T cells. Okairo also had been collaborating with NIAID on the Ebola work; GSK inherited it.

Intense focus, pressure, and funding put wind in the sails of these partnerships. During late summer 2014 the WHO convened the scientific and regulatory community, manufacturers, and governments. Funding followed. For the ZEBOV Phase I trials, for example, the Wellcome Trust underwrote one of the arms and the NIH managed it. The fact that Ebola eventually landed in London and the US might also have played a factor in putting a charge into the response. "It's in the domestic interest of countries to invest as an insurance policy for their own populations," says Moorthy. "Because if there's a problem 'over there,' there's probably going to be a problem 'over here' soon," he says.

One reason there is no vaccine currently on the market for Ebola or many other emerging pathogens is because they are not commercially viable. Racaniello suggests one future option would be developing vaccines and antivirals for emerging pathogens to the point of preclinical development or perhaps Phase I safety testing. "And then they'll be stored until an outbreak happens," he says, which would position them for fast-track studies.

But some researchers would like to go much further than this, calling for new ways to stimulate investment in vaccines that do not have a commercial incentive. Stanley Plotkin, an executive advisor to Sanofi Pasteur and researcher who helped discover the rubella vaccine, joined Princeton University molecular biology and infectious disease expert Adel Mahmoud and Jeremy Farrar, director of the

UK's Wellcome Trust, in calling for a \$2 billion global vaccine development fund to fill the gaps from market inefficiency and public-sector inability or unwillingness to fund vaccine development for infectious diseases (*NEJM* 373, 297, 2015).

Encouraging and formalizing long-term public-private partnerships could also be a model for speeding up drug and vaccine development. "The Ebola effort had a lot of really positive features," says Mark Feinberg, Merck Vaccines' former Chief Public Health and Science Officer and the newly appointed chief executive of the International AIDS Vaccine Initiative. Feinberg helped to guide the public-private partnership developing rVSV-EBOV-GP while he was with Merck. "It also highlights how we need to be more proactive and more strategic."

For specific diseases it would make sense to establish foundational data and stand ready to evaluate efficacy should an outbreak occur. But there are known pathogens for which we don't have vaccines or therapeutics that need to be addressed before a pandemic occurs, Feinberg says. "Deciding our priorities here will be important. Developing platform technologies which allow us to be nimble and expeditious in bringing forward vaccines against newly-emerging pathogens is a way in which we could make progress," he says. Another step that's necessary is figuring out how to realistically engage the private sector in a way that makes most use of their expertise, enabling technologies, and intellectual resources. "It should do so in a way that works for them, in a way that doesn't show itself to be a major opportunity cost, or in a way that can't be accommodated amidst their work to develop other kinds of therapies."

The public sector also needs to get more engaged. "It's all going to depend on public-sector investment and the understanding that it's in the interest of those with resources to invest ahead of time," Moorthy says. "The bottom line is that it will have to be public-sector funds mobilized in order to incentivize researchers and developers and manufacturers."

Ballou says however future scenarios unfold, there must be a better way than what's just happened. "Our experience with this pandemic is that this is no way to respond. The idea that we drop everything we're doing, shifting resources from critical internal ongoing programs to respond to a global need—we do that because it is the right thing to do. But it is a very disruptive activity that puts the whole business at risk in the long run," he says. "We think there needs to be a fundamentally different way of doing this. I think governments need to recognize that investment is required to

protect their populations, and that this cannot be done strictly and solely with multinational vaccine developers of which there are only a handful that can actually address this kind of work."

Feinberg takes a number of lessons from the Ebola vaccine development experience. "It demonstrated pretty vividly the benefits of current models of collaboration and how people can work together in new ways," he says. "But it's just the beginning in thinking of how we can do far better in that regard. Generalizing those models to meet established threats—such as HIV—will be all to the good."

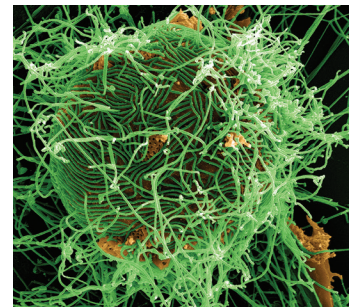
Certainly one of the fringe benefits of Ebola vaccine development is that it is helping to advance the development of viral vector platforms. For the first time the VSV and ChAd vectors are getting widespread testing in humans. VSV is a vector of interest to HIV researchers. It's also potentially interesting for malaria, TB, and several other pathogens. As Moorthy points out, only one recombinant viral vector vaccine that he knows of is already licensed, that being Sanofi's yellow fever platform used for its vaccine against Japanese Encephalitis. "The increasing maturity of viral vectors in vaccine development is manifest in Ebola vaccines."

Ebola will also have a lasting impact on vaccine development and distribution practices. The latest outbreak led to the introduction of tools such as Intellectual Ventures' ArcTec chamber, which can keep vaccine at minus 80 degrees centigrade for up to five days. New diagnostics, essential for distinguishing Ebola from other causes of hemorrhagic fever, also made it into the field.

Moorthy says the WHO is already drafting plans for vaccination scenarios. They want two classes of vaccine: one for use in ring vaccinations in the context of an ongoing outbreak, another that would confer durable protection for specific target groups, such as frontline health workers, or even as long-term prophylaxis for the general population.

The US Centers for Disease Control and Prevention's (CDC) deputy director, Anne Schuchat, thinks there's a path to licensure for the Ebola vaccines given all the trial data gathered during the outbreak as well as data from animal studies. The CDC set up permanent offices in the three outbreak countries. "We need to develop public health capacity with countries and global partners," she says. "Detecting, responding to, and preventing emerging infections is vital to protecting the rest of the world." ■

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

# *In* BRIEF

## Boot Camp Emphasizes Industry-Style Approach to HIV Vaccine Development

Industry typically leads the development of new products, conducting the translational and clinical research that is required to turn an innovative scientific discovery or early-stage product that is initially hatched in an academic or government laboratory into an actual drug or vaccine. But this process isn't as straightforward for HIV vaccine development. HIV vaccine research is led by multitudes of researchers in academic and government laboratories, product-development partnerships, and within the pharmaceutical industry.

Part of the reason is that there are substantial, even unprecedented challenges to developing an HIV vaccine. Several candidates in development, including some developed in partnership with industry, have failed to provide any protection in efficacy studies. Only one vaccine candidate tested to date—a modified vaccinia Ankara (MVA) vector-based candidate in combination with a recombinant protein boost—showed any protection against HIV. These candidates, tested in the RV144 trial in Thailand, provided a marginal 31% efficacy. And while follow-up studies to both understand the mechanisms of this protection and to augment it by modifying the vaccine candidates are either underway or in the works, most other vaccine concepts are in the early stages of research or clinical development. There is also no reliable animal model of HIV infection or definitive understanding of what a protective immune response against the virus even entails. This suggests development of an HIV vaccine is a high-risk endeavor and therefore the traditional model of industry-led product development may not be feasible. To address this, the Global HIV Vaccine Enterprise and Shift Health, a healthcare strategy consultancy, convened a two-day product development Boot Camp on November 15-16 in New York City, bringing together 50 leading vaccine research and product development experts to discuss how industry's expertise in product development could be integrated in the HIV vaccine field at large.

"The Enterprise had a meeting about a year ago to talk about the interaction between the public and the private sector. One of the important things that came out of that meeting is that you have to think from the beginning to the end all at the same time. So that was the impetus for this project," said William Snow, director of the Enterprise Secretariat. "We are trying to educate people about how people who know how to make vaccines, make vaccines." The idea is that incorporating a more industrial-like approach into the HIV vaccine discovery process now may expedite the testing and development of an eventual HIV vaccine. "It will make us more efficient. It will make us smarter," adds Snow.

The workshop focused on several key components of product development, including strategies for managing pipelines and

portfolios, creating target product profiles, translational research, preparing for the risks and potential outcomes of clinical trials, and the best practices for product-development partnerships (PDPs) that are a mainstay of the HIV vaccine field today.

In a session on product and portfolio strategy, speakers from the US National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH; the largest funder of HIV vaccine research in the world), the pharmaceutical industry, and the Bill & Melinda Gates Foundation (BMGF), compared and contrasted how their organizations make decisions about what ideas to support and prioritize. While industry's portfolio management is guided by medical need, companies are also driven by the expected net present value of a product, which relies on the commercial market potential for a given drug or vaccine. This makes investment in HIV vaccine research and development a hard sell for many companies and is why foundation and government support is so critical to advancing the field.

"I get the question a lot about how we decide what diseases we work on. It's not rocket science. It's quite simple: you just look at the top 10 causes of death in low-income countries," said Penny Heaton, director of vaccine development at BMGF. "The other thing that may not be that apparent to all, is that we want to fund things that are orthogonal to what others are funding. We don't want just to duplicate what others are doing," she elaborated. This means taking on ideas or approaches that would be much too early stage or risky for industry to consider. "We also want to make sure that we're investing in those things that have the potential of being transformational," Heaton said.

The differences in how foundations, government research agencies, and industry all manage their portfolios made it clear why PDPs are a necessary part of HIV vaccine development. "Partnerships are really the name of the game here," said Snow, the first to mention a recurring theme of the two-day workshop.

Part of what drives the growing number and broadening landscape of PDPs in the HIV vaccine field is the steep financial investment required to bring an eventual HIV vaccine to those most in need. "No single entity or sector has individually the resources that are needed to move an HIV vaccine forward in different populations worldwide," says Ryan Wiley, president of Shift Health. There is also different expertise in each of the sectors involved in research and development for HIV vaccines. "I think we all understand the value that different sectors bring: in terms of innovation and science from academia, resources to mitigate risk and spread risk through foundations and government, and the

industrial manufacturing and ultimately marketing and distribution expertise of industry.”

Jerry Sadoff, senior advisor on viral vaccines at Janssen Infectious Diseases and Vaccines, which is now part of Johnson & Johnson, suggested that without these partnerships industry would be unlikely to work in HIV vaccine development at all. “There’s a real need in HIV, in my view, to have these partnerships,” he said. Without these partnerships, “I just don’t think industry would be interested.”

Other industry representatives at the Boot Camp echoed the financial benefits of partnering with government and non-profit institutions, but also recognized that these groups bring more to the partnership than just funding. “Within partnerships you get added values and skills,” said Carols DiazGranados, director of clinical sciences vaccine development at Sanofi Pasteur.

Two of the most prominent partnerships in the HIV vaccine field today involve a variety of funders and academic/industrial partners working to advance candidates into clinical testing. How these partnerships were formed, what their aims are, and how they can provide a model for other partnerships was a major focus at the Boot Camp.

The Pox-Protein Public-Private Partnership or P5 is a large consortium charged with leading the follow-up of the RV144 trial. “The goal of the P5 partnership has been to translate the RV144 learning to South Africa and test modified vaccine components from RV144 that are based on clade C inserts with the goal of both improving the efficacy that was observed in RV144, and ideally prolonging that protection,” said Nina Russell, deputy director of HIV at BMGF.

The P5 involves two major funders: BMGF and the NIH. The clinical expertise is provided by the HIV Vaccine Trials Network (HVTN) and the US Military HIV Research Program (MHRP), which are involved in planning and implementing the RV144 follow-up studies. The P5 also involves two industrial partners: Sanofi Pasteur, which is manufacturing the modified vaccinia Ankara prime, and GlaxoSmithKline, which recently acquired Novartis Vaccines and will provide the p120 protein boost.

As the P5 prepares for eventual efficacy studies in South Africa, its members are actively engaging with regulators, communities, and government health agencies to prepare for multiple possible outcomes. “The path from establishing vaccine efficacy to licensure and rollout will ultimately be a multi-year and complex process,” said Russell. “So that’s what we are thinking about very intensively.”

The other major consortium includes Janssen, Beth Israel Deaconess Medical Center (BIDMC), Harvard, the HVTN, NIAID, MHRP, the Ragon Institute, and the International AIDS Vaccine Initiative (IAVI). This partnership aims to advance an adenovirus sero-

type 26 (Ad26) vector-based candidate expressing mosaic antigens designed to tackle the diversity of HIV in combination with either an Ad26, an MVA vector, or a purified gp140 protein boost. These candidates are currently in Phase I/IIa clinical trials, spurred by encouraging protection data in preclinical animal studies, with a development plan that aims to test the most promising combination of these vaccine candidates in eventual efficacy trials. The preclinical protection data was what convinced Janssen to get involved. “A bit of exciting preclinical data, even though it’s not proof, is enough,” said Sadoff. “Of course we did get some correlates out of these that looked promising, and having correlates makes things even easier to develop. So that was a second reason why we thought we might be able to develop a vaccine using these constructs.”

Getting Janssen involved was what really propelled these candidates toward a product development pathway. “One of many critical features that allowed a transition from research-oriented to product-oriented development was the committed industry partner,” said Dan Barouch, director of the Center for Virology and Vaccine Research at BIDMC, referring to his partnership with Janssen. “I think that can’t be overstated in terms of the importance of that.”

Other factors that were cited as essential to the success

of both of these partnerships was having robust project management, including multiple full-time dedicated staff members committed to advancing the program; close personal relationships between the partners; solvable legal issues; a feasible and scalable manufacturing process; and a clear path to a licensable product. Many times, finding consensus between numerous partners and funders isn’t easy and several speakers addressed some of the issues they’ve faced in making these partnerships work. “It has to be something that not only is a compromise between everybody but also makes sense. I think it’s challenging, but I think it can be done,” said Sadoff.

Although industry partnerships in the HIV vaccine field are few today, Barouch hopes more may be on the horizon. “I think the science has advanced to the point where the HIV vaccine field is worthy of true pharmaceutical investment,” said Barouch. “We’ve seen that with one company and hopefully we’ll see that with others in the next few years. Time will tell.” In the meantime, the Boot Camp provided a diverse group of HIV vaccine researchers from academia, government, and non-profit organizations with a crash course in the types of product development skills that can advance HIV vaccine research, even without an industrial partner.

More information about the Product Development Boot Camp, including a webcast, is available at <http://www.vaccineenterprise.org/product-development-bootcamp>. —Kristen Jill Kresge

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**By championing greater integration of the industry capabilities in early development and testing of HIV vaccine products and concepts, there’s an opportunity to accelerate product development, not only in HIV but in other priority disease areas.”**

*—from Global HIV Vaccine Enterprise’s Report on the HIV Vaccine Industry Think Tank, held Sep. 2014*

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# Upcoming HIV-Related Meetings



## JANUARY 2016

### *18th Bangkok International Symposium on HIV Medicine*

January 13-15; Bangkok, Thailand

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

## FEBRUARY 2016

### *6th International Workshop on HIV & Women 2016*

February 20-21; Boston, Massachusetts

More information: [www.virology-education.com/event/upcoming/international-workshop-hiv-women-2016](http://www.virology-education.com/event/upcoming/international-workshop-hiv-women-2016)

### *CROI 2016*

February 22-25; Boston, Massachusetts

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

### *Keystone Symposia: T Follicular Helper Cells and Germinal Centers*

February 26 - March 1; Monterey, California

More information: [www.keystonesymposia.org/index.cfm?e=web.Meeting.Program&meetingid=1401](http://www.keystonesymposia.org/index.cfm?e=web.Meeting.Program&meetingid=1401)

## MARCH 2016

### *Keystone Symposia: HIV Persistence: Pathogenesis and Eradication*

March 20-24; Olympic Valley, California

More information: [www.keystonesymposia.org/index.cfm?e=web.Meeting.Program&meetingid=1413](http://www.keystonesymposia.org/index.cfm?e=web.Meeting.Program&meetingid=1413)

### *Keystone Symposia: HIV Vaccines*

March 20-24; Olympic Valley, California

More information: [www.keystonesymposia.org/index.cfm?e=web.Meeting.Program&meetingid=1412](http://www.keystonesymposia.org/index.cfm?e=web.Meeting.Program&meetingid=1412)

## 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)

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