Scientists tend to work in confined fields because of the way research is funded, the need for hyper-specialized expertise, and the intensity of the work. But if the struggle against HIV proves anything, it’s that a combination of efforts unleashes the biggest effect. From combination antiretroviral therapy to the idea of knitting together partially effective HIV prevention strategies, now more than ever researchers are realizing the power of collaboration.

So it was last month in Cape Town, South Africa, at the debut of HIV R4P—the R4P referring to research for prevention—the first-ever conference dedicated to every aspect of biomedical HIV prevention. It became clear at the conference that research results are blurring the division among HIV prevention, treatment, and cure efforts. For example, scientists are experimenting with new microbicides that would employ the same broadly neutralizing antibodies that serve as a crux of vaccine research, administered via contraceptive-like devices. And the use of the same antiretrovirals used to treat HIV infection will be studied in newborns to see if very early treatment can possibly lead to a cure.

“All the fields now are mixing and mingling based on scientific opportunity. That’s what you would hope would bring the innovation that we all need,” says Carl Dieffenbach, AIDS division director at the US National Institute of Allergy and Infectious Diseases (NIAID). HIV R4P organizers aimed to create a crossroads for researchers and advocates from areas such as vaccine and cure research; the use of antiretroviral drugs to prevent infection, so-called pre-exposure prophylaxis (PrEP); as well as health policy, activism, and social science.

No one theme or star finding dominated HIV R4P, held Oct. 28-31, but the whole might be greater than the sum of its parts. The week produced encouraging results in trials using passive administration of antibodies which can neutralize a broad number of HIV viral strains, so-called broadly neutralizing antibodies (bNAbs); progress in designing vaccine candidates using the atomic-level binding characteristics of antibody to virus; ongoing debate about the pros and cons of different kinds of animal models for experiments; and the successful testing of microbicides and antiretroviral-based PrEP. Research is also emerging on how people might—or might not—actually use these products.

**Place of good hope**

The Cape Town setting felt vital to HIV R4P. Although attendees spent most of the week in rooms that could have been in climate-controlled convention halls anywhere in the world, in South Africa the HIV epidemic is very real. Two million people globally are infected with HIV every year, and the virus still kills a million a year. Two-thirds of those deaths are in sub-Saharan Africa. South Africa alone is home to the largest population of people in the world living with HIV, says Glenda Gray, executive director of the Perinatal HIV Research Unit in Soweto, Johannesburg. Amid strong calls for a boost in research efforts from African teams, a third of presenters selected by HIV R4P organizers came from the continent, with organizers granting 300 full and partial scholarships to researchers and advocates who otherwise wouldn’t have attended.

Of the many vaccine-related efforts talked about at HIV R4P, Gray presented preliminary findings from a study in South

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**Rainbow Nation Redux**

A full spectrum of interests in HIV prevention research, brought together for the first time.

By Michael Dumiak

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**Also in this issue**

- Understanding Advances in Therapeutic Vaccine Research
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immune responses to the vaccine candi-
six men either overweight or obese. and 49 women, with 28 of the women and volunteers. Sites in Soweto, Cape Town, and
researchers are equally expansive to those induced in Thai volunteers—if not more so—even given that the vaccine regimen was not designed to protect against that strain of HIV.
Researchers were concerned at the start of this follow-up trial, billed as HVTN 097, because prior studies with DNA and replicative defective pox and adenoviral vectors showed larger people—specifically larger women—had weaker immune responses to the vaccine candidate. Obesity rates are on the rise in South Africa and the population is distinctly different, genetically speaking, from Thais. Researchers wanted to see what immune responses to this vaccine regimen would be like in a group of South African volunteers. Sites in Soweto, Cape Town, and Klerksdorp enrolled 100 volunteers: 51 men and 49 women, with 28 of the women and six men either overweight or obese.
During seven months of trial follow-up, immune responses to the vaccine candidates among the South African volunteers were even better than their Thai counterparts—for example, 69.2% of the South Africans had a CD4+ T-cell response to a specific HIV protein, versus 50.3% of the Thai volunteers.
The non-neutralizing antibody concentra-
thons following vaccination are also simi-
lar to that seen in the RV144 participants, Gray said. It remains to be seen, however, if the good cross-clade immunogenicity implies an equivalent efficacy. More trials are needed for that—and more are coming. In January researchers will start a Phase I study evaluat-
ing a clade C version of the Thai vaccine, delivered along with a new adjuvant, known as MF59, aimed at boosting the potency of the vaccine candidates and the durability of the immune responses they induce. Researchers plan to conduct further trials, involving as many as 7,000 volunteers.

**Antibody action**

Antibodies that can neutralize a broad variety of HIV strains continue to fuel vaccine research efforts in labs around the globe: some call it a renaissance in vaccine development. Barney Graham at NIAID’s Vaccine Research Center (VRC) released initial results in Cape Town from safety trials of so-called passive immunization—directly inject-
BNAbs into the body—while immunolo-
gists, including Peter Kwong, chief of the structural biology section at the VRC, presented on the possibilities for crafting vaccine immunogens—substances which trigger an immune response—based on better understanding of the protein structure of HIV.

Two Phase I studies of passive immunization conducted by NIAID aim to establish the safety of using the VRC’s isolated-and-pro-
duced VRC01 antibody as either a means of preventing HIV infection or as a therapy in those already infected with the virus. Two vol-
unteer groups are involved in the studies, one infected with HIV (VRC 601) and one unin-
ected (VRC 602). Researchers are adminis-
trating VRC01 at different dosage levels both intravenously and subcutaneously, Graham says, ranging from one milligram per kilo to 40 milligrams per kilo in different subgroups. Results show no serious adverse events after more than 80 doses, he says. Early data for five-milligram doses show intravenous delivery produces peak concentrations of the antibody in blood within a few hours following administration; the 20-milligram doses produce much higher antibody concentrations. At the higher dosage, antibody concentrations remain in the body at what Graham calls a “meaningful” level for a month.

Graham and his colleagues are also developing other variations of the VRC01 antibody with mutations that make the antibody more potent and longer lasting. In an effort to improve the lifespan and potency of VRC01, VRC scientists are manipulating the antibody’s amino acid structure. One variation, an antibody billed VRC07-523LS, shows both greater concentrations and broader efficacy than VRC01.

Meanwhile, the team is planning further efficacy tests administering VRC01 shortly after birth to babies born to HIV-infected mothers to prevent HIV transmission to the baby. Monthly antibody injections would continue until the end of the breastfeeding period to prevent subsequent transmission through breast milk. That would be in addition to stan-
ard antiretroviral therapy, which is already proven to be up to 95% effective in preventing mother-to-child HIV transmission.

Whatever the method, the goal remains the same: to create long-lasting, low-mainte-
nance, effective ways to stop HIV. “Can an antibody with a particular level of neutralizing activity prevent HIV infection, either in the setting of mother-to-child transmission or in the setting of high-risk adult exposures?” Graham asks. The idea is that a long-acting product could cover the gaps in adherence.

Researchers would like to get the body to produce these antibodies on its own rather than having to deliver regular infusions. The way to do that is to design a vaccine immu-
nogen that can provoke the immune system to generate such powerful antibodies against HIV. This is Kwong’s focus at the VRC. He specializes in an emerging discipline seeking to use advances in computing and atomic-
level observation to reverse-engineer antibodies and ultimately vaccine immunogens.

Kwong's team applied its structural methods in recent years to creating powerful experimental vaccines against the pediatric respiratory syncytial virus (RSV), which can lead to severe lower respiratory tract infections. This work earned the team a mention in Science as one of 2013's top 10 breakthroughs.

At HIV R4P, Kwong presented his emerging structural model of how to approach the HIV envelope protein, which is what makes up the outer surface of the virus. This is the first fruit from applying techniques devised in the RSV work toward HIV. Whether they will work against a cagier virus like HIV is unclear. “The jury is still out. We don’t have an answer,” Kwong says.

One plus one equals?

While vaccine research remains a painstakingly slow process, combining vaccines with antiretroviral-based microbicides is a new effort that received attention in Cape Town. Robin Shattock, a virologist at Imperial College London, collaborated with French immunovirologist Roger LeGrand and colleagues to test a vaccine candidate combined with a 1% tenofovir gel—an antiretroviral-based microbicide—in three groups of rhesus macaques, all compared to a group of untreated control monkeys.

Pharmaceutical company Novartis provided a nasally-delivered vaccine candidate derived from two HIV proteins that researchers administered to the monkeys along with an adjuvant meant to enhance immune responses. This was followed by two booster injections of MF59, another adjuvant, developed by Novartis and used to improve immune response to its influenza vaccine. Although the vaccine on its own failed to provide protection, when used together with the microbicide, the combination provided a higher level of protection than the microbicide alone. “Can we get more out of putting vaccines and microbicides together?” Shattock asks, a question at the heart of HIV R4P.

Shattock's findings will gain a boost if the tenofovir microbicide gel gains regulatory approval following an ongoing Phase III trial in South Africa expected to produce results next year.

Another combination in development is using the VRC01 bNAb in a vaginal microbicide film or ring, an idea that Deb Anderson, a Boston University obstetrics professor and microbiologist, is exploring in collaboration with Kevin Whaley of Mapp Biopharmaceuticals. Safety trials are expected to start this spring of the VRC01 antibody (grown and harvested in tobacco plants) combined with an antibody that prevents herpes simplex virus infection.

Latency and cure

Even though the focus of HIV R4P was on prevention, Dieffenbach provided a reminder that a big-picture goal of the scientific community is not just HIV prevention, but a cure for those already infected with the virus.

Much of the cure-related talk in Cape Town was specifically about the Mississippi Baby case—an infant who contracted HIV at birth and received antiretroviral therapy beginning 30 hours after birth. After a month, the infant had no detectable virus, and after two years, the child remained HIV-free, firing hopes that a cure was achieved. Unfortunately the child’s virus eventually rebounded after discontinuing antiretroviral therapy.

Still, the concept is tantalizing and researchers want to see if antiretroviral treatment given in the first two days to babies testing HIV positive after birth can lead to viral remission, allowing the children to eventually stop treatment for an extended period. Pediatrics professor Yvonne Bryson at the University of California, Los Angeles, will lead such a study, called IMPAACT P1115, which will enroll nearly 500 volunteers.

“With a cure agenda, we hope to expand studies into larger populations,” says Debbie Persaud of Johns Hopkins University, one of the researchers in the Mississippi Baby case.

Hard won lessons

As these studies come closer to providing real-world interventions, there needs to be a clear idea of what to do with them and how to get new products and drugs to those who need it most. At HIV R4P, Helen Rees, virologist and director of the Wits Reproductive Health and HIV Institute, joined South African science minister Naledi Pandor in arguing for social science research to support future HIV prevention.

Thinking ahead to a time when an HIV vaccine may come, Rees pointed to the country’s vaccine rollout against the sexually transmitted human papillomavirus, which causes genital warts and can lead to cervical cancer, as a potential model for delivery. Even with something as intractable as HIV vaccine research, Rees says, advance planning and an understanding of the environments where it might be used are vital to making a vaccine effective. “Can we introduce vaccine service delivery in schools?” Rees says. “How do we reach nine- to 13-year-olds not targeted for immunization?”

Gray says if there is a breakthrough, there needs to be follow-through. That’s why another focus of HIV R4P was the social science needed to turn study results into meaningful interventions for those at risk of HIV infection. Attitudes toward these products can greatly influence their real-world effectiveness, as Makarere University’s Teopista Nakyamuzi pointed out in showing why Ugandan women didn’t join an otherwise promising study on topical HIV prophylaxis. Her studies suggest one main reason women didn’t enroll was the fear of knowing their HIV status; another is that many did not have any financial income and feared losing support from their partners if they were involved in the trial. Ariane van der Straten, an expert in female-initiated HIV prevention at RTI International in San Francisco, says more broadly that there’s a view that women who use HIV prevention products are promiscuous—which then implies that pre-exposure prophylaxis, for instance, is only appropriate for promiscuous women.

Rees cites the World Bank President Jim Kim in trying to bring attention to these concerns. “I am just asking that we bring the same kind of rigorous approach and scientific thinking,” she quotes the former physician and anthropologist, “to actually delivering these tools for health that we bring to creating them.”

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Understanding Advances in Therapeutic Vaccine Research

The word vaccine is generally used to describe any substance administered to confer immunity and therefore prevent disease. However, HIV researchers, as well as researchers in fields such as cancer, are pursuing another type of vaccine that is intended as therapy. These so-called therapeutic vaccines are administered to individuals that already are infected with the virus or have the disease, and are intended to boost the immune responses against the pathogen. Or in the case of HIV, induce better immune responses than what the body makes naturally (see VAX March 2013 Primer on Understanding Therapeutic Vaccination).

One of the reasons HIV is so hard to control is that the immune responses the body naturally mounts against the virus are, in all but rare cases, insufficient to effectively control HIV. Therefore, for a therapeutic vaccine to work, it will need to induce immune responses that are different than those induced in natural infection.

Interest in therapeutic HIV vaccines started off strong, but following the introduction of highly successful antiretroviral therapy in the 1990s, and mostly disappointing results from clinical trials of therapeutic vaccine candidates, the field languished for some time. None of the early candidates were found to improve the overall health of the HIV-infected volunteers in the trials or slow their rate of disease progression. Now, the relatively young and promising field of HIV cure research has rejuvenated interest in therapeutic vaccination.

While there are still many missing pieces to the HIV cure puzzle, a therapeutic vaccine is considered a key component to achieving a cure. Therapeutic HIV vaccine research is also benefitting from recent advances in preventive vaccine research. Now more than ever, the fields of therapeutic and preventive vaccine research, treatment, and cure research are overlapping (see Spotlight, this issue).

The biggest obstacle

Once a person is HIV infected, the virus hides out in cells that are inactive (not replicating) and therefore is impervious to the effects of antiretroviral therapy. However, if therapy is interrupted, this sleeping or so-called latent virus can come roaring back and begin actively replicating. The pool of latent virus, known collectively as the viral reservoir, is one of the main obstacles to an HIV cure. Take for example the recent case of an infant who began antiretroviral treatment within hours after birth (see VAX July 2014 Spotlight article, Melbourne’s Rallying Cry: Step Up The Pace). Even in this infant, whose HIV infection was treated almost immediately, HIV began replicating to detectable levels once antiretroviral treatment was interrupted.

To counter this problem, scientists are testing various compounds designed to root HIV out of its hiding spots. Once exposed, therapeutic vaccination is one method researchers are exploring to enable the immune system to clear these HIV-infected cells, thereby reducing or even eliminating the viral reservoir.

Scientists in Denmark, for instance, just began a Phase I study involving HIV-infected volunteers to evaluate a therapeutic vaccine candidate called Vacci4x, along with a cancer drug that in a previous study was able to wake up latent HIV in inactive (or resting) T cells. This combination approach, sometimes referred to as “kick and kill,” is relying on the therapeutic vaccine candidate to generate a strong enough immune response to kill the virus that is reawakened in the body.

Antibodies for prevention and therapy

The same antibodies that are the focus of preventive vaccine research these days may also have a role in therapeutic vaccination. An ongoing study at the US National Institute of Allergy and Infectious Diseases that began last year is testing what is called passive transfer of antibodies in both HIV-infected and uninfected volunteers. In passive transfer studies, broadly neutralizing antibodies (those capable of inactivating a wide variety of HIV strains) are injected directly into the body to see if they can either prevent HIV infection or induce prolonged suppression of the virus in HIV-infected volunteers (see VAX March 2014 Primer on Understanding the Expanding Role for Broadly Neutralizing Antibodies). Another strategy is using gene therapy to deliver just the genes for the broadly neutralizing antibodies, which are taken up by cells that then produce the antibodies, rather than injecting the antibodies directly.

Similar to the preventive vaccine field, therapeutic vaccine researchers are also testing combination strategies to try to induce broader immune responses to HIV. However, there are still significant gaps in understanding how to design and assess such candidates in HIV-infected individuals. Designing clinical trials to evaluate therapeutic vaccines is more difficult because there isn’t an accurate way, currently, to measure the size of the viral reservoir or therefore the impact a vaccine candidate has on reducing it. And, interrupting antiretroviral treatment in HIV-infected individuals can be fraught.

While animal models are one of the best ways to evaluate the safety and efficacy of new medicines and vaccine candidates, the lack of a perfect animal model for HIV—one that mimics this uniquely human disease—has been problematic in defining how well a candidate will perform in people. To address this issue, some researchers are suggesting using a stepwise series of small clinical research trials be carried out in HIV-infected volunteers to find the most useful targets for therapeutic immunization.

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