Nearly two decades later, around 15,000 researchers, advocates, and policy experts flooded into Durban, South Africa’s International Conference Center from July 18-22 for AIDS 2016 (the 21st International AIDS Conference). The meeting started, appropriately enough, on the Rainbow Nation’s Nelson Mandela Day. Had the great man still been around, he would have seen the boundless energy of thousands of individuals: some living with HIV, others using science to try to defeat it, and still others trying to keep the spotlight on it while terrorism, emerging diseases, geopolitics, and contentious elections likewise vie for the world’s attention.

Speakers highlighted huge strides that have been made in expanding access to HIV treatment since Durban last played host, but also cast a spotlight on the colossal gaps in preventing new infections that remain an obstacle to ridding the world of AIDS.

**Progress on parade**

At the time of the 2000 conference, a watershed moment in the HIV/AIDS response, a meager 690,000 HIV-infected people were receiving antiretroviral therapy (ART) worldwide. By 2015, those getting the lifesaving drugs jumped to 17 million in a herculean feat of scaling that many thought was impossible. Because of that, the number of people dying from AIDS fell from 2.8 million in 1999 to 1.1 million in 2015.

Scientific advances and broader access to drugs have also sparked progress in preventing new HIV infections in some populations. Mother-to-child transmission rates are falling around the world—many countries are close to stopping it, and others like Thailand and Armenia have eliminated it altogether. In South Africa alone, efforts over just the last five years have reduced mother-to-child transmission by 84 percent. Because of these and other HIV prevention efforts, 2.1 million people acquired HIV in 2015 compared to 5.4 million in 1999.

“Sixteen years ago, Nelson Mandela addressed the International AIDS Conference here in Durban. He called it, ‘A gathering of human beings concerned about turning around one of the greatest threats humankind has faced,’” said United Nations (UN) Secretary-General Ban Ki-moon. “He called for access to treatment equity and human rights. That was a turning point that led to remarkable global progress. For every one person who received lifesaving treatment back then, there are now 17 who have it today.”

The conference was not all good news though. While those with access to ART can now expect to live nearly as long as uninfected people, the end goal—made concrete by the
In 2005, 4.9 million people became newly infected with HIV, a number that began decreasing rapidly because of declining mother-to-child transmission rates, risk reduction education, and behavioral changes. In the most recent UNAIDS update that came out before June’s UN meeting, the organization found that “declines in new HIV infections among adults have slowed alarmingly in recent years,” with the total number of new infections remaining basically unchanged at around 2.1 million since 2010. The new study published in The Lancet HIV, however, paints a bleaker picture. According to the improved modeling work used by more than 1,700 collaborators from 124 countries, researchers concluded that 74 countries actually had an increased rate of new HIV infections over the last decade. Countries as diverse as Egypt, Mexico, Russia, and the Philippines are among the group that saw an uptick. The study’s authors used improved surveillance data collected from the comprehensive Global Burden of Diseases, Injuries, and Risk Factors Study to make these calculations.

Haidong Wang, a University of Washington demographer and lead author of the study, said the findings point out how big a challenge it will be to meet the UN goal of eradicating AIDS by 2030. “The obvious conclusion is that much still needs to be done,” he said.

His colleague, Peter Piot, who is the director of the London School of Hygiene and Tropical Medicine and was not involved in the study, agreed. “It’s staggering. It’s still an enormous burden,” Piot, who previously led UNAIDS, said. “It’s very hard to imagine that we can reduce new infections to 500,000 in the next few years.”

**Helping those at highest risk**

Over the ensuing days of the conference, it became clear that the largest hurdle to preventing more infections from occurring—absent an effective vaccine or cure—is reaching the most vulnerable communities, which governments often overlook. Campaigners who took to the conference’s multiple stages repeatedly called for meaningful access to prevention and treatment programs for MSM, young women, the transgender community, sex workers, injection drug users, and prisoners. They said reaching these people is key to getting the epidemic under control—in 2014, 90 percent of new infections in Central Asia, Europe, North America, the Middle East, and North Africa occurred in these groups.

Ben Plumley, chief executive officer of the international nonprofit advocacy group Pangaia Global AIDS, and others spoke at a pre-conference meeting about what it will take to achieve global targets set by the UN. He voiced concern that the tone now being taken by officials is that the page has already been turned on AIDS. “All the governments at [the UN High-Level Meeting on Ending AIDS] said the fight against HIV is over—all that is left is the AIDS benefit concert,” Plumley said. “Yes, we have had some progress in treatment since 2001, but we’ve failed fundamentally in prevention. Yet again our governments couldn’t bring themselves to speak of the communities that will turn this epidemic around.”

Perhaps the most invisible of the key populations that need access to prevention and treatment are the world’s 10.2 million men, women, and children being detained as prisoners. According to a special edition of The Lancet released in time for AIDS 2016, this population is at especially high risk of HIV infection. Modeling studies showed that 3.8 percent of this group have HIV, compared with a global prevalence rate of 0.8 percent in 2015. The main factor contributing to this difference is drug laws that criminalize intravenous substance abuse and force an already high-risk population infected with the virus to concentrate in prisons. Severely limited access to injecting equipment can amplify the infection risk if prisoners gain access to drugs.
Also at particularly high risk are girls and young women aged 15 to 24. UNAIDS’s official statistics show that in sub-Saharan Africa, this group now accounts for 25 percent of new HIV infections among adults, and women of all ages make up 56 percent of new infections among adults. The organization says this unequal burden is the result of harmful gender norms, insufficient access to education and sexual and reproductive health services, poverty, food insecurity, and violence. “Fifty-six percent of people with HIV are women. Funders must put their money where the problem is,” said activist Yvette Raphael. “Women are at the center of this and I can say we are nowhere near the end of HIV/AIDS. We are still dealing with some of the same issues we were dealing with 15 years ago when I was diagnosed.”

The plight of girls and women surfaced throughout AIDS 2016, with experts from different specialties saying that as women go, so too goes the effort to eradicate the disease. “We must think gender,” said Elizabeth Bukusi, the co-director of the Kenya Medical Research Institute-University of California, San Francisco Training Program. “Gender matters for prevention. Gender matters for treatment. The goals we’ve set for 2020 are off-track. A reason for that is our inattention to gender.”

In response, many projects are taking a more aggressive approach to controlling HIV in these at-risk populations. Some start organically, like a Kenyan advocacy group securing ART for its community that began as a group where ostracized women with AIDS took care of other women as they died. Vancouver, meanwhile, is now one of dozens of cities around the world offering injection drug users supervised injection sites—safe rooms that give them access to clean needles and healthcare services. San Francisco and other US cities are now considering launching their own. Meanwhile, Thailand has launched an online program that offers supervised at-home HIV self-testing, counseling, and registration at treatment clinics. The program hopes to reach more MSM and transgender women in the digital space.

Improving prevention

Leaders in the research and advocacy communities agreed that at-risk people, especially those comprising the now globally recognized key populations, need access to every HIV prevention modality currently available: risk reduction education, clean needles for injection drug users, condoms, oral pre-exposure prophylaxis drugs (PrEP; the use of ART to prevent HIV infection), and male circumcision. But having the tools, getting them into the hands of those who need them most, and then ensuring they are used consistently are three very different things.

For cultural or supply reasons, it is still often difficult for people who need them to access condoms, the cheapest and easiest way to prevent infection. Nduku Kilonzo, the director of Kenya’s National AIDS Control Council, lamented how her country has not yet effectively gotten the message out about using protection during sex. “We invest a lot in the new kid on the block and remove money from older things we know work well, like condoms,” she said. “In Kenya, every single young person knows where to go to get more airtime for their mobile phones. What have we done wrong that they don’t know where to get a condom?”

Researchers also discussed a new way to use PrEP, which they say increases the options for those who might not want to take a pill every day for HIV prevention. Early studies in monkeys suggested that taking the two-drug combination known as Truvada one, three, or seven days before and two hours after rectal exposure to the monkey form of HIV was just as effective as taking the pill every day. Another study from 2012 showed that monkeys given Truvada a day before and two hours after vaginal exposure was also protective.

Then, results from a trial known as the IPERGAY study released last year showed that among 400 MSM, there was an 86 percent relative reduction in the incidence of HIV infection when participants took the two drugs in Truvada just before and after sex. Specifically, volunteers were told to take two pills two to 24 hours before sex, another pill a day after taking the first two, and a fourth pill a day after that. Jean-Michel Molina at the University of Paris Diderot, who led the research team, said on-demand PrEP isn’t for everyone since it requires people plan to take the pills in advance of sexual encounters. But while Robert Grant, an investigator at the University of California, San Francisco School of Medicine, agrees, he argues that while sexual event-driven dosing is complicated, it might find a receptive audience among those who participate in higher-risk behavior infrequently. “There are some who do very well with on-demand, particularly older gay men,” Grant said. “If you’re having risky sex once a month or less, there’s really no call to take a pill every day.”

Taking a shot

Meanwhile, many think that it is a vaccine that will most successfully drive down the number of new HIV infections and bring the epidemic to an end. “The only way we’ll eliminate HIV in the next 100 years is with a vaccine. There’s no other way,” said Paul Stoffels, the executive vice president and chief scientific officer of Johnson & Johnson.

One area of interest in vaccine research is understanding and improving on the surprising results of the RV144 trial in Thailand, which has so far provided the only evidence of vaccine-induced protection against HIV. Interim results announced in Durban from HVTN 100, a small ongoing study of 252 people in South Africa that is a small-scale follow-up study to RV144, provided enough of a green light for researchers to pursue the first large-scale efficacy trial since RV144. This effort, known as HVTN 702, is a Phase III randomized controlled trial of 5,400 adults in South Africa (see Primer, page 4).

“All the criteria were met unequivocally and, in many instances, the HVTN 100 outcomes exceeded both our own criteria and the immune responses seen in RV144,” said Linda-Gail Bekker, the chair of the HVTN 100 protocol and deputy director of the Desmond Tutu HIV Center.

Whether the vaccine candidates under test in HVTN 702 will be successful or not, a clear message coming out of AIDS 2016 was that the current efforts to prevent the virus’s spread are insufficient. “We are not going to end AIDS with the tools we have,” said David Wilson, the World Bank’s global AIDS program director. “What an extraordinary success we’ve already had in treating the infected. But it’s also increasingly clear that in the real world tablets are not going to stop this epidemic. We have to reinvigorate R&D. We’ve never stopped a disease without a vaccine or a cure.”

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Seven years ago, a large efficacy trial in Thailand known as RV144 provided the first—and thus far only—clinical evidence of vaccine-induced protection against HIV. The two vaccine candidates tested in what is referred to as a prime-boost combination appeared to lower the risk of HIV infection by about 31%. This level of efficacy was not high enough for licensure of the vaccine regimen in Thailand, but it did provide a welcome turning point for a vaccine field that was characterized by two decades of disappointments.

Since then scientists have conducted numerous analyses and follow-up studies to try and determine which types of immune responses induced by the RV144 vaccine candidates may have led to the modest efficacy, a hunt for the so-called immune correlates of protection. Researchers have also tried modifying the vaccine candidates and the timing of the vaccinations in an attempt to strengthen and improve the durability of the immune responses and thereby improve the efficacy of this or similar regimens. This includes testing related vaccine candidates in countries or regions where the prevalence of HIV is highest, including sub-Saharan Africa, or in specific populations at highest risk for acquiring HIV, such as men-who-have-sex-with-men or high-risk heterosexual men and women.

These post-trial analyses have been enormously helpful in determining what immune responses contributed to the modest efficacy observed in RV144. The Pox-Protein Public Private Partnership or P5—which consists of representatives from the US National Institute of Allergy and Infectious Diseases (NIAID), the Bill & Melinda Gates Foundation (BMGF), the South African Medical Research Council, the HIV Vaccine Trials Network (HVTN), Sanofi Pasteur, GlaxoSmithKline, and the US Military HIV Research Program—was formed in 2010 to test variants of the RV144 regimen in future trials as well as learn more about vaccine-induced protection in that trial. Now the P5 is preparing for a large-scale AIDS vaccine efficacy trial in South Africa—the first to launch since the RV144 results were reported. This trial will test a modified prime-boost vaccine regimen and is expected to launch this November. The Phase IIb/III trial known as HVTN 702 will enroll 5,400 HIV-uninfected men and women ages 18-35 at risk for HIV infection at 15 clinical research sites. NIAID and BMGF are funding the US$130 million trial, which is being conducted by the HVTN.

**Decoding protection**

A vaccine can induce many different types of immune responses, including antibodies (typically Y-shaped proteins that bind to viruses and prevent them from infecting cells), cellular immune responses (CD4+ and CD8+ T cells that orchestrate the killing of virus-infected cells), as well as the body’s built-in or innate immune responses. The regimen tested in RV144 appeared to induce antibodies, but not the type that bind the virus and neutralize it. Rather the antibodies induced in some RV144 vaccine recipients appeared to latch onto HIV-infected cells and trap them until other components of the immune system could swoop in for the kill. This process is referred to as antibody-dependent cellular cytotoxicity (see VAX Sep. 2011 Spotlight article, More Surprises Stem from RV144).

From these initial findings, researchers went on to identify what they called “correlates of risk” associated with this vaccine regimen. Those studies revealed that one antibody response correlated with a reduced risk of HIV infection, while another correlated with an increased risk of infection (see VAX Sep. 2011 Spotlight article, More Surprises Stem from RV144).

But the most relevant data to support another large efficacy trial came from a P5-sponsored Phase I/II study known as HVTN 100 that is ongoing in South Africa. The trial, involving approximately 230 HIV-uninfected men and women, is evaluating the safety and immunogenicity of the same prime-boost vaccine regimen that will be tested in HVTN 702. The non-infectious viral vector prime and engineered HIV protein boost candidates are similar to those tested in RV144 but are based on clade CHIV, the strain that is predominant in South Africa. In RV144 the candidates were based on clade B/E, the most prevalent serotype in Thailand. An interim analysis showed that the vaccine regimen in HVTN 100 was eliciting similar immune responses to those induced in the RV144 trial. This helped convince trial sponsors to go forward with HVTN 702.

**A modified regimen**

In addition to the vaccine candidates being based on a different clade, there are some other significant differences between the HVTN 702 vaccine regimen and that tested in RV144. One is the dosing schedule. In RV144 six vaccinations were administered sequentially over six months. In HVTN 702, five vaccinations will take place: three by month six and two more at month 12. The hope is this will extend the early protective effect observed in the RV144 trial, which showed protection was as high as 60 percent in the first year.

A new adjuvant is also being tested in HVTN 702. Although researchers don’t know precisely how they work, adjuvants help to boost the immune responses induced by vaccines. RV144 used an alum adjuvant, which consists of insoluble aluminum salts, while the HVTN 702 trial will utilize MF9, a biodegradable oil that is used in influenza vaccines in Europe.

Researchers hope that results from the HVTN 702 trial, which are expected by 2020, will provide a clear answer about whether these vaccine candidates can protect against HIV infection.

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