More than two million people around the world are still infected with HIV each year. Given this stubbornly high rate of new infections, prevention remains a top priority. The limited number of early prevention methods have, over the years, mushroomed into a range of available or experimental preventative measures, including condoms, male circumcision, vaccines, microbicides, pre-exposure prophylaxis (PrEP), and behavioral modifications. October’s HIV Research for Prevention (HIVR4P) conference in Chicago took attendees on a whirlwind tour of the state of the art for many of these approaches. More than 1,400 leading scientists, advocates, and government officials discussed a number of potential vaccine strategies, microbicidal gels and rings, and different uses of antiretrovirals (ARVs) and antibodies for preventing HIV infection in the research and development pipeline.

But the conference laid bare the fact that the HIV community is wrestling with two very different realities. On the research front, significant technical progress is being made, with presenter showing new data that is expanding the community's understanding of transmission of the virus and work to prevent its spread. Meanwhile, speakers highlighted how cultural and behavioral challenges affecting whether prevention tools are widely accepted and adopted are still creating serious obstacles to breaking the sustained high transmission rates.

### Tantalizing treatment results

Given HIVR4P is the preeminent meeting on HIV prevention, it was a bit ironic that this year’s conference may most be remembered for a study that wasn’t even about prevention. Rather, the headline was a study on a potential new treatment strategy. There are currently 37 million HIV-infected people around the world, and 17 million of them are now receiving life-saving antiretroviral therapy (ART). But these drugs are not a cure—ARVs do not completely clear the virus and lifelong therapy is required to keep the residual virus under control.

In the week leading up to the conference, an article in a prestigious research journal authored by scientists from the National Institutes of Health and Emory University sent waves through the HIV research community. The study, led by Anthony Fauci, head of the National Institute of Allergy and Infectious Diseases, revealed that monkeys given ART plus an engineered antibody, the immune system proteins that attack foreign objects, entered long-lasting remission. The study’s results, presented by Fauci during HIVR4P’s opening plenary, offered an unexpected and tantalizing clue into a new avenue of research.

In the small study, a subset of 18 monkeys infected with a monkey form of HIV were given ART along with a lab-produced antibody called anti-α4β7. This antibody works by blocking a receptor on a specific subset of immune cells that are most often targeted by HIV and its monkey equivalent. After three months of receiving this combination therapy, these monkeys maintained undetectable levels of virus in their system for 23 months.
“The experimental treatment regimen appears to have given the immune systems of the monkeys the necessary boost to put the virus into sustained remission,” Fauci said. “All of this in my mind, as a human immunologist and HIV clinician, will only be important if it works in humans.”

Exactly how this combination therapy worked, though, and whether these results will translate to humans is not yet known. But the research team is already moving to answer these questions. In August, they launched a small clinical study in humans using a drug already approved by the US Food and Drug Administration (FDA) that works the same way the antibody they tested in monkeys does.

David Margolis, director of the University of North Carolina School of Medicine’s HIV Cure Center who was not involved in the research, said he was as surprised as other experts in the field at the study’s findings. “The work is impressive, and unexpected,” Margolis said. But because the mechanism that allowed the monkeys to start controlling infection is neither understood nor known to work the same way in people, he awaits results from the human study before drawing any firm conclusions. “This might lead to a way to prevent infection, or allow durable control of infection without lifelong antiviral drug therapy.”

**Vaccine research progress**

The conference was also abuzz with talk about the initiation of large-scale clinical efficacy trials of different prevention strategies. One of these trials, the Pox-Protein Public Private Partnership (P5)’s HVTN 702 vaccine study, began in South Africa just before the conference started. This trial, which is expected to include 5,400 South African men and women, builds upon the modest efficacy seen in the RV144 trial in Thailand, still the only vaccine regimen to show any ability to prevent HIV infection. The 702 study will test a regimen similar to that used in the RV144 trial, which has been modified to work against the strains of HIV commonly found in South Africa and to induce a more durable immune response (see VAX August 2016 Primer on Understanding the Rationale for the HVTN 702 Trial).

While many routes of inquiry into finding an effective vaccine have led to dead ends, scientists spoke hopefully about new vaccination strategies that center around broadly neutralizing antibodies (bNAbs)—infection fighting proteins that can inactivate most of the HIV variants circulating around the world. In fact, bNAbs, which are naturally made by a small percentage of HIV-infected people, were at the center of the conversation at HIVR4P. This work involves two different approaches: administering the antibodies themselves directly to people (so-called passive administration) or designing molecules that, when administered via a vaccine, could coax the human immune system to make these antibodies.

In another large-scale trial that began earlier this year, researchers are testing the efficacy of the passive administration approach by seeing if infusions of one bNAb, VRC01, are sufficient to block the virus from establishing an infection. This effort is known as the Antibody-Mediated Prevention (AMP) Study.

“This is a good year. Now, after long preparation, the field has embarked on a number of efficacy trials,” said William Snow, the then director of the Global HIV Vaccine Enterprise. “They should, in a short number of years, clarify what really works and why.”

Meanwhile many researchers are pushing forward with basic science experiments to understand exactly how to train a person’s immune system to make bNAbs. It’s a complex road to get there, though, because these antibodies are highly specialized and are not easily induced through vaccination.

Devin Sok, an IAVI research scientist, is one of many working on this problem. He presented research on successfully priming the immune systems of mice to encourage them to make bNAbs similar to some of those that researchers have successfully isolated from HIV-infected humans. His team is designing an immunogen, the active ingredient of a vaccine, to trigger production of immature versions of the potent antibodies they are aiming for. Then, in a step-wise manner, Sok and colleagues are developing other immunogens to push these initial antibodies to develop into the more broadly neutralizing type that an eventual vaccine would need to induce (see VAX October 2016 Primer on Understanding Sequential Immunization Strategies). “We believe that the elicitation of broadly neutralizing antibodies is an important component of an HIV vaccine,” Sok said.

Other teams exploring similar lines of investigation also presented their data at R4P.

**Urgent need for better prevention**

While vaccine research continues its hopeful march toward eventual clinical success, there is growing emphasis on how the current crop of preventive tools can be used more reliably. In recent years, PrEP emerged as a highly effective tool for reducing HIV infection risk, yet globally the number of new infections has plateaued.

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“The challenge is that the people that need to be using them [the current prevention tools] either aren’t using them correctly or aren’t interested in using them,” said Tom Hope, professor of cell and molecular biology at Northwestern University. “We have to understand what the population is willing to do to slow down the spread of HIV and then we need to provide things in a way that makes them want this because it can protect them. But we need to get this to the point where people want to use them and say, ‘Where is my PrEP?’. If we can get to that point then I think we can really start to have an impact.”

Noël Gordon, Jr., a senior program specialist for the Human Rights Campaign, said there is still a very long way to go until key populations are armed with the information they need, and have access to PrEP. With almost 50,000 people still being infected every year and a majority of the burden falling on the shoulders of young black men who have sex with men, the US is a good example of the realities that still need to be addressed everywhere. These gaps demand that the world push to improve technologies and increase access.

“Existing HIV prevention tools, while necessary, are insufficient to help end this epidemic,” he said. “That’s why it’s so important that we have tools like pre-exposure prophylaxis, post-exposure prophylaxis, treatment as prevention, and other biomedical tools entering the HIV prevention toolbox.”

Another part of the problem that has become clear recently is that of adherence. In studies, many at-risk people put on a PrEP method like oral Truvada that requires regular, even daily use, are failing to use it as prescribed. To that end, presenters report they are investigating a new generation of prevention tools that try to mitigate the reliance on adherence, including long-acting injectable antiretrovirals that could be used for treatment or PrEP.

One of these products is the long-acting drug known as cabotegravir. The drug is injected intramuscularly and forms a depot at the injection site where it slowly gets absorbed by the body. A Phase IIb/III trial of 4,500 men and transgender women who have sex with men is ongoing and expected to provide results in 2020. If it works as hoped, investigators think it could replace a daily PrEP pill with a single injection every two or three months.

Nina Russell, deputy director of the Bill & Melinda Gates Foundation’s HIV vaccine strategy program, said many other possibilities are now being investigated for longer-acting prevention. Some of these have shown promise in animal studies and others have already entered the clinic. Recent research has shown, for instance, that a single injection of the bNAb VRC01, VRC01-L5, 3BNC117, and 10-1074 protected monkeys for up to almost six months.

Another strategy for prevention is microbicides. The key, said Hillier, is to create solutions that fit with how real users want to employ them in their everyday lives, and to empower these users to take control of their own sexual health. “What we have in front of all of us is a really rich opportunity to find the right prevention tools for the people who need them that allows them to express sex as intimacy and pleasure rather than disease prevention.”

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– Sharon Hillier

Despite weekly exposure to the monkey version of HIV. A Phase I clinical trial involving 24 participants is now testing the safety and induction of immune responses following an intravenous infusion of two of these antibodies, 3BNC117 and 10-1074, given in combination. Other HIVR4P presenters also showed progress in developing novel systems to deliver ARVs over longer periods, including using polymer films, inserts, and suspensions that slowly degrade.

“Why are we talking about long-acting prevention? While PrEP is important and offers opportunities for people, we need to do better,” Russell said. “Ultimately, a variety of prevention methods including those that are highly effective, long-acting, passively administered, and affordable are really going to be required...to maximize the use and impact of prevention methods.”

Microbicides also garnered considerable attention during HIVR4P. Because they can deliver high doses of ARVs to the initial sites of infection during sexual transmission, Sharon Hillier, director of reproductive infectious disease research at the University of Pittsburgh’s Magee-Womens Hospital, said a number of microbicides and delivery systems are under development. Among these are vaginal rings that last for a month or longer and deliver ARVs like dapivirine or tenofovir; multipurpose prevention technologies that can protect against HIV, pregnancy, and other sexually transmitted infections all at the same time; and vaginal or rectal inserts, films, and douches.

Hillier discussed findings of the ASPIRE study to investigate whether a ring loaded with dapivirine would prevent infection. She said researchers were “subdued” about the initial results that found it reduced HIV risk by a meager 27 percent overall. But a subsequent look teased out a much more robust 60 percent reduction in HIV transmissions when considering women over the age of 25. Those who used the ring consistently saw a risk reduction of 73 percent. But in research reported at the conference that looked more closely at one group in the study, one external factor played a big role in adherence. Five percent of women in the ASPIRE study (85 participants of the 2,629 total) said they were subject to or feared violence from their partner. Those who had recently experienced abuse were 2.5 times less likely to use their ring compared to all respondents.

The key, said Hillier, is to create solutions that fit with how real users want to employ them in their everyday lives, and to empower these users to take control of their own sexual health. “This is just the beginning,” said Hillier. “What we have in front of all of us is a really rich opportunity to find the right prevention tools for the people who need them that allows them to express sex as intimacy and pleasure rather than disease prevention.”

Another strategy for prevention is ensuring wider access to ART because as many researchers have long suspected, treatment is prevention. Myron Cohen, the University of North Carolina School of Medicine’s Associate Vice Chancellor for Global Health, said the fields of treatment and prevention are now married after studies have shown that viral suppression in an
infected person translates to decreased or no HIV transmission to their uninfected partners. In an interim analysis his team conducted of data from the HIV Prevention Trials Network 052 study, which looked at HIV transmission in couples where one partner was HIV infected and the other was not, there was a 93 percent reduction in HIV transmission amongst the almost 1,800 couples when ART was started early and other prevention options were used. The analysis looked at five years of follow-up data, showing this protective effect was stable over time. “What’s really important is that we saw no transmission, zero transmission, when HIV replication was suppressed,” he said. “So the only linked transmissions we saw were when the drug failed for whatever reason, and that was a rare event.”

Michael Keller reports from the frontiers of science, technology, and international affairs. His writing has appeared online and in newspapers, magazines, and books, including the graphic novel Charles Darwin’s On the Origin of Species.