Can HIV Treatment Prevent All Transmission of the Virus?

A decade after learning that antiretrovirals prevent sexual transmission of HIV, researchers address unanswered questions about breastfeeding and injection drug use.

June 28, 2021 By Heather Boerner

Back in 1988, Myron “Mike” Cohen, MD, of the University of North Carolina (UNC), was studying the presence of gonorrhea in the genital tract when he had a conversation with a scientist at a party that would change the course of his career and the lives of people living with HIV.

The party was celebrating the upcoming publication of data showing that AZT (Retrovir, or zidovudine) didn’t only reduce HIV viral load in test tubes; the new study showed that it also stopped the decline of CD4 cells in people with AIDS. It was there that Cohen met a researcher who offered to share some AZT with him so he could study whether the drug could change the presence of HIV in the genital tract.

Myron Cohen, MDLIZ Highleyman

Twenty-three years later, in July 2011, Cohen stood on a stage in Rome while more than 1,000 HIV activists, researchers and clinicians at the International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention gave him and his team a standing ovation. His HPTN 052 study had just provided a definitive answer to the question Cohen had asked himself at that 1988 party: Does consistent, effective antiretroviral treatment diminish the presence of HIV in the body so much that people living with the virus don't transmit it to their sexual partners?

"It took time to generate the evidence," says Cohen, now director of UNC's Institute for Global Health and Infectious Diseases and cochair of the HIV Prevention Trials Network (HPTN). "But it shifted people very quickly, almost overnight by public health standards."

It's been 10 years since that study changed the HIV landscape and ushered in a new way to think about and live with the virus. Since then, other studies have further solidified the earlier findings, showing that whatever kind of sex people are having, if they have a durably undetectable viral load, they don't transmit the virus. Now, researchers are trying to find out if antiretroviral

treatment can prevent all transmission of HIV, including via breastfeeding and injection drug use.

Scientific Signals

Of course, Cohen wasn't alone in working on the science behind the concept now known as Undetectable Equals Untransmittable (U=U). In fact, the first hint that treatment could prevent transmission came not from sex but from the exchange of blood and nutrients between pregnant people and their fetuses.

In 1991, sensing that they might not have another chance to study pregnancy and postpartum treatment and prevention, scientists launched the AIDS Clinical Trials Group 076 study to pull triple duty. In one trial, researchers put pregnant women on AZT after their first trimester to see whether treatment would reduce viral load enough to prevent HIV transmission to the fetus. Then they administered the drug intravenously to women during delivery to protect infants as they were being born and gave infants six weeks of pediatric doses of AZT to prevent transmission after birth. In other words, they offered treatment as prevention, pre-exposure prophylaxis (PrEP) through delivery and post-exposure prophylaxis (PEP) all at once.

The hope was that AZT would cut mother-to-child transmission of HIV by maybe 40% or by half at most, said Lynne Mofenson, MD, then associate branch chief for clinical research, pediatric, adolescent and maternal AIDS for the Eunice Kennedy Shriver National Institute for Child Health and Development at the National Institutes of Health. But what researchers discovered, on Presidents Day weekend in 1994, was that the treatment reduced HIV transmission to infants by two thirds.

"I was shocked," Mofenson says. "That wasn't U=U, because AZT is not as potent as giving a three-drug regimen. But with the use of potent therapy like we have today, I would say U=U [for mother-to-child transmission as well]."

Lynne Mofenson, MDCourtesy of Lynne Mofenson, MD

The Science of Sexual Transmission

In 1999, Cohen and other physician-scientists published a paper in the journal AIDS puzzling over the varying rates of HIV transmission via different routes and with different antiretrovirals.

“Antiviral therapy can be expected to reduce the transmission of HIV,” the study authors wrote. “Patients need to be carefully informed about the significance of treatment-induced reduction of genital shedding of HIV,” in particular warning them that, at the time, not all drugs fully suppressed viral load.

In 2008, the Swiss Federal Commission for AIDS issued a statement to its colleagues, informing them of a change in how they should counsel their patients living with HIV. If people had an undetectable viral load for at least six months, were supported to engage in regular care and take medications daily, and they and their partners had no other sexually transmitted infections, clinicians no longer had to tell patients they needed to use condoms. People with HIV who met those criteria “do not transmit HIV sexually,” the statement said.

At the time, other researchers, including those at the Centers for Disease Control and Prevention (CDC) and the World Health Organization, issued statements calling the Swiss Statement premature. Other doctors were more blunt. They called it hasty, irresponsible and unscientific.

It would be another three years before Cohen and his team stood on the stage at the conference in Rome to present the results from HPTN 052. But when they did, those findings confirmed what the Swiss Statement proposed.

In a trial of 1,763 mixed-status couples in which half of the HIV-positive partners started antiretroviral treatment right away and half waited for their CD4 cells to fall, the risk of HIV transmission was 96% lower in the immediate treatment arm. And when the researchers reported the final data in 2015, they showed that the one HIV transmission in the early treatment group occurred before the participant had reached an undetectable viral load.

This was it: Just as with women and their babies, HIV treatment prevented transmission of the virus via vaginal sex. Science Magazine named this discovery 2011’s Breakthrough of the Year.

Since then, data have continued to accumulate about sexual transmission. While HPTN 052 was open to all couples, Cohen says only heterosexual couples ended up participating. So whether people having “gay sex” would receive the same benefit from treatment remained an open question. Or, actually, Cohen puts it another way.

“It’s not about heterosexual or homosexual,” he says. “It’s about anal intercourse. We know that the biology of transmission from anal intercourse is different than penile-vaginal intercourse. So what was really missing was the empirical evidence that the drugs are distributed in such a way and the sexual behaviors are taking place in such a way that the same benefits would be realized with anal intercourse.”

It took only three more years for those data to start to come through. Results from the PARTNER study, reported at the 2014 Conference on Retroviruses and Opportunistic Infections and published in 2016, showed that regardless of the kind of condomless sex they had, gay and straight couples had zero cases of HIV transmission that were genetically linked to their partner when the HIV-positive partner was on suppressive treatment and had a viral load below 200.

The Opposites Attract trial, set primarily in Australia, reached the same conclusion in a study that enrolled more than 400 mixed-status gay male couples. As long as a person living with HIV had an undetectable viral load, he didn't transmit the virus to his partner. Then the PARTNER2 trial, presented at the 2018 International AIDS Conference in Amsterdam, offered further evidence: No genetically linked HIV transmissions resulted from more than 77,000 condomless sex acts among 800 gay couples. That study's lead investigator, Alison Rodger, MD, of University College London, announced in the large conference hall, "If you are on suppressive [antiretroviral therapy], you are sexually noninfectious. The risk is zero."

Soon thereafter, the CDC issued a statement declaring, "Findings from PARTNER2…provided conclusive evidence that U=U is as applicable to gay, bisexual and other men who have sex with men as it is to male-female couples."

The Making of a Movement

In 2012, a year after the HPTN 052 results were announced, Bruce Richman, a Harvard-trained attorney and social branding expert living with HIV, learned that he could no longer transmit the virus. His HIV viral load was undetectable by modern tests and had been since 2010. So when his doctor told him he didn't need to worry after a condom broke, he didn't believe it.

He trusted his doctor, he wrote in a 2016 POZ blog post, but his partner in the broken condom incident "was now terrified of me," according to Richman, who had long ago given up the idea that he'd ever feel really safe during sex again.

But here he was, and doctors were still reluctant to tell their patients about the science. One called Richman "a danger to gay men's holistic health" when he tried to talk about the research. That's when he knew the science needed to move from the pages of medical journals to the streets—and into the lives of people with HIV.

It took four more years after his eye-opening talk with his doctor for the movement to really get off the ground. In 2016, the Prevention Access Campaign (PAC) was born.

Suddenly, the abstract language of "treatment as prevention" was rendered concrete. Richman and a core team of founding task force members used his branding expertise to launch U=U. One of the team's goals, according to Richman, was to "help agencies catch up with and communicate the science" in a way that would mean something to people affected by HIV.

A U=U consensus statement issued in 2016 was similar to the one the Swiss commission issued back in 2008: People with HIV on antiretroviral treatment with an undetectable viral load in their

blood have a “negligible to nonexistent” risk of sexual transmission of HIV. PAC later launched a messaging guide that discouraged the media and clinicians from using the word negligible to describe the risk; the language has since changed to “zero risk” to reflect the additional research.

Since then, the U=U consensus statement has expanded from its eight original signatories to now include more than 1,025 groups in 102 countries.

Bryan C. Jones, the founder of the DIRT (Direct Inspiring Reachable Teachable) advocacy movement, is an activist who had been living with HIV for decades and never thought U=U would apply to him. Like many people with lots of medications under their belt, Jones didn’t have a fully suppressive regimen available to him. His CD4 cells were at 150, and he had a viral load of 250,000.

Jones didn’t think he’d live long enough, he says, to see U=U impact his own life. But then Selzentry (maraviroc) came out in 2007. Within two weeks of starting the new drug, his viral load evaporated and his T cells started to rise. All of a sudden, U=U was relevant to him too. For Jones, the science behind U=U and the community-led movement not only mean that almost anyone could reach U=U as new antiretrovirals continue to be approved but they also give power to people living with HIV.

“Understanding what your medication is doing for you is something that gives you respect for the medication and is part of your acceptance of the condition. And that respect for the medicine and knowing what adherence to the medication can do are more powerful than just taking a pill,” he says. “It’s time for us to embrace the science, use it to our advantage and use it to celebrate each other.”

Unanswered Questions

The future of U=U seems pretty bright, but a few issues still need to be worked out. For instance, treatment prevents sexual transmission of HIV among people who inject drugs, but we don’t know exactly how much it prevents transmission via shared drug injection equipment.

Some population-level studies show an association between HIV transmission rates and lower viral load in communities of people who inject drugs, and the HPTN 074 trial saw zero transmissions to injection partners of people living with HIV. But that trial didn’t have enough participants to provide definitive proof of U=U when sharing injection equipment.

Then there’s the ongoing question of how undetectable, exactly, one has to be to reap the benefits of U=U. All the studies on sexual transmission show that a viral load below 200 is sufficient to prevent transmission. But for pregnant people, maintaining a viral load below 50 before, during and after pregnancy is essential to eliminate transmission to the baby. And for breastfeeding, it’s unclear how low that would need to go. Mofenson, now a pediatric HIV scientific adviser at the Elizabeth Glaser Pediatric AIDS Foundation, says two incidents of HIV transmission via breast milk from women with viral loads below 50 have been reported.

The risk of transmission via breastfeeding is vanishingly low—less than 1%—but it's still there. That could change, Mofenson says, with better research on antiretroviral therapy during pregnancy and postpartum. For instance, we know that antiretrovirals eliminate HIV from the fluid around the cells in breast milk, but does it eliminate the virus within those cells themselves? And some medications concentrate more in breast milk than others. So what would be the ideal drug cocktail that concentrates well in breast milk, keeps viral load below 50 throughout pregnancy and postpartum, is safest for the fetus and will eliminate that niggling residual risk? Could injectable treatments fit the bill?

No one knows, Mofenson says. Studies of new antiretrovirals in pregnancy and postpartum lag behind approval for nonpregnant people by a median of six years. If trial protocols were revised to begin the preclinical research into potential birth defects earlier, pregnant women could more easily participate and remain in clinical trials. That would give researchers data that could answer those questions.

"You could look at what is the [drug] penetration into breast milk; you could look at genital penetration in the vagina," she says. "I don't think we have to prove transmission anymore. What we have to do is find the safest, easiest regimen for pregnant women."

For Cohen, who is now bringing lessons on prevention, treatment and cure to COVID-19 research, the story of modern HIV treatment is "pretty much perfect."

"The data always move in the same direction," he says. "The dissipation of the fear and stigma—that's not complete, but they're not independent of all we've just talked about. They're not independent of the development of the drugs and the recognition that drugs prevent transmission, the recognition that the drugs allow people to lead normal lives. So it's just a different world we're living in."

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http://beta.docker.poz.com/article/can-hiv-treatment-prevent-transmission-virus