Treatment as Prevention in the Real World

A Chinese study proves that antiretroviral therapy can indeed reduce transmissions among serodiscordant heterosexual couples—but the results also underscore noteworthy limitations.

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With the August 2011 publication of a groundbreaking study that showed antiretroviral (ARV) treatment could reduce infection rates among heterosexual serodiscordant couples by 96 percent, the gathering treatment-as-prevention movement received a major jolt. By the International AIDS Conference in Washington, DC, a year later, slogans about a future "AIDS-free generation" abounded.

However, what the HPTN 052 study, as it's called, lacked was proof that treatment-as-prevention works in a real-world setting. In their strictly controlled clinical trial, the researchers recruited highly motivated participants and gave them intensive adherence counseling, free condoms, as well as viral load tests taken quarterly, and even more frequently at the outset. This created an ideal setting in which to ensure successful suppression of HIV and thus the likelihood of transmission, aiding the researchers with their effort to achieve what's known as a "proof of concept" of the treatment-as-prevention theory. But the setting was too ideal to compare with the average scenario of HIV-positive people taking therapy worldwide.

Enter a group of Chinese researchers, who last month published a paper in The Lancet in which they drew upon the country's rich database of surveillance information about its HIV population to determine whether starting ARV therapy reduced infection rates among cohabitating heterosexual serodiscordant couples. With a massive study size, including data spanning 2003 through 2011 and including nearly 39,000 couples and over 100,000 cumulative "person years" of follow-up for the HIV-negative partners, the researchers stood to make a solid prediction.

After adjusting for variables such as age and CD4 count that differed between the treated and untreated groups, the Chinese found that ARV treatment reduced transmission rates by 26 percent in the first year after beginning therapy. (They could not make statistically significant speculations about years two through five.)

At first glance, comparing 26 percent to 96 percent appears to suggest that treatment-as-prevention wasn't nearly as foolproof as the HIV community may have believed, and that all the

years of increasing hype and excitement about reducing “community viral” load, and thus infection rates may have been vastly overblown.

Sten Vermund, MD, PhD, director of the Institute for Global Health at Vanderbilt University Medical Center in Tennessee, who wrote an accompanying editorial to the Chinese study in The Lancet, says, “I think [the Chinese study] suggests a confirmation in a real-world circumstance of the basic concept of treatment-as-prevention, but it also cautions us that the gap between an idealized, optimized protective effect. We’re a long way from seeing that in a real-world effect.”

“I think it’s suggestive that treatment does have a prevention benefit,” agrees Connie Celum, MD, MPH, a professor of global health at the University of Washington in Seattle who was the coauthor of a recent literature review of treatment-as-prevention research. “But we probably should be using these kind of [lower] numbers,” she says, “as well as talking about HPTN 052, so people don’t have an overly high expectation of what you can achieve.”

Part of the chaos of the real-world effect versus the ideal settings of a clinical trial is the fact that viral load, as opposed to simply treatment itself, is the most important variable that determines infectivity. To that end, the one person in the treatment arm of the HPTN study who transmitted, and thus drew the treatment-as-prevention statistic down from 100 to 96 percent effective, had not yet reached a suppressed viral load at the time of transmission. In other words, no one with a fully suppressed viral load in the study transmitted the virus.

Ultimately, one word makes the biggest difference in a real-world setting: adherence.

ARV treatment is “not protective if somebody is not on drug,” Vermund says, “or if somebody is on drug and taking it inconsistently. It’s that simple. If people take their drugs absolutely consistently, every single day, with viral suppression, the likelihood of transmission is minimized. If you want to have your risk of transmitting to others be zero, be on antiretrovirals religiously and also use condoms.”

Unfortunately, the Chinese study had no information about treatment adherence, and there is good reason to believe that a lack of it contributed to the lowered rate of protection against transmission.

Also, unlike the HPTN 052 study, in which the researchers were able to test the source of transmissions through viral linkage screens, the Chinese lacked any data outside of self-reports about how the initially HIV-negative partner was infected. This is one reason to suggest that the 26 percent figure may be low, considering that an untreated person outside of the couple may have infected that person through sex or needle sharing.

Further, while the Chinese benefitted from surveillance information about age, CD4 counts, marital status, the initial route of infection in the HIV-positive partner, as well as frequent antibody test results from the HIV-negative partner, they lacked viral load screens. As a consequence, they could not draw direct conclusions about how this key variable affected transmission rates. Nor was

there any data on condom usage.

The Chinese did know that, when beginning ARVs, the treatment cohort had a median CD4 count of only 168, while those not taking medications had a median of 441 CD4s. (China recommended beginning therapy below 200 CD4s until 2008, when they switched to a benchmark of below 350 CD4 cells.) Thus, people in the treated group likely had higher viral loads, at least at the outset, and were more infectious. On the one hand, this hints that the benefit of therapy as a protection against infection may be greater for those who begin earlier in the course of HIV disease, as is recommended in the United States.

On the other hand, because they were sicker, and also older, the treated group was probably having sex less frequently, thus protecting them against the likelihood of transmission for these reasons over the fact that they were on ARVs.

“At the end of the day,” Tim Horn, HIV project director at Treatment Action Group, writes in an email, “while I don’t expect many ‘real-world’ cohort studies to confirm that the treatment-as-prevention benefit is 96 percent, I do hope that other evaluations will demonstrate a benefit that exceeds 26 percent.”

Myron Cohen, MD, associate vice chancellor for global health at the University of North Carolina at Chapel Hill Medical Center and the lead author of the HPTN 052 study, suggests four key points to ensuring individuals with HIV reduce their likelihood of transmitting to others:

1. Adherence. This means finding the most effective, easiest to tolerate regimens with the lowest pill burden—preferably one pill a day therapy.
2. Starting treatment earlier. Those with more advanced HIV disease likely have higher viral loads, making them more infectious and probably requiring more time for them to fully suppress the virus. Furthermore, evidence suggests there is a benefit to overall health from getting into therapy early in the game.
3. Reduce risk of sexual transmission through condom use. Further research is needed, Cohen says, to better understand how anal sex transmission rates may different from vaginal rates.
4. Don’t share needles or works. More study is also needed, he says, to determine how treatment affects infection rates among injection drug users.

But at the end of the day, Celum says, the decision to begin therapy is everyone’s to make on his or her own.

“We shouldn’t shy away from saying that there are clinical benefits and making it all about prevention,” she says. “But I also think that we do have to honor people’s decisions.” What’s more, Celum points out, there’s no way that you can expect people to be adherent or as adherent if they are ambivalent or not ready to start treatment. “I think you need to work with people on an individual level to try to provide as much information and encouragement,” she says, “but ultimately they have to make their own decision.”

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