Injectable PrEP Is Even More Effective Than Daily Truvada

The placebo-controlled trial compared injections of cabotegravir given every eight weeks versus daily Truvada as PrEP.

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A recent study found that ViiV Healthcare's long-acting injectable drug cabotegravir given every eight weeks was even more effective at preventing HIV acquisition on a population level than daily Truvada as pre-exposure prophylaxis (PrEP).

That said, both forms of PrEP proved highly effective at preventing HIV.

The ongoing Phase IIb/III randomized, double-blind, placebo-controlled HPTN 083 trial enrolled 4,570 HIV-negative men who have sex with men (MSM) and transgender women (12% of the participants) who have sex with men. All were considered at risk of contracting the virus.

Raphael Landovitz, MD, MSc, of the University of California, Los Angeles, presented findings from the trial at the virtual International AIDS Conference on Tuesday.

In mid-May, ViiV released an interim analysis of the study, called HPTN 083, showing that the HIV acquisition rate among the participants randomized to receive long-acting cabotegravir injections was 69% lower than among those who received Truvada (tenofovir disoproxil fumarate/emtricitabine).

At that time, the study authors could only state with confidence that the two forms of PrEP were comparably effective at preventing HIV.

The new analysis presented at the conference indicates that long-acting injectable cabotegravir PrEP led to a 66% lower HIV acquisition rate than Truvada and that this difference was statistically significant, meaning it was not the result of chance.

This analysis indicated that if the study were run 20 times, those who received cabotegravir would wind up with a 38% to 82% lower HIV rate than those who received Truvada. Because the upper limit of this estimate range was less than 100%, cabotegravir was established as statistically superior to Truvada.

ViiV intends to use the HPTN 083 findings as the basis of an application to the Food and Drug Administration (FDA) for approval of long-acting cabotegravir as PrEP.

“Medicines that help prevent new HIV incidence are essential to our ongoing global fight to end the HIV epidemic,” Myron S. Cohen, MD, the trial’s co–principal investigator and a professor of microbiology and immunology and epidemiology at the University of North Carolina at Chapel Hill, said in a ViiV press release. “It’s exciting to discover that with injectable, long-acting cabotegravir, we now have compelling clinical evidence of another effective PrEP option that could play a critical role in helping to reduce HIV transmission that will ultimately save lives.”

HPTN 083 began enrolling participants in November 2016. Upon entering the study, participants were randomized to receive either long-acting cabotegravir injections given every eight weeks (which requires a clinic visit) or Truvada to take daily. Neither the participants nor the trial investigators knew which regimen the participants received. To keep the study blinded, all participants were given daily pills to take and received injections every eight weeks, not knowing which regimen was the placebo.

Prior to starting the injections, those in the cabotegravir received five weeks of a daily oral version of the drug plus a Truvada placebo, while those in the Truvada group received five weeks of daily Truvada plus an oral cabotegravir placebo.

Originally, the study slated everyone to receive 148 weeks of PrEP, be it cabotegravir or Truvada, following the five-week lead-in period.

But in May 2020, a scheduled interim review of the study’s data by its independent data and safety monitoring board indicated that long-acting cabotegravir was highly effective at preventing HIV. Consequently, the researchers ended the placebo phase of the study early.

The investigators are in the process of telling all participants which regimen they received. All those in the Truvada group will be offered long-acting cabotegravir injections as soon as the medication becomes available. Everyone will also have the option to keep taking Truvada or to switch to Truvada in the case of those in the cabotegravir group.

The participants live in Argentina, Brazil, Peru, South Africa, Thailand, the United States (37% of the participants) and Vietnam. Two out of three are younger than 30; the median age is 26. Among the U.S. participants, half are African American (844 people) and the other half are white.

Fifty-two participants had contracted HIV by the time the placebo phase of HPTN 083 was terminated, including 13 people in the long-acting cabotegravir group and 38 people in the daily Truvada group.

This meant that for each 1,000 cumulative years of follow-up, the participants contracted HIV at a rate of 4.1 infections among those in the cabotegravir group and 12.2 infections in the Truvada group. Consequently, cabotegravir was associated with a 66% lower HIV rate than Truvada.

The investigators conducted a preliminary analysis of a random subset of 372 people who received Truvada and found that 87% had any detectable tenofovir, one of the two drugs in Truvada, in their bloodstream. Seventy-five percent had concentrations of tenofovir that indicated they were taking Truvada daily.

Truvada's efficacy as PrEP declines when MSM take fewer than four doses per week, according to previous research.

The high level of adherence to PrEP in the Truvada group of the HPTN 083 trial makes the much greater efficacy of long-acting cabotegravir all the more remarkable.

Landovitz was keen to stress that the study's findings in no way impugn the effectiveness of Truvada as PrEP.

Previous research has further indicated that if MSM take Truvada daily, this lowers their risk of HIV by more than 99%.

Both forms of PrEP were well tolerated throughout the trial. Most adverse health events were mild or moderate, and they occurred at similar rates across the two study arms. Reactions at the injection site, fever and high blood pressure were more common in the cabotegravir group, while nausea was more common in the Truvada group.

Specifically, 80% of those in the cabotegravir group experienced pain or tenderness at the injection site, compared with 31% of those in the Truvada arm after receiving their placebo injections. A total of 2.2% of those in the cabotegravir arm discontinued that drug due to injection-site reactions, while none of the participants in the Truvada arm did so.

Overall, the HPTN 083 participants were apparently engaging in sex that without PrEP would have put them at high risk of contracting HIV, considering their rate of sexually transmitted infection acquisition. For every 100 cumulative years of follow-up, there were 5.1 syphilis diagnoses in the Truvada arm and 5.5 in the cabotegravir arm; a respecitve 10.9 and 11.0 rectal gonorrhea infections; and a respective 17.8 and 15.7 rectal chlamydia infections.

Overall, those who received cabotegravir gained an average of 2.9 pounds per year, while those who received Truvada gained 0.7 pounds per year. The difference between these weight-gain rates was statistically significant. However, according to Landovitz, those on Truvada lost weight during their first year on PrEP, and then proceeded to gain weight at the same pace as those in cabotegravir arm.

A separate ongoing study, HPTN 084, launched in 2017, is assessing long-acting cabotegravir PrEP among more than 3,000 sexually active cisgender (non-trans) women living in seven African nations. That study also received a recent interim review from its data safety monitoring board, which concluded that the trial should continue as planned.

"It's great to see such a high level of efficacy in a potential additional HIV prevention option and to

see the high level of efficacy for an already available option, daily oral PrEP," Mitchell Warren, the executive director of AVAC, said in a press release. "As we celebrate this exciting new data, we also must ensure that the companion HPTN 084 study of the same product in cisgender women finishes as quickly as possible and simultaneously work to ensure broader access and support for daily oral PrEP in communities where it is needed now."

One subject the ongoing HPTN 083 study has not yet addressed is the extent to which long-acting cabotegravir remains in the body after injections are discontinued—a phenomenon known as the drug's "tail". A new analysis of the Phase IIa HPTN 077 trial of long-acting cabotegravir as PrEP, just published in The Lancet HIV, indicated that at 52 to 60 weeks after their final injection of the drug, 23% of men and 63% of women in the trial still had detectable cabotegravir in their blood. At 76 weeks after the last injection, 13% of men and 42% of women still had detectable cabotegravir.

Such findings are concerning because in theory, after the cabotegravir level in the body has declined below the threshold that provides maximum protection against HIV acquisition, people may become vulnerable to contracting the virus. And if they do then contract HIV at a time when cabotegravir remains in the body, albeit at a low level, the virus may develop resistance to it. This could then limit their antiretroviral treatment options.

In the original design of the HPTN 083 trial, participants were slated to discontinue the long-acting cabotegravir injections at the 148-week mark and transition to daily Truvada as PrEP for 48 weeks in order to cover cabotegravir's tail. But now that the placebo phase has been discontinued early, this part of the study design will be adjusted, according to Landovitz.

Thus far, those who have stopped receiving the cabotegravir injections and who have not contracted HIV have been given daily Truvada for 48 weeks.

In March, Canada became the first nation to approve a long-acting injectable HIV treatment regimen: ViiV's Cabenuva, which includes cabotegravir plus rilpivirine. In December, the FDA held up approval of the regimen in the United States, citing concerns about the manufacturing process. ViiV has indicated that the company is working with the FDA to address these concerns with the goal of bringing that regimen to the U.S. market in the near future.

To read a National Institutes of Health (NIH) press release on the study, click here.

To read the AVAC press release, click here.

To read a ViiV press release about HPTN 083, click here.

To read the HPTN 077 analysis abstract, click here.

For more information on HPTN 083, click here.

To see all POZ coverage of AIDS 2020: Virtual, click here.