Intercourse-Based PrEP Dosing Lowers HIV Risk in Gays, But Why?

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A strategy of taking Truvada (tenofovir/emtricitabine) as pre-exposure prophylaxis (PrEP) only in the days surrounding intercourse, instead of daily as is typical, reduced the overall risk of HIV by 86 percent among a group of men who have sex with men (MSM). However, the ongoing study has thus far failed to determine whether the dosing protocol itself was responsible for the reduction in risk, as opposed to the fact that the study participants ultimately wound up taking Truvada with some level of regularity.

Preliminary results from randomized, placebo-controlled IPERGAY trial were presented at the 20th International AIDS Conference in Melbourne, Australia, in July. Researchers presented these updated results at the 2015 Conference on Retroviruses and Opportunistic Infections (CROI) in Seattle.

The study, which began in February 2012, included 414 HIV-negative MSM at six sites in France and one in Canada. The participants, who were at high risk for HIV because they did not use condoms consistently with their sexual partners, were randomly assigned to receive either Truvada or a placebo. They were instructed to take two doses of the drug between 24 and two hours before intercourse (or one pill, if the most recent dose was taken between one and six days before), and then, if intercourse did occur, to take one dose every 24 hours after that first dose, until they had taken two pills since the last time they had anal sex. This means that during a week in which someone had sex he would take a minimum of four pills, or a maximum of eight.

All the participants received risk reduction counseling, repeated HIV and sexual transmitted infection testing, with treatment for STIs if necessary, as well as vaccination for hepatitis A and B viruses (HAV and HBV), condoms and personal lubricant.

In October, IPERGAY's data safety monitoring board recommended that the study's investigators discontinue the placebo arm and offer Truvada to all participants. They did so based on an analysis that found that the intent-to-treat, or population level, effectiveness of the intercourse-based dosing strategy was "much higher" than the 44 percent found in the 2010 iPrEX study of daily PrEP among MSM and transgender women.

After a median follow-up of 8.8 months (the 25th to 75th percentile range was 4.3 to 20.5 months of follow-up), 16 participants contracted HIV, including 14 members of the placebo arm. This

resulted in an HIV incidence rate of 6.75 per 100 person-years in the placebo group, and an HIV incidence rate of 0.94 in the Truvada group. Consequently, Truvada lowered the risk of HIV by 86 percent in the Truvada group as a whole when compared with the placebo group. The estimate range for the true effectiveness of the intercourse-based dosing strategy, the investigators stated, was between 39.4 percent and 98.5 percent. (Effectiveness is another way of saying how well PrEP, or any other means of combating HIV transmission, reduces risk.)

The two men who contracted HIV in the Truvada arm both reported they had stopped taking the drug several weeks before becoming infected.

Pointing out that 34 percent of the participants contracted another sexually transmitted infection during the study—including gonorrhea, syphilis, hepatitis C virus (HCV) and chlamydia—study coordinator Jean-Michel Molina, MD, of the Hôpital Saint-Louis, in Paris, said in a press release, "It is important not to abandon the prevention policies that have proven effective so far: routine use of condoms, regular screening for HIV infection and other sexually transmitted diseases, and their treatment."

This study does not provide solid evidence that the intercourse-based dosing strategy itself was responsible for the high level of protection from HIV. Rather, it could be that the men were protected by the simple fact that they were taking Truvada with some regularity. The participants reported a median of 10 sex acts per month and eight partners every two months. Meanwhile, according to their self reports, they were taking a median of 14 pills a month, with the 25th to 75th percentile monthly pill usage running between eight and 20 pills a month. On average, they took about three to four pills a week. By comparison, the investigators in the iPrEx open-label extension study, which was published in July 2014, estimated that taking Truvada two to three times a week reduced the risk of HIV by 81 percent (with an estimate range of 12 percent to 99 percent).

"It is not known whether the [intercourse-based dosing] regimen will work if taken only a few hours or days before sex, without any buildup of the drug from prior use," Jonathan Mermin, MD, MPH, director of the CDC's National Center for HIV/AIDS, Viral Hepatitis, STD & TB Prevention, cautioned in a press release. "Studies suggest that it may take days, depending on the type of sexual exposure, for the active drug in PrEP to build up to an optimal level for preventing HIV infection.

"There are also no data on how effective this regimen would be for heterosexual men and women and injection drug users or on adherence to this relatively complex PrEP regimen outside a trial setting. CDC continues to recommend only daily use of PrEP, as approved by the FDA. IPERGAY findings combined with other recent research suggest that even with less than perfect daily adherence, PrEP may still offer substantial protection if taken consistently."

"There's growing demand for daily oral PrEP, and the data suggest that there might be other ways to use this strategy that can provide benefit," Mitchell Warren, executive director of the global HIV advocacy group AVAC, said in a different press release. "For the sake of clarity and impact,

providers, advocates and end users need to work together to develop clear, consistent messages that explain what's known and not known about levels of protection in the context of different types of sex and different patterns of use."

Truvada was generally well tolerated. The only side effect experienced at greater rates among those on Truvada was mild nausea and abdominal pain, with 13 percent of those on the drug experiencing those side effects, compared with 6 percent of those on the placebo.

The study will continue until March 2016.

To read the study abstract, click here.

To view the slide presentation from CROI and hear a presentation from Molina, click here.

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