Non-Daily PrEP Study Raises Doubts of Its Real-World Applicability

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Researchers have published in the New England Journal of Medicine their findings from the IPERGAY trial of an intermittent dosing schedule of Truvada (tenofovir/emtricitabine) as pre-exposure prophylaxis (PrEP) among men who have sex with men (MSM). Preliminary results from the study, which found that the non-daily dosing protocol reduced the risk of HIV infection by 86 percent in the double-blind, placebo-controlled trial, were presented at the February 2015 Conference on Retroviruses and Opportunistic Infections (CROI) in Seattle and the 20th International AIDS Conference in Melbourne, Australia, in July 2014.

In the published study, the study investigators cautioned that PrEP's effectiveness in this trial may have been exaggerated by the fact that the placebo arm was discontinued early. The relative brevity of the time participants spent in the placebo phase—a median nine months, compared, for example, with 1.2 years in the global iPrEx study of daily PrEP—may have inflated the results, as the participants may have become less adherent if more time had passed.

The researchers also cautioned that the IPERGAY findings may not apply to individuals who follow the study's PrEP dosing protocol and take fewer than 15 pills per month, which was the median number of pills the men in the study took. Previous research has estimated that taking four daily doses of Truvada per week confers maximum protection against HIV. The protection the men in IPERGAY's Truvada arm experienced may be more related to their taking the drug at about that frequency, rather than the particulars of the actual dosing schedule.

Participants were recruited at six sites in France and one in Canada between February 2012 and October 2014. Four hundred MSM were randomized into two groups; 201 received a placebo and 199 received Truvada. At enrollment, the participants all reported condomless anal intercourse with at least two partners during the previous six months.

The participants were instructed to take two doses between two and 24 hours before intercourse, or one pill if the most recent dose was taken between one and six days before. If intercourse did occur, they were 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. The participants all received enough tablets to take one per day throughout the study.

Participants made clinic visits four and eight weeks after they were enrolled in the trial and then

every eight weeks after that. At each visit they received a comprehensive package of HIV and sexually transmitted infection (STI) prevention services, including counseling, free condoms and lubricant, STI and HIV testing, and any necessary STI treatment.

The researchers measured use of Truvada or the placebo by having participants bring their pill bottles to each study visit so that unused tablets could be counted. The first 113 people to be enrolled also had their blood tested for levels of the two components of Truvada. The test could detect if at least one pill had been taken within nine days. Adherence was also measured through computerized interviews.

On October 23, 2014, the trial's independent data safety monitoring board, after determining that those in the Truvada arm were experiencing a considerable reduction in HIV risk, recommended the discontinuation of the placebo arm. The current analysis reflects data collected during the double-blind phase of the trial, through January 2015. The study has since continued under an open-label protocol in which all participants know they are receiving Truvada.

Forty-nine participants (12 percent) dropped out of the study. All told, participants contributed 431 person-years of follow-up (person-years reflect the cumulative years participants spend in a study), with a median of 9.3 months per person. (The 25th percentile was 4.9 months and the 75th percentile 20.6 months.)

The participants in both arms of the study took a median 15 tablets per month, with a 25th to 75th percentile range of 11 to 21 tablets in the Truvada group and 9 to 21 tablets in the placebo group. There was considerable variability in the individual and overall patterns of pill taking during the study.

Eighty-six percent of the participants in the Truvada arm had detectable tenofovir at the study visits, and 82 percent had detectable emtricitabine at the visits. Eight people in the placebo group (4 percent) had detectable Truvada, including three that were receiving post-exposure prophylaxis (PEP).

According to the computer interviews, 28 percent of the participants did not take Truvada or the placebo at all, 29 percent took the assigned drug at a suboptimal level, and 43 percent took it correctly.

The computerized interview findings contrast the drug-testing figures, for one, because only the first 113 of the 400 participants who enrolled had their drug levels tested. According to the study's lead author, Jean-Michel Molina, MD, chief of the department of infectious diseases at Paris's Hôpital Saint-Louis, these particular participants may have been more likely to adhere because they enrolled earlier. Also, since the drug tests only indicate that someone took at least one pill during the previous nine days, a test showing detectable drug may be indicative of an individual who fell into the suboptimal category or the ideal adherence category.

The participants did not report changing their sexual practices during the study.

Forty-one percent of those in the Truvada group and 33 percent of the placebo group were diagnosed with an STI during the study. Thirty-nine percent of the STIs were rectal infections. Eighty-one participants (20 percent) were diagnosed with chlamydia, 88 (22 percent) with gonorrhea, 39 (10 percent) with syphilis, and 5 (1 percent) with hepatitis C virus (HCV).

Research suggests Hep C can transmit sexually among MSM, and there is considerable evidence of an emerging epidemic of sexually transmitted HCV among HIV-positive MSM. HIV-negative MSM appear to be at lower risk, for reasons that are poorly understood. Two people out of more than 600 MSM receiving PrEP through a San Francisco clinic have contracted hep C, apparently sexually, leading to a call from physicians for regular screening of the virus among PrEP users.

Sixteen participants contracted HIV during the IPERGAY study, two in the Truvada group (for an incidence of 0.91 per 100 person-years) and 14 in the placebo group (for an incidence of 6.6 per 100 person years). This meant the Truvada group had an 86 percent lower risk of HIV. The estimate range for this risk reduction was wide, 40 to 98 percent, which means that the true risk reduction may lie anywhere in between those figures.

The two members of the Truvada arm who did contract HIV were not taking the drug at the time: At the visits when they tested positive for the virus, they returned a respective 60 and 58 of the 60 pills they were given at the study visit eight weeks prior, and neither had detectable Truvada in their blood.

No one in the study experienced grade 3 or 4 adverse health events. Gastrointestinal side effects, including nausea, vomiting, diarrhea, abdominal pain and other GI disorders, occurred among 14 percent of the participants in the Truvada group, compared with 5 percent in the placebo group.

Thirty-five members (18 percent) of the Truvada group and 20 members (10 percent) of the placebo group experienced elevations in serum creatinine levels, an indication of potential problems with kidney function. All but one of these elevations were grade 1 and none led the participants to discontinue participation in the study. Two participants (1 percent) in the Truvada group had a transient decrease in creatinine clearance to below 60 milliliters per minute.

To read the study, click here.

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