Further Studies Confirm Effectiveness of Injectable Cabotegravir PrEP for Women

New analyses show that the long-acting injections may be even more effective than previously reported.

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Injectable cabotegravir administered every other month is a highly effective pre-exposure prophylaxis (PrEP) option for women, according to two studies presented at the 11th International AIDS Society Conference on HIV Science (IAS 2021).

Cabotegravir, from ViiV Healthcare, is a novel integrase inhibitor. In January, the Food and Drug Administration approved long-acting injections of cabotegravir plus rilpivirine (Cabenuva) as a once-monthly HIV treatment regimen. But cabotegravir alone is sufficient for HIV prevention.

The HPTN 084 trial compared the safety and effectiveness of every-other-month injections of cabotegravir versus daily oral Truvada (tenofovir disoproxil fumarate/emtricitabine) in more than 3,000 cisgender women in sub-Saharan Africa. The parallel HPTN 083 study enrolled more than 4,000 gay and bisexual cisgender men and transgender women who have sex with men.

As previously reported, women randomly assigned to receive cabotegravir injections had an 89% lower risk of acquiring HIV compared with those who used daily Truvada. There were just four new cases of HIV among women who used cabotegravir (an annual incidence of 0.21%), compared with 34 among those who used Truvada (an annual incidence of 1.79%). In HPTN 083, cabotegravir injections reduced the risk of infection by 66% compared with Truvada.

But the long-acting injections may be even more effective for women than previously reported.

Sinead Delany-Moretlwe, MBBCh, PhD, of the University of the Witwatersrand in Johannesburg, and colleagues conducted a follow-up analysis of the four HIV cases in the cabotegravir group of HPTN 084 and the 36 infections (two more than originally reported) in the Truvada group.

In the Truvada group, all but one of the women who acquired HIV had poor or inconsistent adherence around the time they tested positive, as shown by pill counts and measurement of tenofovir drug levels. Several of them showed evidence of drug resistance mutations.

In the cabotegravir group, two of the HIV-positive women never actually received the injections (one never showed up for her first injection visit and the other switched to Truvada when she became pregnant). A third woman missed or delayed several injections and had not received a shot for 16 weeks before she tested positive.

The fourth woman already had HIV when she enrolled in the study, retrospective testing showed. She had received five cabotegravir injections and had adequate drug levels before she tested positive. The researchers suggested that exposure to cabotegravir was associated with diminished or delayed antibody detection and delayed HIV diagnosis, which was also seen in a small number of participants in HPTN 083. Fortunately, the woman did not show evidence of integrase inhibitor resistance mutations.

After reclassifying the woman who already had HIV, the revised incidence was 0.15% for the cabotegravir group and 1.85% for the Truvada group, reflecting a 92% risk reduction.

For ethical reasons, prevention trials must compare new PrEP methods against the best available option, which at the time of this study was daily Truvada. But mathematical modeling can be used to compare effectiveness against a hypothetical placebo control derived from previous studies.

Mia Moore, PhD, of the Fred Hutchinson Cancer Research Center in Seattle, and colleagues employed this kind of modeling to compare new HIV infections among women who used injectable cabotegravir in HPTN 084 versus a so-called counterfactual placebo.

To estimate incidence in a hypothetical placebo group, the researchers used previous placebo group data from the VOICE trial, which tested Truvada, Viread (tenofovir disoproxil fumarate alone) and a tenofovir vaginal gel in more than 5,000 women in South Africa, Uganda and Zimbabwe. The model was validated using data from four other studies conducted in sub-Saharan Africa between 2005 and 2019: FEM-PrEP (testing Truvada), HPTN 035 (testing vaginal microbicides), ASPIRE (testing a dapivirine vaginal ring) and ECHO (testing whether contraceptives affect HIV acquisition).

The researchers adjusted risk estimates using responses to a survey developed for VOICE, which asked about factors such as age, marital status, sexually transmitted infections and alcohol use. They also took into account HIV rates and viral suppression among men in the trial site communities, as this would affect women's likelihood of acquiring HIV.

They calculated that a counterfactual HPTN 084 placebo group would have an annual HIV incidence of 2.20%. Comparing this against the initially reported incidence of 0.21% in the cabotegravir group, they estimated that the injections would be 91% effective compared with a placebo. But Truvada fared worse, appearing to be only about 15% more effective than a placebo.

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