Daily Oral PrEP Is Effective for Women

TDF/FTC is effective for cisgender women who take at least four pills per week, but many struggle to reach this level of adherence.

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Cisgender women who consistently took tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) for pre-exposure prophylaxis (PrEP) were protected as well as gay men, but well under half of women in PrEP demonstration projects achieved this level of adherence, according to an analysis presented at the 30th Conference on Retroviruses and Opportunistic Infections (CROI). Another recent study suggests that women might require even higher adherence than men to be adequately protected against HIV.

Studies have shown that daily TDF/FTC (Truvada or generic equivalents) is more than 99% effective for gay men and transgender women who have sex with men. But research has shown that PrEP effectiveness appears to be lower for cisgender women due to poorer adherence and perhaps biological differences.

Jeanne Marrazzo, MD, of the University of Alabama at Birmingham, and colleagues conducted a multinational pooled analysis of data from 6,296 women who participated in 11 PrEP demonstration projects in six countries since the approval of TDF/FTC for PrEP in 2012. Most lived in Kenya (45%), Botswana (28%) or India (21%). The median age at PrEP initiation was 25 years.

The researchers evaluated adherence by assessing levels of tenofovir-diphosphate—the active form of the drug—in blood plasma (a short-term measure reflecting adherence over the past two to seven days) and in dried blood spots (a longer-term measure reflecting the last 12 weeks). They also included data from electronic pill cap monitoring, pill counts, self-reports and reports from study investigators.

Marrazzo's team categorized adherence as excellent (seven or more PrEP pills per week), good to very good (four to six pills), fair (two to three pills) or poor (fewer than two pills per week). The 2,954 women with available adherence data were divided into four groups according to adherence trajectories over 96 weeks: consistent daily adherence (17%), consistently high adherence (22%), high but declining adherence (39%) and consistently low adherence (21%).

During follow-up, a total of 32 women on PrEP acquired HIV, for an overall incidence rate of 0.72 per 100 person-years. Younger women were more likely to acquire HIV than older women (1.33 versus 0.24 per 100 person-years, respectively); this was also the case for married women and

those with no children.

Women over age 25 were more likely to maintain good PrEP adherence compared with younger women. Objective drug level measurements showed substantially lower adherence than self-reports and other subjective measures. But based on both types of measures, overall adherence declined over time.

No new cases of HIV were observed among women with consistent daily adherence, and there was only one case among those with consistently high adherence (0.13 per 100 person-years). For these women, the adherence-to-efficacy relationship was similar to that of gay men. In contrast, HIV incidence rates were 0.49 per 100 person-years for those with high but declining adherence and 1.27 for those with consistently low adherence.

This large real-world assessment of PrEP adherence and HIV incidence in cisgender women "supports the high effectiveness of [TDF/FTC] for PrEP in women with consistent adherence," the researchers concluded. However, they added, "over half of all participants did not use [TDF/FTC] consistently, highlighting the urgent need for additional prevention options such as long-acting modalities."

Does Biology Play a Role?
While adherence goes a long way toward explaining why oral PrEP works better for men than for women, biology also appears to play a role. Prior research has shown that tenofovir reaches higher concentrations in rectal tissue compared with vaginal tissue, though it is not clear whether PrEP effectiveness depends on drug levels at the site of exposure or levels in the blood.

In another study, published in Clinical Infectious Diseases, Peter Anderson, PharmD, of the University of Colorado, and colleagues looked at the relationship between PrEP adherence and efficacy in men and women. Here, too, they measured tenofovir diphosphate levels in blood plasma and dried blood spots.

This analysis included data from men and transgender women randomly assigned to the daily TDF/FTC group in study HPTN-083 and cisgender women randomized to the TDF/FTC arm in HPTN-084. Both trials compared daily oral PrEP versus long-acting cabotegravir injections (Apretude) for HIV prevention.

In HPTN-083, there were 39 new HIV diagnoses among participants taking TDF/FTC versus 12 among those on Apretude. In HPTN-084, there were 36 and three new diagnoses, respectively. These trials showed that Apretude was 66% more effective than oral PrEP for men and trans women but 91% more effective for cisgender women—a difference attributable to lower TDF/FTC efficacy in the women's study. While nearly three quarters of HPTN-083 participants took at least four TDF/FTC pills per week, this fell to just 3% in HPTN-084.

Everyone who acquired HIV in the TDF/FTC arm of HPTN-083 was either not taking the pills at all or taking fewer than two doses per week. Even with just two doses per week, men gained some protection. In contrast, effectiveness for cisgender women taking TDF/FTC started to drop off if

adherence declined to four to six pills per week. Women who took fewer than two doses had essentially no protection.

Based on tenofovir levels in red blood cells, the researchers calculated that men achieved approximately 99% efficacy at a lower adherence threshold of two or more pills per week, while women required daily dosing, “suggesting higher adherence is needed for women versus men.”

While daily oral PrEP has been shown not to work as well for women in real-world use, Apretude is highly effective for women as well as men. Another study presented at CROI found that women in the Apretude arm of HPTN-084 had higher and more durable drug levels than men in HPTN-083. This analysis suggests that receiving injections quarterly (matching the schedule of some injectable contraceptives) instead of every other month might be feasible for women, but more research is needed to confirm these findings.

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