Oral PrEP Works Well for Women if Used Consistently

TDF/FTC PrEP pills can be equally effective for cisgender women if they maintain good adherence.

April 19, 2024 By Liz Highleyman

It's a common belief that pre-exposure prophylaxis (PrEP) pills do not protect cisgender women as well as gay and bisexual men. Several studies have seen suboptimal PrEP efficacy in this population, but new research suggests that oral PrEP may work just as well for women if they use it consistently.

While daily PrEP adherence is optimal, one study found that a minimum of four doses per week of tenofovir disoproxil fumarate/emtricitabine, or TDF/FTC (Truvada or generic equivalents) "is expected to provide effective protection for most females." Women who consistently took four to six doses per week had about a 90% lower HIV incidence rate than those who took less than two doses per week.

Prior studies of once-daily TDF/FTC showed that it is highly effective for men and transgender women who have sex with men. The iPrEx trial, for example, found that daily pills reduced the risk of acquiring HIV by 44% overall, but this rose to 92% for participants who had blood drug levels indicating good adherence. Two French studies showed that "on-demand" PrEP taken before and after sex also works well. Most experts agree that for gay men, daily TDF/FTC reduces the risk of HIV acquisition via sex by around 99% when taken as prescribed.

Two trials of heterosexual serodiscordant couples in Africa (Partners PrEP and TDF2) found that daily TDF/FTC PrEP reduced the likelihood of HIV acquisition by around 60% to 75%. But large studies of cisgender women have been disappointing. The Fem-PrEP and VOICE trials, for example, did not show a significant protective effect of TDF/FTC for women in Africa. Participants' blood drug levels were low, however, indicating that they did not take the pills consistently.

Studies have found that tenofovir levels are lower in vaginal and cervical tissue compared with rectal tissue. This has led many experts to assume that oral PrEP may be less "forgiving" for cisgender women, and that they may need to take TDF/FTC more consistently than men. This assumption also led to recommendations against on-demand PrEP for women. Research on tissue drug levels and PrEP effectiveness remains inconclusive—levels in blood cells are likely more important—but recent analyses indicate that protection primarily depends on adherence, not biology.

Recent PrEP Studies

Jeanne Marrazzo, MD, MPH, now director of the National Institute of Allergy and Infectious Diseases (NIAID), and colleagues performed a mathematical modeling analysis of real-world data from 11 post-marketing studies of TDF/FTC PrEP conducted between 2012 and 2020. Oral PrEP has now been approved in 69 counties, and an estimated 5.6 million people have initiated PrEP worldwide, according to NIAID.

The analysis was based on data from 6,296 cisgender women in Kenya (46%), South Africa (28%), India (21%), Uganda (3%), Botswana (2%) and the United States (1%). About 60% were under age 25. Measures of adherence—ranging from self-report to electronic pill-cap monitoring to drug levels in blood samples—were available for 2,955 participants.

As reported in JAMA, the researchers found that none of the 498 women who took PrEP pills every day acquired HIV. Among the 658 women with consistently high adherence, meaning they took four to six doses per week, only one seroconverted—similar to the incidence rate for gay men. But HIV incidence was higher among the 1,166 women whose adherence started out high but declined over time and the 632 women with consistently low adherence. In addition, women under age 25 had substantially higher incidence than older women.

“Evidence gaps have led to cisgender women being counseled to follow oral PrEP dosing with complete rigidity, which can undermine their motivation to use this highly effective tool,” Marrazzo said in a NIAID news release. “By combining data from several moderately sized studies, we have revealed a trend in prevention-effective use that suggests brief dosing interruptions should not stop cisgender women from experiencing the potentially life-changing benefits of oral PrEP.”

In another study, Mia Moore, PhD, of Fred Hutchinson Cancer Center, and colleagues used data from previous PrEP trials to calculate adherence–efficacy curves for cisgender women based on HIV incidence and tenofovir plasma concentrations. They compared these against data from HPTN 082, a study that evaluated youth-friendly media and community interventions to increase PrEP uptake and adherence among adolescent girls and young women, achieving 95% adherence.

As reported last fall in Nature Medicine, they found that two TDF/FTC pills per week reduced HIV incidence by 59%, four doses lowered it by 84% and seven doses lowered it by 96%. “The curve suggests that high adherence confers high protection in cisgender women,” they concluded. “However, the lower efficacy with partial adherence highlights the need for new PrEP products and interventions to increase adherence.”

A third study by Lanxin Zhang, a PhD student at the Robert Koch Institute in Berlin, and colleagues used mathematical modeling to predict protective PrEP adherence levels in cisgender women. As reported in Nature Medicine, they estimated that women with some detectable drug in their blood—suggesting they took TDF/FTC at least twice a week—had 90% to 100% protection, while those who took PrEP less often had no significant protection. What’s more, they found that PrEP effectiveness was not dependent on tenofovir levels in vaginal or cervical tissue. If it were, they

calculated that efficacy would likely be much lower even with consistent use.

These two modeling studies "offer compelling evidence that less-than-perfect adherence to HIV pre-exposure prophylaxis can still provide reasonable protection for cisgender women—providing optimism for a more person-centered approach and lower discontinuation rates," Maryam Shahmanesh, PhD, of the Africa Health Research Institute, and colleagues wrote in an accompanying commentary.

Taken together, these studies confirm that oral PrEP can be as effective for cisgender women as it is for gay men if used as directed. Unfortunately, many women—more than 60% in Marrazzo's study—do not achieve the necessary level of adherence.

There are multiple reasons for suboptimal adherence, some of which may be particularly relevant for women in low-income settings. These include forgetting to take a pill every day, interrupted access due to cost or lack of availability, poor social support and reluctance to have pill bottles that could reveal their risk for HIV, potentially subjecting them to stigma, discrimination and violence.

"Although questions remain about the role of biological factors, findings from this study, coupled with recent pharmacologic studies, indicate that the protection achieved in cisgender women is more similar to that in [men who have sex with men] than previously thought," Anandi Sheth, MD, of Emory University School of Medicine, and colleagues wrote in an editorial accompanying the JAMA report. "A shift in narrative that cisgender women also have protection from PrEP with high, but less-than-perfect, adherence can alleviate anxiety around missed doses and help refocus conversations toward an individual's motivations and challenges."

Reviewing the recent study findings during a symposium at the Conference on Retroviruses and Opportunistic Infections in March, Jenell Stewart, DO, MPH, of the Hennepin Healthcare Research Institute in Minneapolis, argued that even on-demand or event-driven oral PrEP could be feasible for some cisgender women—for example, those with partners who are seasonal workers—and they should not be denied this option due to "dogma."

For women who are unable to take oral PrEP consistently, Apretude (long-acting cabotegravir), an injection administered by a health care provider every other month, may be a preferable option. The HPTN 084 study showed that Apretude reduced the risk of HIV acquisition by about 90%. Researchers are currently evaluating the HIV capsid inhibitor lenacapavir for PrEP, which could be given just twice a year.

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