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Priority Updates from the Research Literature from the Family Physicians Inquiries Network

Kathryn Justesen, MD; Shailendra Prasad, MBBS, MPH
North Memorial Family Medicine Residency, University of Minnesota, Minneapolis

DEPUTY EDITOR
James J. Stevermer, MD, MSPH
Department of Family and Community Medicine, University of Missouri-Columbia

On-demand pill protocol protects against HIV

Finally, there's an effective prevention strategy—other than condoms—that can be used, as needed, by patients at high risk for HIV infection.

PRACTICE CHANGER

Offer patients at high risk for human immunodeficiency virus (HIV), particularly men who have sex with men, preexposure prophylaxis (PrEP) with a combination pill of tenofovir disoproxil fumarate and emtricitabine (TDF-FTC) on an on-demand basis to decrease HIV-1 infection rates.

STRENGTH OF RECOMMENDATION

B: Based on one good quality randomized controlled trial.[1]

Molina JM, Capitant C, Spire B, et al. On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. *N Engl J Med.* 2015;373:2237-2246.

ILLUSTRATIVE CASE

Your patient is a 31-year-old man who has sex with men. He is sexually active with several different partners. He asks you if there is anything he can do to decrease his risk of becoming infected with human immunodeficiency virus (HIV). Besides recommending condom use, what should you offer him?

In most high-income countries, including the United States, HIV-1 infection continues to occur in high-risk groups, especially among men who have sex with men (MSM).[2] Without a vaccine, condom use has served as the primary method of preventing infection.

In 2014, the Centers for Disease Control and Prevention (CDC) began recommending daily use of tenofovir disoproxil fumarate and emtricitabine (TDF-FTC) in high-risk individuals, as a form of preexposure prophylaxis (PrEP).[3-5] This recommendation is based primarily on the Preexposure Prophylaxis Initiative (iPrEx) trial, which showed a relative reduction of 44% (number needed to treat [NNT]=46 over 1.2 years) in the incidence of new HIV-1 infection among men and transgender women who have sex with men when TDF-FTC was used on a daily basis.[6] However, the effectiveness of this strategy in the real world has not been as high as hoped, presumably because of the difficulty in getting patients to take the medication on a daily basis.[7,8]

While it would likely improve adherence rates, the use of prophylaxis in an on-demand manner is not currently recommended.[5] That is because, until now, there have been no studies demonstrating the effectiveness of PrEP used episodically and taken only around the time of potential exposure.

STUDY SUMMARY

Fewer pills improves adherence, reduces HIV infection rates

The Intervention Preventive de l'Exposition aux Risques avec et pour les Gays (IPERGAY) study was a double-blind, multicenter study conducted in France and Canada that assessed the efficacy and safety of prophylaxis with TDF-FTC used in an on-demand fashion by MSM.[1] The study hypothesis was that adherence would be higher if chemoprophylaxis was taken only around the time of inter-

course, rather than daily, and that this would further reduce the risk of HIV infection.

The study randomized 414 participants who were considered to be at high risk for acquiring HIV-1 infection. The investigators defined high risk as having a history of unprotected anal sex with at least 2 partners in the previous 6 months. Other inclusion criteria included age ≥18 years, and male or transgender female sex. Exclusion criteria included current HIV infection, hepatitis B or C infection, creatinine clearance <60 mL/min, alanine aminotransferase level >2.5 times the upper limit of normal, and significant glycosuria or proteinuria.

The pill and visit schedule. After excluding those who withdrew consent, were lost to follow-up, or who acquired HIV-1 infection, the study participants (199 in the TDF-FTC group and 201 in the placebo group) were randomized to take TDF-FTC or placebo before and after sexual activity. The dose of TDF-FTC was fixed at 300 mg of TDF and 200 mg of FTC per pill. The participants were instructed to take a loading dose of 2 pills of TDF-FTC or placebo with food 2 to 24 hours prior to intercourse, followed by a third pill 24 hours after taking the first 2 pills, and a fourth pill 24 hours after the third pill. If there were multiple consecutive days with episodes of sexual intercourse, participants were to take one pill on each of the days of intercourse, and then the 2 post-exposure pills. If sexual activity resumed within a week of the prior episode, participants were instructed to take only one pill when resuming the preexposure prophylaxis; otherwise, they were to begin again with 2 pills 2 to 24 hours prior to intercourse and repeat the protocol.

Study coordinators followed participants 4 and 8 weeks after enrollment, and then every 8 weeks subsequently. The investigators tested the participants for HIV-1 and HIV-2 at each visit and assessed adherence by pill count and drug levels in plasma, as well as with an at-home, computer-assisted interview completed by each participant prior to each visit.

Participants received counseling from a peer community member and were offered preventative services and testing for other sexually transmitted infections. They were given free condoms and gel at each visit, as well as enough pills (TDF-FTC or placebo) to cover daily use until their next visit.

Forty-three percent took the pills correctly. The participants were followed for a median of 9.3 months. Overall, 72% of the participants took the study drugs (TDF-FTC or placebo), although 29% took a suboptimal dose. There was no change in the sexual behavior of the participants during the study. The study was unblinded after 20 months and is continuing as an open-label study because of the discontinuation of another preexposure prophylaxis study in the United Kingdom, which showed an NNT of 13 to prevent one new HIV infection per year.[3]

An independent data and safety monitoring board recommended the unblinding because the placebo group was considered to be at significantly increased risk of contracting HIV without PrEP. The open-label part of the study, iPrex-OLE, completed enrollment and data gathering in November 2013, and the data analysis and results are presently pending.[9]

Eighty-six percent relative reduction in HIV. The primary end-point was the diagnosis of HIV-1 infection, and the results were based on an intention-to-treat analysis. HIV-1 infection was diagnosed in 19 study participants, with 3 of those new cases occurring between the time of randomization and enrollment. Fourteen of the cases were in the placebo group (6.6 infections per 100 person-years) and 2 of the new cases were in the TDF-FTC group (incidence 0.91 per 100 person-years). This translated to a relative reduction in the incidence of new HIV-1 seroconversion in the TDF-FTC group of 86% (95% confidence interval, 40%-98%; *P*=.002; NNT=17 over 9.3 months).

The 2 study participants in the TDF-FTC group diagnosed with new HIV-1 were found to be non-adherent to the prescribed prophylaxis, as they returned 58 and 60 of the 60 pills administered to them, and no study drugs were found in their plasma samples.

Adverse events included gastrointestinal symptoms of nausea, vomiting, diarrhea, and abdominal pain and were seen at a greater rate (14% vs 5%, *P*=.002; number needed to harm=11) in the treatment group

We suspect the higher benefit of an on-demand PrEP is likely due to increased compliance with medication use.

than in the placebo group. There were also mild increases in serum creatinine level (seen in 18% of the TDF-FTC group), but only 2 participants had a transient decrease in creatinine clearance to <60 mL/min. None of the participants discontinued medications due to renal issues.

WHAT'S NEW

Risk reduction with on-demand use is nearly double that of daily use

This is the first study to look at on-demand preexposure prophylaxis with TDF-FTC to decrease the incidence of HIV-1 infection in high-risk MSM. The risk reduction in this study (86%) was much better than the 44% seen in the prior study that used daily PrEP in this population.[6] We suspect the higher benefit of on-demand PrEP is likely due to increased compliance with medication use.

CAVEATS

Is fewer pills enough to maintain adherence over time?

The median length of follow-up in the study was 9.3 months. One concern is that adherence may wane over time, decreasing the efficacy of the prophylaxis. Continued efforts to improve compliance with this type of PrEP may be needed to ensure efficacy. Since the study was shortened and reported early, we will need to wait for the results of the open-label study to fully assess the risks of adverse events.

CHALLENGES TO IMPLEMENTATION

Efficacy and convenience come at a cost

The main challenge to implementation could be the cost of TDF-FTC, the retail price of which is about $50 per dose.[10] Insurance coverage for the medication varies. **JFP**

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