

## Interim Guidance for Clinicians Considering the Use of Preexposure Prophylaxis for the Prevention of HIV Infection in Heterosexually Active Adults

In the United States, an estimated 48,100 new human immunodeficiency virus (HIV) infections occurred in 2009 (1). Of these, 27% were in heterosexual men and women who did not inject drugs, and 64% were in men who have sex with men (MSM), including 3% in MSM who inject drugs. In January 2011, following publication of evidence of safety and efficacy of daily oral tenofovir disoproxil fumarate 300 mg (TDF)/emtricitabine 200 mg (FTC) (Truvada, Gilead Sciences) as antiretroviral preexposure prophylaxis (PrEP) to reduce the risk for HIV acquisition among MSM in the iPrEx trial, CDC issued interim guidance to make available information and important initial cautions on the use of PrEP in this population. Those recommendations remain valid for MSM, including MSM who also have sex with women (2). Since January 2011, data from studies of PrEP among heterosexual men and women have become available, and on July 16, 2012, the Food and Drug Administration (FDA) approved a label indication for reduction of risk for sexual acquisition of HIV infection among adults, including both heterosexuals and MSM.\* This interim guidance includes consideration of the new information and addresses pregnancy and safety issues for heterosexually active adults at very high risk for sexual HIV acquisition that were not discussed in the previous interim guidance for the use of PrEP in MSM.

Data from the four randomized, double-blind, placebo-controlled, clinical trials of oral PrEP with TDF and FTC that have been conducted in HIV-uninfected, heterosexually active adults were reviewed. Medical epidemiologists in the Division of HIV/AIDS Prevention of the National Center for HIV, Viral Hepatitis, STD, and TB Prevention at CDC developed this interim guidance. Subject matter experts at other federal health agencies, academic researchers, health department HIV policy stakeholders, and community representatives have participated in working groups and consultations to inform content for comprehensive U.S. Public Health Service (PHS) guidelines for PrEP use currently in development; those ideas also were used in developing this interim guidance.

### Rationale and Evidence

The Partners PrEP trial evaluated a daily dose of a fixed-dose combination of 300 mg TDF and 200 mg FTC, and daily TDF alone (300 mg), for the HIV-uninfected male or female partner in HIV-discordant couples (where one partner is infected with HIV and the other is not) in Kenya and Uganda (3). The TDF2 trial evaluated daily TDF/FTC in adult women and

men in Botswana (4), the FEM-PrEP study evaluated daily TDF/FTC in women in Kenya, South Africa, and Tanzania (5), and the VOICE trial in women in Uganda, South Africa, and Zimbabwe included one group to assess daily oral TDF/FTC, a second group to assess daily oral TDF alone, and a third group to assess daily use of a 1% tenofovir vaginal gel (6). These four trials compared HIV infection rates in participants randomized to receive antiretroviral medication compared with rates in participants randomized to receive placebo pills. All participants in these four trials received regular risk-reduction counseling, condoms, medication adherence counseling, and testing for sexually transmitted infections with treatment as indicated (Table 1).

No serious toxicities were identified in any of the four trials comparing participants receiving daily oral TDF/FTC with those receiving placebo pills; however, in the first 1–2 months on medication, nausea and vomiting were more common in those receiving TDF/FTC than in those receiving placebo. The Partners PrEP trial reported 75% efficacy for TDF/FTC (95% confidence interval [CI] = 55%–87%) and 67% efficacy for TDF (CI = 44%–81%), with 97% medication adherence by returned pill count. In the trial, no statistically significant difference in efficacy between the two regimens was observed, and efficacy was reported for both men and women independently (Table 2). The TDF2 trial found 62% efficacy (CI = 22%–83%) in men and women combined, with 84% medication adherence by returned pill count. Among persons tested who were assigned to receive TDF/FTC, the drug was detected in the blood of 81% of persons in Partners PrEP and 81% of persons in TDF2. In Partners PrEP, within a subgroup of persons who received TDF/FTC and had plasma drug levels tested, having measurable TDF concentrations was associated with a 90% risk reduction compared with placebo.

The FEM-PrEP trial and the oral TDF portion of the VOICE trial were stopped early by their data safety monitoring boards when they concluded that no evidence of efficacy would be found (futility). In the FEM-PrEP trial, researchers reported very low levels of medication adherence. Frequency of drug detection in the blood of FEM-PrEP participants overall was not reported but was <27% among women who acquired HIV infection and <38% among matched uninfected controls. No interim analysis data were provided from the VOICE trial because the trial remains blinded, and the oral TDF/FTC and placebo study groups are continuing, with final results anticipated in late 2013.

The findings in this report are subject to at least three limitations. First, the assessment of adherence by drug-level testing

\* Available at <http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/hivandaidsactivities/ucm312264.htm>.

TABLE 1. Study design and methods used in four PrEP efficacy trials with daily oral TDF/FTC\*

Study	Population	No. and sex of participants	Design	Total follow-up time (per participant median)	No. of incident HIV infections		
					Placebo	TDF/FTC	Total
iPrEx	MSM	2,499 (100% male)	RDBPCT	3,324 person-yrs (1.8 yrs)	64	36	100
Partners PrEP	Heterosexual HIV-discordant couples	4,758 couples (38% with female HIV+ partner) <sup>†</sup>	RDBPCT	7,830 person-yrs (23 mos)	52	13	65 <sup>†</sup>
TDF2	Heterosexual men and women	1,216 (46% female)	RDBPCT	1,563 person-yrs (1.1 yrs)	24	9	33
FEM-PrEP	Heterosexual women	2,056 (100% female)	RDBPCT	1,407 person-yrs (NR)	35	33	68

**Abbreviations:** PrEP = preexposure prophylaxis; TDF/FTC = tenofovir disoproxil fumarate/emtricitabine; MSM = men who have sex with men; HIV = human immunodeficiency virus; RDBPCT = randomized, double-blind, placebo-controlled clinical trial; NR = not reported.

\* Restricted to trials of oral TDF/FTC only; this guidance does not address use of other antiretroviral regimens.

<sup>†</sup> For TDF/FTC and placebo groups only.

TABLE 2. Measures of efficacy in four PrEP efficacy trials with daily oral TDF/FTC,\* by medication adherence

Study	Population	mITT <sup>†</sup> % reduction in HIV incidence (95% CI)			Combined self-report and pill-count medication adherence measures (95% CI)		Pill-count medication adherence measures (95% CI)	TDF blood detection <sup>§</sup> (95% CI)
		All	Men	Women	>50% <sup>¶</sup>	>90% <sup>¶</sup>		
iPrEx	MSM				>50% <sup>¶</sup>	50% (18%–70%)	NR	92% (40%–99%)
					>90% <sup>¶</sup>	73% (41%–88%)		
Partners PrEP	Heterosexual HIV-discordant couples	75% (55%–87%)	84% (54%–95%)	66% (28%–84%)	NR		100%** (87%–100%)	90% (58%–98%)
TDF2	Heterosexual men and women	62% (22%–83%)	80% (25%–97%)	49% (-21%–81%, NS)	NR		NR	84% (-62%–98%, NS)
FEM-PrEP	Heterosexual women	NS	NS	NS	NR		NR	NS

**Abbreviations:** PrEP = preexposure prophylaxis; TDF/FTC = tenofovir disoproxil fumarate/emtricitabine; mITT = modified intent to treat analysis; CI = confidence interval; MSM = men who have sex with men; HIV = human immunodeficiency virus; NR = not reported; NS = finding not statistically significant.

\* Restricted to trials of oral TDF/FTC only; this guidance does not address use of other antiretroviral regimens.

<sup>†</sup> Excluded only those enrolled participants later found to be infected at randomization and those with no follow-up visit or HIV test.

<sup>§</sup> The percentage of reduction in HIV incidence among persons with TDF detected in blood, compared with those without detectable TDF.

<sup>¶</sup> The percentage reduction in HIV incidence, compared with the placebo group, is presented for two groups: those with 50% medication adherence and those with 90% adherence.

\*\* In a substudy of participants who provided counts via home-based unannounced pill counts with supplementary adherence counseling if the counts were <80%.

currently is incomplete in trials with heterosexually active adults and is likely to provide important additional information regarding the relationship of efficacy to medication adherence that will need to be addressed in clinical practice. Second, women who became pregnant during the PrEP trials described in this report were discontinued promptly from medication, so the safety of chronic fetal exposure could not be assessed adequately. Therefore, decisions to continue PrEP during pregnancy require additional consideration. Both TDF and FTC have been used among HIV-infected pregnant women to prevent perinatal transmission, have been studied for use by discordant couples attempting conception, and have been examined in antiretroviral treatment trials that included HIV-infected women who continued therapy during their pregnancies. Data from these sources and the Antiretroviral Use in Pregnancy Registry<sup>†</sup>

indicate no evidence of adverse effects among fetuses exposed to TDF or FTC (7). In addition, the higher risk for HIV transmission to uninfected women during pregnancy (compared with uninfected women who are not pregnant) might indicate an added value to continuing PrEP during pregnancy (8). Finally, sexual risk behaviors and adherence to PrEP medications among persons taking TDF/FTC for PrEP in clinical practice, when users are made aware of trial results, might be different from adherence by heterosexually active adults in PrEP trials who were unaware of their assignment to active drug or placebo and could not know the impact of adherence on efficacy.

### Recommendation for Clinicians

Daily oral TDF/FTC use in two studies has been shown to be safe in reducing the risk for sexual HIV acquisition by heterosexual women and men when consistently used. In a third study

<sup>†</sup> Available at <http://www.apregistry.com>.

with heterosexual women, PrEP was not found to be effective, and results are pending in a fourth study. The conflicting trial results for efficacy of TDF/FTC in heterosexual women can be partially explained by the low medication adherence in FEM-PrEP compared with the higher adherence in Partners PrEP and TDF2. As yet unidentified factors also might have influenced the results.

Until comprehensive PHS guidelines are available, CDC's January 2011 interim recommendations should help guide the use of PrEP in MSM (2). On the basis of the new data regarding PrEP use in heterosexually active adults, CDC now provides the following interim guidance for clinicians considering the use of PrEP for adults at very high risk for HIV acquisition through heterosexual sex (e.g., those with partners known to have HIV infection): 1) TDF/FTC is contraindicated for PrEP in persons with unknown or positive HIV status; 2) in women and men at very high risk for acquiring HIV from penile-vaginal sex, daily doses of TDF/FTC can be safe and effective in reducing the risk of HIV infection; 3) PrEP use may be one of several options (9,10) to help protect the HIV-negative partner in discordant couples during attempts to conceive; and 4) women of reproductive age should have a documented pregnancy test before beginning PrEP and if not pregnant at initiation, at regular intervals while being prescribed PrEP. If women are either pregnant before initiating PrEP or become pregnant while being prescribed PrEP, health-care providers should discuss currently available information regarding potential risks and benefits of continuing PrEP so that an informed decision can be made. If a woman takes PrEP while pregnant, providers are encouraged to prospectively and anonymously submit information about the pregnancy to the Antiretroviral Use in Pregnancy Registry.

Health-care providers should be aware, and should inform their patients that 1) the efficacy of TDF/FTC for HIV prevention is highly dependent on adherence to daily doses of medication, and 2) its long-term safety in HIV-uninfected adults or following fetal exposure is not yet determined. Health-care providers should report any serious adverse events resulting from prescribed TDF/FTC for PrEP to the FDA's MedWatch.<sup>§</sup>

CDC and other PHS agencies are developing PHS guidelines on the use of PrEP as part of a comprehensive set of HIV prevention services that will include specific recommendations for use with MSM and heterosexually active adults at very high risk for HIV acquisition. The guidelines will be updated as information about factors affecting efficacy and safety for all transmission risk groups becomes available from additional studies.

## Important Reminders

PrEP has the potential to contribute to safe and effective HIV prevention for heterosexually active adults as well as MSM. CDC

advises clinicians and patients to use this interim guidance as a basis to prescribe or use PrEP for heterosexually active patients until full PHS guidelines are available (Box). When PrEP is used by heterosexually active adults, it is important to ensure that 1) PrEP is targeted to persons at very high risk for HIV acquisition (11), especially uninfected persons whose regular sexual partners are known to have HIV infection; 2) the importance of adherence to daily medication and its influence on efficacy is clearly discussed; 3) couples understand that although no adverse effects have been found among infants exposed to TDF/FTC during pregnancy and breastfeeding, these data are incomplete for women in HIV-discordant couples using TDF/FTC to prevent acquisition of HIV; 4) PrEP is delivered as part of a comprehensive set of prevention services, including risk-reduction, PrEP medication adherence counseling, and ready access to condoms; 5) sexually transmitted infection treatment is provided when indicated by laboratory screening tests conducted at least every 6 months, and 6) PrEP is accompanied by monitoring of HIV status, pregnancy status, side effects, adherence, and risk behaviors at each quarterly follow-up visit.

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<sup>§</sup> Available at <http://www.fda.gov/safety/medwatch>.

**BOX. Interim guidance for health-care providers electing to provide preexposure prophylaxis (PrEP) for the prevention of human immunodeficiency virus (HIV) infection in heterosexually active adults who are at ongoing, very high risk for sexual acquisition of HIV infection\*****Before initiating PrEP***Determine eligibility*

- Document negative HIV antibody test immediately before starting PrEP medication.
- Test for acute HIV infection if patient has symptoms consistent with acute HIV infection or reports unprotected sex with an HIV-positive person in the preceding month.
- Determine if women are planning to become pregnant, are currently pregnant, or are breastfeeding.
- Confirm that patient is at ongoing, very high risk for acquiring HIV infection.
- If any sexual partner is known to be HIV-infected, determine whether receiving antiretroviral therapy; assist with linkage to care if not in care or not receiving antiretroviral therapy.
- Confirm that calculated creatinine clearance is  $\geq 60$  mL per minute (Cockcroft-Gault formula<sup>†</sup>).

*Other recommended actions*

- Screen for hepatitis B infection; vaccinate against hepatitis B if susceptible, or treat if active infection exists, regardless of decision regarding prescribing PrEP.
- Screen and treat as needed for sexually transmitted infections (STIs).
- Disclose to women that safety for infants exposed during pregnancy is not fully assessed but no harm has been reported.
- Do not prescribe PrEP to women who are breastfeeding.

**Beginning PrEP medication regimen**

- Prescribe tenofovir disoproxil fumarate (TDF) 300 mg plus emtricitabine (FTC) 200 mg (i.e., one Truvada [Gilead Sciences] tablet) daily.
- In general, prescribe no more than a 90-day supply, renewable only after HIV testing confirms that patient remains HIV-uninfected. For women, ensure that pregnancy test is negative or, if pregnant, that the patient has been informed about use during pregnancy.

- If active hepatitis B infection is diagnosed, consider using TDF/FTC, which may serve as both treatment of active hepatitis B infection and HIV prevention.
- Provide risk-reduction and PrEP medication–adherence counseling and condoms.

**Follow-up while PrEP medication is being taken**

- Every 2–3 months, perform an HIV antibody test (or fourth generation antibody/antigen test) and document negative result.
- At each follow-up visit for women, conduct a pregnancy test and document results; if pregnant, discuss continued use of PrEP with patient and prenatal-care provider.
- Evaluate and support PrEP medication adherence at each follow-up visit, more often if inconsistent adherence is identified.
- Every 2–3 months, assess risk behaviors and provide risk-reduction counseling and condoms. Assess STI symptoms and, if present, test and treat for STIs as needed.
- Every 6 months, test for bacterial STIs, even if asymptomatic, and treat as needed.
- Three months after initiation, then every 6 months while on PrEP medication, check serum creatinine and calculate creatinine clearance.

**On discontinuing PrEP (at patient request, for safety concerns, or if HIV infection is acquired)**

- Perform HIV test(s) to confirm whether HIV infection has occurred.
- If HIV-positive, order and document results of resistance testing, establish linkage to HIV care.
- If HIV-negative, establish linkage to risk reduction support services as indicated.
- If active hepatitis B is diagnosed at initiation of PrEP, consider appropriate medication for continued treatment of hepatitis B infection.
- If pregnant, inform prenatal-care provider of TDF/FTC use in early pregnancy and coordinate care to maintain HIV prevention during pregnancy and breastfeeding.

\* E.g., those with partners known to have HIV infection.

<sup>†</sup> Additional information available at Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31–41.

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