Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Weekly / Vol. 60 / No. 3
January 28, 2011

Interim Guidance: Preexposure Prophylaxis for the Prevention of HIV Infection in Men Who Have Sex with Men

An estimated 56,000 human immunodeficiency virus (HIV) infections occur each year in the United States (*1*). Men who have sex with men (MSM) account for 53% of the estimated incident infections, and surveillance data suggest that the annual number of new HIV infections among MSM has been rising since the mid-1990s (*1*). Strategies for reducing acquisition of HIV infection by MSM have included 1) expanded HIV testing so that infected persons can be treated and their risk for transmitting infection minimized; 2) individual, small-group, and community-level behavioral interventions to reduce risk behaviors (*2*); 3) promotion of condom use; 4) detection and treatment of sexually transmitted infections (*3*); and 5) mental health and substance abuse counseling when needed. On November 23, 2010, investigators for the Pre-Exposure Prophylaxis Initiative (iPrEX) study announced results from a multinational, randomized, double-blind, placebo-controlled, phase III clinical trial of daily oral antiretrovirals (tenofovir disoproxil fumarate [TDF] and emtricitabine [FTC]) to prevent acquisition of HIV infection among uninfected but exposed MSM (*4*). This report provides interim guidance to health-care providers based on the reported results of that trial, which indicated that TDF plus FTC taken orally once a day as preexposure prophylaxis (PrEP) is safe and partially effective in reducing HIV acquisition among MSM when provided with regular monitoring of HIV status and ongoing risk-reduction and PrEP medication adherence counseling.

The iPrEx study was conducted in Peru, Ecuador, Brazil, Thailand, South Africa, and the United States. Eligible participants were consenting HIV-uninfected men and male-to-female transgender adults (aged ≥18 years) who reported sex with a man and reported engaging in high-risk sexual behaviors during the preceding 6 months, and had no clinical contraindication to taking a combined formulation of 300 mg TDF and 200 mg FTC (TDF/FTC).*

Enrolled participants were randomized to receive either daily doses of TDF/FTC or a placebo pill. Participants were seen every 4 weeks for an interview, HIV testing, risk-reduction and PrEP medication adherence counseling, pill count, and dispensing of pills and condoms. Every 3 months, participants received physical examinations with collection of blood and urine samples for evaluation of renal and liver function, and were tested for sexually transmitted infections and treated as needed. Positive HIV rapid tests were confirmed by Western blot. The cohort was followed for an average 1.2 years with a maximum of 2.8 years. Participants were tested for hepatitis B infection at enrollment, and those found to be susceptible to hepatitis B infection were offered vaccination; 94% accepted.

Based on analysis of data from visits through May 1, 2010, for 2,499 enrolled participants (including 29 male-to-female transgender persons) in the modified "intent to treat" analysis (excluding 10 participants found to be HIV-infected at enrollment and 48 who did not have an HIV test after enrollment), 36 of 1,224 participants in the PrEP arm and 64 of 1,217 participants in the placebo arm who were followed for acquisition of HIV infection. Enrollment in the PrEP arm was associated with a 44% reduction in HIV acquisition (95% confidence interval [CI] = 15%–63%). The reduction was greater in the "as treated" analysis; participants at visits with ≥50% adherence by

* Marketed under the brand name Truvada (Gilead Sciences, Inc., Foster City, California).

INSIDE

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

self-report and pill count/dispensing had a 50% reduction in HIV acquisition (CI = 18%–70%). Reduction in risk for HIV acquisition was 21% among participants at visits with <90% adherence (CI = -31%–52%) and 73% at visits with ≥90% adherence (CI = 41%–88%). Among those randomly assigned to the TDF/FTC arm, drug level testing was performed for all HIV seroconverters and a matched subset of participants who remained uninfected; a 92% reduction in risk for HIV acquisition (CI = 40%–99%) was found in participants with detectable levels of TDF/FTC versus those with no drug detected. TDF/FTC generally was well tolerated, although nausea in the first month was more common among those taking medication than among those on placebo (9% versus 5%). No differences in severe (grade 3) or life-threatening (grade 4) laboratory abnormalities were observed between the active and placebo arms, and no drug-resistant virus was found in the 100 participants infected after enrollment. Among 10 participants who were seronegative at enrollment but later found to have been infected before enrollment, two cases of FTC resistance occurred in the active arm, and one occurred in the placebo arm. Participants in both arms reported lower total numbers of sex partners with whom the participants had receptive anal intercourse and higher percentages of partners who used condoms than reported at baseline.

What is already known on this topic?

HIV infections are increasing among men who have sex with men (MSM) in the United States despite awareness of HIV/AIDS and the protective effect of consistent condom use. A recent international study indicated that HIV infection among MSM can be reduced by daily preexposure prophylaxis (PrEP) with a well-tolerated combination of specific antiviral medications.

What is added by this report?

This report provides interim guidance for health-care providers in the United States based on results of the only large clinical trial testing the efficacy and safety of PrEP for reducing HIV acquisition by MSM.

What are the implications for public health practice?

For MSM whose behaviors place them at high risk for HIV infection and who do not use other effective prevention methods consistently, PrEP might reduce their risk for HIV infection. Until comprehensive U.S. Public Health Service guidelines are available, CDC is providing interim guidance to help guide clinical practice.

Reported by

DK Smith, MD, RM Grant, MD, PJ Weidle, PharmD, A Lansky, PhD, J Mermin, MD, KA Fenton, MD, PhD, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, CDC.

The *MMWR* series of publications is published by the Office of Surveillance, Epidemiology, and Laboratory Services, Centers for Disease Control and Prevention (CDC), U.S. Department of Health and Human Services, Atlanta, GA 30333.

Suggested citation: Centers for Disease Control and Prevention. [Article title]. MMWR 2011;60:[inclusive page numbers].

Editorial Note

This clinical trial demonstrated the safety and efficacy of daily TDF/FTC, in conjunction with behavioral interventions, in reducing sexual HIV acquisition in a multinational population of MSM exposed to HIV through high-risk sex (*4*). A recent safety study of PrEP with TDF among 400 MSM in the United States also revealed few safety concerns (*5*). As a component of a comprehensive HIV prevention intervention, PrEP showed a significant added benefit, although effectiveness was highly dependent on medication adherence.

The findings in this report are subject to at least five limitations. First, the trial was not large enough to evaluate efficacy in each of the sites, and the majority of the participants were in South America; only 10% were in the United States, making it impossible to determine effects on incidence in the United States trial sites specifically. Second, the assessment of adherence by drug-level testing was not performed for all trial participants and was performed for seroconverters at the first clinical visit in which infection was diagnosed; therefore, the findings might not reflect drug levels at the time of infection. Third, the study does not provide information about long-term health effects of TDF/FTC in HIV-uninfected men or men who became HIV-infected while on PrEP medications. Fourth, results of drug-level testing showed that adherence measures in the trial might overstate levels of actual adherence; many of those with high levels of adherence to the daily regimen by self-report, pill count, and bottles dispensed had low levels or no drug measured in their blood (*4*). Finally, sexual risk behavior and adherence to PrEP medications among MSM taking TDF/FTC for PrEP outside of a trial setting, and with awareness of trial results, might be different from what was observed for men in the iPrEx trial.

Based on the results of this study, CDC and other U.S. Public Health Service (PHS) agencies have begun to develop PHS guidelines on the use of PrEP for MSM at high risk for HIV acquisition in the United States as part of a comprehensive set of HIV prevention services. Completing the guidelines and obtaining expert input and public comment will take several months before they can be published. Concerns exist that without early guidance, various unsafe and potentially less effective PrEP-related practices could develop among health-care providers and MSM beginning to use PrEP in the coming weeks and months. These concerns include 1) use of other antiretrovirals than those so far proven safe for uninfected persons (e.g., more than two drugs or protease inhibitors); 2) use of dosing schedules of unproven efficacy (e.g., "intermittent" dosing just before and/or after sex); 3) not screening for acute infection before beginning PrEP or long intervals without retesting for HIV infection; and 4) providing prescriptions without other HIV prevention support (e.g., condom access and risk-reduction counseling). Until the more detailed PHS guidelines are available, CDC is providing interim recommendations to help guide clinical practice (*3,6–9*) (Box).

Until the safety and efficacy of PrEP is determined in trials now under way with populations at high risk for HIV acquisition by other routes of transmission (*10*), PrEP should be considered only for MSM. The iPrEX trial results provide strong evidence that support for adherence to the prescribed medication regimen must be a routine component of any PrEP program. To minimize the risk for drug resistance, PrEP should not be started in persons with signs or symptoms of acute viral infection unless HIV-uninfected status is confirmed by HIV RNA testing or a repeat antibody test performed after the viral syndrome resolves (*6*). When evaluating MSM for the prescription of PrEP medications, it is important to establish whether other effective risk-reduction measures (e.g., condom use) are not being used consistently and to ascertain that the risk for HIV acquisition is high (e.g., frequent partner change or concurrent partners in a geographic setting with high HIV prevalence) because these patients might benefit most from the addition of PrEP to their HIV prevention regimen. Health-care providers and patients should be aware that HIV prevention is not a labeled indication for the use of Truvada[†] and that its long-term safety in HIV-uninfected persons is not yet known. Health-care providers should report any serious adverse events resulting from prescribed TDF/FTC for PrEP to the Food and Drug Administration's MedWatch.[§] In addition, because the medication is costly, ensuring that patients understand the financial implications of starting PrEP is critical.

PrEP has the potential to contribute to effective and safe HIV prevention for MSM if 1) it is targeted to MSM at high risk for HIV acquisition; 2) it is delivered as part of a comprehensive set of prevention services, including risk-reduction and PrEP medication adherence counseling, ready access to condoms, and diagnosis and treatment of sexually transmitted infections; and 3) it is accompanied by monitoring of HIV status, side effects, adherence, and risk behaviors at regular intervals.

[†] These recommendations do not reflect current Food and Drug Administration–approved labeling for TDF/FTC.

[§] Available at http://www.fda.gov/safety/medwatch.

References

1. Hall HI, Song RG, Rhodes P, et al. Estimation of HIV incidence in the United States. JAMA 2008;300:520–9.
2. CDC. Diffusion of Effective Behavioral Interventions. Atlanta, GA: US Department of Health and Human Services, CDC; 2010. Available at http://www.effectiveinterventions.org/en/home.aspx. Accessed January 20, 2011.

BOX. CDC interim guidance for health-care providers electing to provide preexposure prophylaxis (PrEP) for the prevention of HIV infection in adult men who have sex with men and who are at high risk for sexual acquisition of HIV

Before initiating PrEP

Determine eligibility

- Document negative HIV antibody test(s) immediately before starting PrEP medication.
- Test for acute HIV infection if patient has symptoms consistent with acute HIV infection.
- Confirm that patient is at substantial, ongoing, high risk for acquiring HIV infection.
- Confirm that calculated creatinine clearance is ≥60 mL per minute (via Cockcroft-Gault formula).

Other recommended actions

- Screen for hepatitis B infection; vaccinate against hepatitis B if susceptible, or treat if active infection exists, regardless of decision about prescribing PrEP.
- Screen and treat as needed for STIs.

Beginning PrEP medication regimen

- Prescribe 1 tablet of Truvada* (TDF [300 mg] plus FTC [200 mg]) daily.
- In general, prescribe no more than a 90-day supply, renewable only after HIV testing confirms that patient remains HIV-uninfected.
- If active hepatitis B infection is diagnosed, consider using TDF/FTC for 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; document negative result.
- 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 STI as needed.
- Every 6 months, test for STI even if patient is asymptomatic, and treat as needed.
- 3 months after initiation, then yearly while on PrEP medication, check blood urea nitrogen and serum creatinine.

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 and 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.

Abbreviations: HIV = human immunodeficiency virus; STI = sexually transmitted infection; TDF = tenofovir disoproxil fumarate; FTC = emtricitabine.

Sources: CDC. Sexually transmitted diseases treatment guidelines, 2010. MMWR 2010;59(No. RR-12).

Schacker T, Collier AC, Hughes J, Shea T, Corey L. Clinical and epidemiologic features of primary HIV infection. Ann Intern Med 1996;125:257–64.

CDC. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part II: immunization of adults. MMWR 2006;55(No. RR-16).

Food and Drug Administration. Truvada: highlights of prescribing information (package insert). Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021752s017lbl.pdf. Accessed January 20, 2011.

Liaw YF, Chu CM. Hepatitis B virus infection. Lancet 2009;373:582–92.

* These recommendations do not reflect current Food and Drug Administration–approved labeling for TDF/FTC.

3. CDC. Sexually transmitted diseases treatment guidelines, 2010. MMWR 2010;59(No. RR-12).
4. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med 2010;363:2587–99.
5. Grohskopf L, Gvetadze R, Pathak S, et al. Preliminary analysis of biomedical data from the phase II clinical safety trial of tenofovir disoproxil fumarate (TDF) for HIV-1 pre-exposure prophylaxis (PrEP) among U.S. men who have sex with men (MSM). Presented at the 18th International AIDS Conference, Vienna, Austria, July 2010.
6. Schacker T, Collier AC, Hughes J, Shea T, Corey L. Clinical and epidemiologic features of primary HIV infection. Ann Intern Med 1996;125:257–64.
7. CDC. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part II: immunization of adults. MMWR 2006;55(No. RR-16).
8. Food and Drug Administration. Truvada: highlights of prescribing information (package insert). Available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021752s017lbl.pdf. Accessed January 20, 2011.
9. Liaw YF, Chu CM. Hepatitis B virus infection. Lancet 2009;373:582–92.
10. AIDS Vaccine Advocacy Coalition. Global advocacy for HIV prevention. Ongoing PrEP trials. Available at http://www.avac.org/ht/d/sp/i/3507/pid/3507. Accessed January 20, 2011.