WISCONSIN AIDS/HIV PROGRAM NOTES

June 2011

HIV Preexposure Prophylaxis: Recent Developments, Considerations and Interim Clinical Guidelines

Despite the progress that has been made in HIV prevention and care services over the past thirty years, an estimated 2.6 million persons worldwide, including 56,000 persons in the U.S., are newly infected with HIV each year. The prevalence of HIV infection remains high among men who have sex with men (MSM) and many MSM are unaware that they are infected. This is especially true among minority MSM, a group of men who are disproportionately affected by HIV. There is a growing need to expand new and effective HIV prevention methods, particularly ones that address populations at greatest risk, including MSM and populations in areas where HIV is spreading rapidly such as Africa, Asia, and South America.

On November 23, 2010, the National Institute of Allergy and Infectious Diseases (NIAID) at the National Institutes of Health (NIH) announced a major advance in HIV prevention. This development, known as preexposure prophylaxis or PrEP, is an HIV prevention strategy involving the use of HIV antiretrovirals (ARVs) to reduce the risk of HIV acquisition among HIV-negative persons. Until recently, the routine and widespread use of HIV-related PrEP has been limited to preventing perinatal transmission of HIV from an infected woman to her fetus/infant.

There have been two major studies reporting recent findings on the use of ARVs to reduce the risk of HIV infection in HIV-negative persons. The study known as PreExposure Prophylaxis Initiative (iPrEx) focused on men who have sex with men (MSM). The FEM-PrEP study examined the use of ARVs in preventing the acquisition of HIV by heterosexual women.

PreExposure Prophylaxis Initiative (iPrEx) clinical trial

NIAID's November 2010 historic announcement focused on a large international PrEP clinical trial known as iPrEx, a double-blind controlled trial and the only efficacy trial to date among MSM for the use of PrEP. iPrEx was sponsored by the NIH through a grant to the Gladstone Institutes, a nonprofit independent research organization affiliated with the University of California at San Francisco. Additional support for iPrEx was provided by the Bill and Melinda Gates Foundation.

Study findings demonstrated that, among MSM, a daily dose of an oral ARV drug reduced the risk of acquiring HIV infection by 43.9 percent. iPrEx was conducted at 11 sites in six countries (Brazil, Ecuador, Peru, South Africa, Thailand, and the United States) and enrolled a total of 2,499 HIV-negative MSM and transgender women who have sex with men.

Study participants were randomly assigned to receive either a daily placebo pill or a daily ARV tablet containing a combination of emtricitabine (FTC 200 mg.) and tenofovir (TDF 300 mg.), known by the brand name Truvada. The FTC/TDF combination of ARVs was selected for the iPrEx study because it has well established safety and efficacy profiles in managing HIV infection, both in clinical studies and medical settings.

All iPrEx study participants were routinely counseled about safe sex practices and provided condoms and treatment for other sexually transmitted diseases. One hundred cases of HIV infection occurred among study participants. Thirty-six HIV infections occurred among the 1,251 participants who received the study drug, compared with 64 HIV infections among the 1,248 participants who received the placebo. The reduction of risk of HIV acquisition was greater among study participants who more closely adhered to the daily drug regimen. Participants who took the drug on 50 percent or more days experienced 50.2 percent fewer HIV infections. Those who took the drug on 90 percent or more days had 72.8 percent fewer HIV infections.

Discontinuation of PrEP clinical trial for heterosexual women

On April 18, 2011, Family Health International (FHI) announced the closing of the FEM-PrEP study of HIV prevention among heterosexuals when data indicated that the trial could not demonstrate efficacy even if it continued to its planned conclusion. FEM-PrEP included nearly 2,000 women at high risk for HIV infection in three African nations and sought to determine if once-daily dosing of FTC/TDF could protect women from HIV infection. It is unclear what factors may have contributed to the FEM-PrEP preliminary outcomes. The CDC is working with FHI in closely examining data to assess any implications for ongoing research. Meanwhile, the CDC cautions against women, injection drug users, and heterosexual couples using PrEP for HIV prevention until conclusive results of FEM-PrEP and other trials are reported.

Considerations for public health

While the iPrEx study shows PrEP to be a potentially promising HIV prevention intervention for select high risk MSM, there are many questions and considerations regarding its implementation, some of which include the following:

- **Resource considerations:** The annual drug costs alone for FTC/TDF will most likely well exceed $7,000 and questions regarding insurance coverage are unanswered. The FDA has yet to officially approve FTC/TDF for PrEP. In addition to medication costs, there will be additional costs associated with ongoing medical monitoring, testing, and risk reduction counseling. For persons with health insurance, some will likely have concerns about maintaining privacy and elect not to utilize insurance coverage even when this is an option. Many MSM who are at high risk for HIV have limited financial resources and will not

be able to cover out-of-pocket expenses for these costs. There is the risk of some persons choosing to take PrEP ARVs intermittently in an effort to save costs. The cost/risk analyses of this intervention will likely be much higher than many HIV-related behavioral prevention interventions. There will likely be limited options for public health programs to implement PrEP widely for high risk MSM.

- **Behavioral considerations:** iPrEx study participants received a range of prevention interventions, including condoms, regular medical monitoring, treatment for sexually transmitted diseases, and risk reduction counseling. If similar services are not provided, some persons might be less likely to adhere to a daily regimen of PrEP and be less motivated to continue following proven prevention methods such as consistent condom use and other safer sex practices.

- **Drug resistance and side effects:** Even though the safety and effectiveness profiles of FTC/TDF are well established in the management of HIV infection, there are unanswered questions regarding development of drug resistance during the long-term use of FTC/TDF in HIV-negative persons. While side effects are less common, renal and liver complications have been reported. This requires that ongoing medical monitoring be part of health routines for anyone participating in PrEP.

CDC's interim guidance on HIV-related PrEP for high risk MSM

The Centers for Disease Control and Prevention (CDC) and other Public Health Service (PHS) agencies are developing guidelines on the use of PrEP for MSM at high risk for HIV as part of a comprehensive set of HIV prevention services. It will take several months before guidelines are finalized. Meanwhile, there are several concerns about possible inappropriate use of PrEP during this interim period, including:

1. use of other ARVs that are not 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 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 CDC and other PHS agencies finalize their clinical guidelines, the CDC released the following interim guidance on January 28, 2011.

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.
- Three 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). Available at: http://www.cdc.gov/std/treatment/2010/STD-Treatment-2010-RR5912.pdf. Accessed June 7, 2011.

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. Available at: http://www.annals.org/content/125/4/257.full.pdf+html. Accessed June 7, 2011.

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). Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5516a1.htm. Accessed June 7, 2011.

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.

In developing these interim guidelines, the CDC identified five specific limitations that should be noted regarding iPrEx findings:

1. the trial size was not sufficient to evaluate efficacy in each site and the majority of participants were in South America (only 10% were in the U.S.);
2. because assessment of adherence by drug level testing was not performed for all trial participants and was performed for seroconverters at first clinical visit when

infection was diagnosed, findings might not reflect drug levels at time of infection;
3. there is no information about long term health effects of TDF/FTC in HIV-uninfected men or men who became HIV-infected while on PrEP medications;
4. adherence measures in the trial might overstate levels of actual adherence since many participants with evidence or reports of high levels of daily adherence to the regimen had low levels or no drug measured in their blood; and
5. sexual risk behavior and adherence to PrEP medications among MSM taking TDF/FTC for PrEP outside of a trial setting may be different from that observed in the iPrEx study.

At this time, the Wisconsin Division of Public Health (DPH) does not recommend routine use of PrEP for the prevention of HIV infection in HIV-negative persons. Additional research is needed before recommendations on the wider application of PrEP can be made for MSM who are at high, ongoing risk of HIV infection. The DPH will carefully monitor future research findings and recommendations for clinical implementation. Clinicians who are considering the use of PrEP among MSM are encouraged to follow CDC's interim guidance, highlighted in this article, and future guidance from the CDC.

For more information

For additional information regarding the iPrEx clinical trials and considerations for implementation of PrEP among high risk MSM, visit the following resources on the web:

AIDS Vaccine Advocacy Coalition
http://www.globaliprex.com/web/index.do

Centers for Disease Control and Prevention
http://www.cdc.gov/hiv/prep/

Family Health International
http://www.fhi.org/en/AboutFHI/Media/Releases/FEM-PrEP_statement041811.htm

Gladstone Institutes, University of California, San Francisco
http://www.gladstone.ucsf.edu/gladstone/site/publicaffairs/content/1/707

National Alliance of State & Territorial AIDS Directors
http://www.nastad.org/Docs/Public/Resource/20101123_Global%20iPrEX%20MSM%20Efficacy%20Study%20Fact%20Sheet.pdf

National Institutes of Health
http://www.niaid.nih.gov/news/QA/Pages/iPrExQA.aspx

New England Journal of Medicine
http://www.nejm.org/doi/full/10.1056/NEJMoa1011205