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**Clinical Advisory**  
**Pre-Exposure Prophylaxis (PrEP) for HIV Infection**  
Using Truvada<sup>®</sup> (emtricitabine/tenofovir disoproxil fumarate)  
**Updated: September 2016**

The U.S. Centers for Disease Control and Prevention (CDC) recommends that pre-exposure prophylaxis (PrEP) be considered as one of several prevention options for persons at high risk for HIV acquisition, including men who have sex with men (MSM), transgender women who have sex with men, persons in a sexual relationship with one or more HIV+ partners, and persons who inject drugs (PWID). The CDC provides guidelines at <http://www.cdc.gov/hiv/pdf/PrEPguidelines2014.pdf>. Consistent with the CDC's recommendation, the Massachusetts Department of Public Health (MDPH) supports the use of Truvada<sup>®</sup> for PrEP for HIV-uninfected persons who inject drugs (PWID) and other persons at higher risk of acquiring HIV infection through sex.

### Background

On July 16, 2012, the Food and Drug Administration (FDA) approved the use of Truvada<sup>®i</sup> for pre-exposure prophylaxis (PrEP) for HIV-uninfected individuals at high risk of sexually acquired HIV infection. CDC also recommends PrEP for HIV-uninfected adults with a history of sharing injection or drug preparation equipment in the last 6 months.<sup>ii</sup> Truvada<sup>®</sup> [emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF)] is an oral, antiretroviral combination medication that has been approved for the treatment of HIV infection since 2004. Truvada<sup>®</sup> PrEP offers an evidence-based approach to preventing the acquisition of HIV infection in certain circumstances, and should be considered when those circumstances are present. This clinical advisory provides background on PrEP, evidence of the efficacy of Truvada<sup>®</sup> as PrEP, guidelines for appropriate use, and sources of further information.

### Clinical Trials<sup>iii</sup>

Clinical trials in several populations have demonstrated efficacy of Truvada<sup>®</sup> as PrEP to prevent HIV acquisition in HIV-uninfected individuals when combined with counseling about safer sex and other risk reduction methods. Clinical trials included:

iPrEx<sup>iv</sup> - a randomized double-blind placebo-controlled multinational study evaluating Truvada<sup>®</sup>. All subjects received monthly HIV testing, risk-reduction counseling, condoms, and management of sexually transmitted infections (STI). The Truvada<sup>®</sup> group achieved a 44% (95% CI: 15% to 63%) reduction of HIV infection as compared to the placebo group.

Partners PrEP<sup>v</sup> - a randomized, double-blind, placebo-controlled three-arm trial conducted in Kenya and Uganda to evaluate the efficacy and safety of TDF alone and Truvada<sup>®</sup> versus placebo in preventing HIV

acquisition by the uninfected partner. The risk reduction for Truvada<sup>®</sup> relative to placebo was 75% (95% CI: 55% to 87%).

**TDF2<sup>vi</sup>** - a randomized, double-blind, placebo-controlled trial of Truvada<sup>®</sup> conducted in Botswana with low retention. All subjects received counseling for risk reduction, screening and treatment for STI, and monitoring for adverse events. Overall efficacy was 62% (95% CI: 22% to 83%); however, efficacy was not statistically significantly better than placebo in women.

**Fem-PrEP<sup>vii</sup>** - a randomized, double-blind, placebo-controlled trial of Truvada<sup>®</sup> combined with counseling in women in Kenya, South Africa, and Tanzania, which **failed** to reduce the rate of HIV infection. Inadequate adherence seems to have undermined the trial's ability to assess efficacy.

**Bangkok Tenofovir Study<sup>viii</sup>** – a randomized, double-blind, placebo-controlled trial conducted to determine the safety and efficacy of tenofovir disoproxil fumarate (TDF) in preventing HIV acquisition among IDUs in Bangkok, Thailand. All subjects received HIV testing, risk reduction counseling, hepatitis B vaccine, monitoring for adverse events; and were offered methadone treatment, condoms, and bleach to clean injection equipment. Female participants were provided with contraceptives. Directly observed therapy (DOT) was available to participants. TDF decreased the risk of HIV infection by 49% (95% CI: 10% -72%).

Clinical Trials and Other Studies: Truvada <sup>®</sup> as pre-exposure prophylaxis to prevent HIV acquisition						
Study	Population	No. and sex of participants	mITT* % reduction in HIV incidence (95% CI)			% reduction in HIV incidence with TDF blood detection† (95% CI)
iPrEx	Men who have sex with men	2,499 (100% male)	44% (15%–63%)			92% (40%–99%)
			All	Men	Women	
Partners PrEP	Heterosexual HIV-discordant couples	4,758 couples (38% with female HIV+ partner)	75% (55%–87%)	84% (54%–95%)	66% (28%–84%)	90% (58%–98%)
TDF2	Heterosexual men and women	1,216 (46% female)	62% (22%–83%)	80% (25%–97%)	49% (-21%–81%, NS)	84% (-62%–98%, NS)
FEM-PrEP	Heterosexual women	2,056 (100% female)	NS	-	NS	NS
Bangkok Tenofovir Study	Injecting drug using men and women	2,413 (20% female)	49% (10-72%)	38% (-18-68%)	79% (17-97%)	70% (2% - 91%)
Ipergay	Men and who have sex with men	400 (100% male)	-	86% (40%-99%)	-	-
Kaiser Permanente	Men who have sex with men	657 (99% male)	100%§			-

Abbreviations: mITT = modified intent to treat analysis; CI = confidence interval; NS = finding not statistically significant at p=0.05.

\*Excluded only those enrolled participants later found to be infected at randomization and those with no follow-up visit or HIV test.

†The percentage of reduction in HIV incidence among persons with TDF detected in blood, compared with those without detectable TDF.

§ At 388 person-years of PrEP use.

In these five clinical trials, resistance to FTC and TDF was observed in some participants who were unknown to be acutely HIV infected upon initiation or who seroconverted during the trial. Therefore, the potential for HIV drug resistance in persons taking PrEP does exist if acute HIV infection is not ruled out on initiation of PrEP or in cases of PrEP failure, which is most likely due to poor adherence. Poor adherence makes selection of resistant viral strains more likely.

A study of “on demand” PrEP with Truvada<sup>®</sup> in the United Kingdom in men who have sex with men who took PrEP before or after high risk sexual activity demonstrated an 86% (40-98%) reduction in HIV infection.<sup>ix</sup> On-demand PrEP refers to a dosing schedule where PrEP is taken intermittently, or only around times of sexual activity instead of every day.<sup>x</sup> Participants took a median of 15 doses of Truvada<sup>®</sup> or placebo per month. While adherence to daily dosing is important when PrEP is used routinely, even intermittent situational PrEP (or post-exposure prophylaxis) may offer significant prevention advantage.

### **Important Considerations**

In determining the appropriateness of Truvada<sup>®</sup> as PrEP, the following points should be considered:

- The majority of available data on efficacy of PrEP are from clinical trials. One recent, observational study by Kaiser Permanente in San Francisco found no new HIV infections among patients on PrEP during more than 32 months of observation. Additional experience outside of a research environment is needed to assess effectiveness in the "real world."
- In the absence of an HIV prevention vaccine, Truvada<sup>®</sup> as PrEP presents an evidence-based prevention option for individuals at high risk of sexual and drug-injection associated acquisition of HIV infection.<sup>xi</sup>
- In all of the trials, Truvada<sup>®</sup> was only one part of a multi-component intervention. Truvada<sup>®</sup> was combined with relatively intensive, standard behavioral interventions, including risk reduction counseling, condom distribution, frequent HIV and STI testing, prompt STI treatment for newly diagnosed infections, and partner services. In the Bangkok Tenofovir Study, IDUs were provided with bleach to clean drug injection equipment and were offered methadone treatment.
- All but one of the published studies were done in the developing world. The iPrEx trial included men who have sex with men (MSM) and transgender women who have sex with men from the United States along with subjects at similar risk from five other countries.
- Adherence to therapy, with adequate blood/tissue levels of active antiviral agents, appears to be the most important determinant of efficacy of Truvada<sup>®</sup> as PrEP.
- While Truvada<sup>®</sup> combined with other antiviral medications is well tolerated in patients being treated for HIV infection, the clinical trials reported variable, but in some instances not insignificant, levels of nausea, vomiting, and dizziness (particularly during the initiation phase), as well as some evidence of diminished bone density, serum creatinine changes, lactic acidosis, and abnormal hepatic

transaminase values. Adverse events in long term administration of Truvada<sup>®</sup> in HIV-uninfected individuals have not been fully assessed. However, in a recent analysis the case is made that, in the short and medium term, user safety of PrEP compares favorably with use of daily aspirin.<sup>xii</sup>

- Among serodiscordant sexual partners, a protection rate of 92- 96% has been demonstrated for the HIV-uninfected partner when the HIV-positive partner is treated early, and effectively with highly active antiretroviral therapy.<sup>xiii,xiv</sup> Thus, "treatment as prevention" may be the best option for stable discordant partnerships.

### **Initiating PrEP**

Research studies demonstrating efficacy of oral PrEP have involved particular high-risk populations, concomitant standardized behavioral interventions, fairly intensive support services, and use of Truvada<sup>®</sup>. Generalizability to other and broader population groups needs further assessment. Use of other antiviral regimens for PrEP cannot be recommended.

In light of the data available from clinical trials and the considerations above, the MDPH identifies certain high risk individuals who may particularly benefit from PrEP, and who should be evaluated for their risk for HIV acquisition, as well as readiness and clinical eligibility for PrEP.

PrEP should only be prescribed for persons who are confirmed to be HIV-uninfected:

- Men who have sex with men (including transgender men) who currently have recent, repeated, condomless anal sex;
- Transgender females who currently have repeated, condomless, anal and/or vaginal sex with men
- Members of heterosexual, serodiscordant couple wishing to conceive and who have been educated about the potential risks/benefit
- Other individuals in a sexual relationship with a known HIV+ partner
- Injecting drug users at risk for HIV acquisition through blood exposure secondary to sharing injection equipment, for whom other HIV prevention strategies are not expected to be effective
- Individuals with recent and/or repeated diagnoses of syphilis, rectal gonorrhea or rectal chlamydia infection indicating risk for HIV infection
- Individuals otherwise deemed appropriate by the prescribing clinician

Once a candidate for PrEP is confirmed at high risk for HIV infection:

- HIV infection should be ruled out by HIV antibody/antigen testing using a 4<sup>th</sup> generation HIV assay.<sup>xv</sup>
- If signs and symptoms suggestive of acute HIV infection are present, rule out acute infection using an RNA test.<sup>xvi</sup> PrEP should not be initiated until results are known.
- The PrEP candidate should be screened for STI and viral hepatitis, and immunized against hepatitis A and B, if susceptible.
- Possible drug interactions should be ruled out.<sup>xvii</sup>

- Female candidates should be tested for pregnancy. If a patient takes PrEP while pregnant, or becomes pregnant during use of PrEP, providers are encouraged to prospectively submit de-identified patient information to the *Antiretroviral Pregnancy Registry*.<sup>xviii</sup>
- Confirm creatinine clearance is greater than or equal to 60mL/min (using the Cockcroft-Gault formula)<sup>xix</sup>

Truvada<sup>®</sup> is excreted via the kidney, and increased drug levels can accumulate with renal impairment. Renal impairment also has been reported with use of TDF. PrEP is not recommended for individuals with creatinine clearance of <60 mL per minute, and all patients treated with Truvada<sup>®</sup> should have renal function monitored three months after initiation and every six months thereafter while using the PrEP regimen.

### **Recommended Protocol**

Tenofovir disoproxil fumarate (TDF) 300 mg plus emtricitabine (FTC) 200 mg, as one Truvada<sup>®</sup> tablet, daily. At this time, the MDPH does not recommend intermittent PrEP based on periodic risk behavior due to questions about the ability of most individuals to correctly anticipate their high-risk behaviors, and concern about the development of antiviral resistance.

### **Follow-up and Discontinuation**

The CDC provides guidance for clinicians on the use of PrEP, with detailed recommendations for follow-up of patients on PrEP in *Preexposure Prophylaxis for the Prevention of HIV Infection in the United States – 2014 Clinical Practice Guideline*.<sup>xx</sup>

Key points for follow-up include ongoing risk reduction, PrEP adherence counseling and ongoing provision of condoms to support sexual risk reduction. Drug injectors should have access to sterile injection equipment, naloxone to prevent overdose, and referral to opioid replacement therapy and/or other drug treatment.

- Every 2-3 months:
  - HIV antibody/antigen testing (4<sup>th</sup> generation)
  - Pregnancy testing for women
  - Evaluation of adherence and need for more intensive support services
  - Screening/treating for STIs and hepatitis C infection
  - Monitoring serum creatinine 3 months after initiation and every 6 months thereafter
- Report adverse events to FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)

Key indications for discontinuation include:

- If the patient tests positive for HIV infection or acute infection is suspected
- If the patient wishes to discontinue treatment
- If the patient is clinically diagnosed with any medical condition or has an abnormal laboratory value inconsistent with the safe administration of Truvada<sup>®</sup> as PrEP
- If the patient expresses diminishing commitment to the treatment protocol

## ADDITIONAL RESOURCES

- Truvada<sup>®</sup> was approved by the FDA with a Risk Evaluation and Mitigation Strategy (REMS). A detailed description of this strategy as well as a list of educational resources for health care professionals is available at <https://www.truvadapreprems.com>.
- The CDC offers current PrEP information and links to additional resources at [www.cdc.gov/hiv/prep](http://www.cdc.gov/hiv/prep) including:
  - [Update to Interim Guidance for Preexposure Prophylaxis \(PrEP\) for the Prevention of HIV Infection: PrEP for Injecting Drug Users](#)
  - [Preexposure Prophylaxis for the Prevention of HIV Infection in the United States – 2014 Clinical Practice Guideline](#).
- Massachusetts Department of Public Health  
<http://www.mass.gov/eohhs/gov/departments/dph/programs/id/hiv-aids/pre-exposure-prophylaxis-prep.html>
- Project Inform at <http://www.projectinform.org/prep/>
- U.S. Department of Health and Human Services Health Resources and Services Administration *Guide to HIV/AIDS Clinical Care* <http://hab.hrsa.gov/deliverhivaidscares/clinicalguide11>

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<sup>i</sup> Emtricitabine/tenofovir disoproxil fumarate (TDF/FTC, Truvada®, Gilead)

<sup>ii</sup> CDC. Preexposure Prophylaxis for the Prevention of HIV Infection in the United States – 2014 Clinical Practice Guideline. At: <https://www.cdc.gov/hiv/pdf/prepguidelines2014.pdf>. Accessed: July 15, 2016

<sup>iii</sup> Further details about completed and ongoing clinical trials can be found at [www.avac.org/ht/d/sp/i/326/pid/326](http://www.avac.org/ht/d/sp/i/326/pid/326).

<sup>iv</sup> 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.

<sup>v</sup> Baeten JM, Donnell D, Ndase P, et al. Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women. *N Engl J Med* 2012; 367:399-410.

<sup>vi</sup> Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral Preexposure Prophylaxis for Heterosexual HIV Transmission in Botswana. *N Engl J Med* 2012;367:423–34.

<sup>vii</sup> Van Damme L, Corneli A, Ahmed K, et al. Preexposure Prophylaxis for HIV Infection Among African Women. *N Engl J Med* 2012;367:411–22.

<sup>viii</sup> Choopanya K, Martin M, Suntharasamai P, et al. Antiretroviral Prophylaxis for HIV Infection in Injecting Drug Users in Bangkok, Thailand (the Bangkok Tenofovir Study): A Randomised, Double-Blind, Placebo-Controlled Phase 3 Trial. *The Lancet* 2013. Published online June 13, 2013 [http://dx.doi.org/10.1015/S0140-6736\(13\)61127-7](http://dx.doi.org/10.1015/S0140-6736(13)61127-7).

<sup>ix</sup> 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; 373:2237-46.

<sup>x</sup> <http://betablog.org/demand-prep-shows-high-efficacy-iper-gay-trial>

<sup>xi</sup> The FDA has approved use of Truvada as PrEP for men who have sex with men and heterosexual men and women. Use of Truvada as PrEP for injection drug users currently represents off-label use.

<sup>xii</sup> Kojima N, Klausner JD. Is emtricitabine-tenofovir disoproxil fumarate pre-exposure prophylaxis for the prevention of human immunodeficiency virus infection safer than aspirin? *Open Forum Infect Dis*. 2016 Jan 6;3(1):ofv221. doi: 10.1093/ofid/ofv221.

<sup>xiii</sup> Donnell D, Baeten JM, Kiarie J, et al. Heterosexual HIV transmission after initiation of antiretroviral therapy: a prospective cohort analysis. *Lancet* 2010; 375:2092-8.

<sup>xiv</sup> Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV Infection with Early Antiretroviral Therapy. *N Engl J Med* 2011; 365:493-505.

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<sup>xv</sup> Development of HIV antibodies can take weeks to months. In June of 2010, a 4th generation HIV diagnostic test was approved by the FDA. This highly sensitive test can detect p24 antigen as well as HIV antibodies thus reducing the time from exposure to detection.

<sup>xvi</sup> Acute retroviral syndrome symptoms appear 2-6 weeks post HIV exposure in close to 70% of those infected. Symptoms may include: fever, rash, fatigue, pharyngitis, generalized lymphadenopathy, urticaria, myalgia, arthralgia, anorexia, mucocutaneous ulceration, headache, retroorbital pain and neurologic symptoms.

<sup>xvii</sup> Full prescribing information can be found at <http://www.truvada.com>.

<sup>xviii</sup> An Antiretroviral Pregnancy Registry (APR) has been established. Register patients by calling 1-800-258-4263.

<sup>xix</sup> See: <http://reference.medscape.com/calculator/creatinine-clearance-cockcroft-gault>. Accessed: July 15, 2016.

<sup>xx</sup> CDC. Preexposure Prophylaxis for the Prevention of HIV Infection in the United States – 2014 Clinical Practice Guideline. At: <https://www.cdc.gov/hiv/pdf/prepguidelines2014.pdf>. Accessed: July 15, 2016.