

Guidance for the use of Pre-Exposure Prophylaxis (PrEP) for the prevention of HIV acquisition in British Columbia

(Guidelines are for information purposes only, and do not imply BC-CfE endorsement or recommendations regarding provincial funding of PrEP in British Columbia)

Background

Pre-exposure prophylaxis (PrEP) refers to the use of daily oral antiretroviral therapy (ART) by HIV negative individuals to reduce the risk of acquiring HIV infection. In this context, PrEP refers to ongoing use of ART prior to (and after) potential exposure to HIV, which differs from standard post-exposure prophylaxis (PEP) where a short course of ART is used following high-risk exposure. Since 2010, four randomized controlled trials involving men who have sex with men (MSM), heterosexual HIV-serodiscordant couples, and people who inject drugs (PWID) have been published showing efficacy of tenofovir-based PrEP (alone or in combination with emtricitabine) as part of an HIV prevention package in individuals with high levels of adherence to medication [1, 2, 3, 4]. Tenofovir-emtricitabine (Truvada) was approved by the US Food and Drug Administration for use as PrEP on the basis of the results of the iPrEx trial [1] in July of 2012 [5]. The United States Centers for Disease Control and Prevention (US CDC) then published interim guidance for the use of PrEP for MSM, which has since been updated to include heterosexual HIV-serodiscordant couples and the PWID population [6, 7] following the results of The Partners PREP Trial, The TDF2 Trial, and the Bangkok Tenofovir Study [2-4]. In 2014, the US CDC released comprehensive clinical practice guidelines for the use of PrEP in the United States [8].

In 2012, the World Health Organization (WHO) released guidance on the use of PrEP for MSM, serodiscordant couples, and transgender females [9]. These guidelines were formulated by WHO in order to encourage demonstration projects aimed at better understanding the societal, cultural and individual factors that may influence the success or failure of PrEP as an HIV prevention tool.

Currently, no antiretroviral medications in Canada are licensed specifically for PrEP; however, physicians may choose to prescribe these medications for **off-label use**, and individuals who receive a prescription for PrEP may pay for it themselves, or in some instances may receive coverage through third-party (private) insurance plans. As such, the Therapeutic Guidelines Committee has been tasked to provide guidance for the use of tenofovir-emtricitabine in the context of PrEP. This information is provided to assist physicians in determining how to use and appropriately monitor patients who are receiving PrEP. **It is important to note the development of this document does not imply any recommendations regarding funding of PrEP in British Columbia.**

Guidance on the use of HIV Pre-Exposure Prophylaxis (PrEP)

(Adapted from references 6,7,8)

Before starting PrEP

- Confirm that patient is at ongoing, **high risk** for acquiring HIV infection.
 - For MSM, this will usually consist of having one or more of the following:
 - One or more HIV-positive sexual partner(s), particularly if the HIV positive partner is not receiving stable ART and/or does not have a consistently undetectable viral load¹
 - Recent (within 6 months) sexually transmitted infection (STI)
 - Multiple sex partners
 - History of inconsistent or no condom use for anal intercourse
 - Involvement in commercial sex work
 - Repeated courses of non-occupational post-exposure prophylaxis (nPEP)
 - For heterosexual men or women, this will usually consist of one or more of the following:
 - One or more HIV-positive sexual partner(s), particularly if the HIV

¹ For individuals in a stable, monogamous relationship with an HIV positive individual, the use of effective antiretroviral therapy by the HIV positive individual as demonstrated by a sustained undetectable HIV viral load has been shown to significantly reduce the risk of HIV transmission by 96% [10]. The added value of PrEP in this setting has not been evaluated, but should be discussed.

- positive partner is not receiving stable ART and/or does not have a consistently undetectable viral load^{1, 2}
 - Involvement in commercial sex work
 - Having sexual partners who are MSM or use injection drugs or who are involved in commercial sex work
 - For people who use injection drugs, this will usually consist of:
 - Sharing injection equipment
 - Injecting once or more times per day in an unsafe setting (outside of safe injection sites)
 - Injecting cocaine or methamphetamine
 - Repeated courses of non-occupational post-exposure prophylaxis (nPEP)
- Confirm negative HIV antibody test immediately before starting PrEP medication, using a 4th generation HIV Antibody/Antigen enzyme immunoassay (EIA).
 - If symptoms suggestive of acute HIV infection within the previous 6 weeks are present, and/or history of high-risk unprotected sex in the previous month, a pooled nucleic acid amplification test (NAAT) for HIV RNA is recommended. This test can be arranged by contacting a virologist at the BC Centre for Disease Control (BCCDC) (604-707-5600). Defer PrEP initiation until acute HIV infection is ruled out.
- For heterosexual women, determine if there are immediate plans to become pregnant, or if the woman is currently pregnant or breastfeeding, as this may alter the risk/benefit ratio for PrEP².
- Confirm adequate renal function: calculated creatinine clearance or estimated glomerular filtration rate (eGFR) ≥ 60 mL per minute, and absence of proteinuria

²For HIV serodiscordant couples planning to become pregnant, pre-assessment counselling regarding the use of PrEP should include information on maximal risk reduction, alternate options for conception and ensuring that timing of intercourse is planned around most fertile period of the menstrual cycle. Clinicians should contact a qualified specialist or The Oak Tree Clinic at BC Women's Hospital (604-875-2212; 1-888-711-3030) for more detailed information.

- on urinalysis and/or quantitative test (urine albumin to creatinine ratio [UACR]).
- Screen for hepatitis B and C virus (see Table 2) and vaccinate against hepatitis B if non-immune. If hepatitis B infection is diagnosed, refer for expert opinion regarding need for hepatitis B treatment.
 - Screen and treat for other sexually transmitted infections (STIs: gonorrhea, chlamydia, syphilis).
 - Review current medications for drug interactions and overlapping toxicities with tenofovir (TDF)/emtricitabine (FTC). Since TDF and FTC are primarily renally eliminated, there is a potential for drug interaction and increased nephrotoxicity with other agents that can affect renal function or compete for active tubular secretion, e.g. acyclovir, valacyclovir, cidofovir, ganciclovir, valganciclovir, aminoglycosides, non-steroidal anti-inflammatory drugs (NSAIDs) [11].
 - As TDF has been associated with decreases in bone mineral density in both HIV treatment and PrEP settings [12-14], it should be used with caution in persons with a history of fragility fractures or significant risk factors for osteoporosis.
 - Counsel with regard to adherence, risk reduction, and need to seek immediate attention for management if symptoms of acute HIV develop.

Prescribing PrEP medication

- Prescribe 1 tablet of Truvada (tenofovir disoproxil fumarate (TDF) 300 mg with emtricitabine (FTC) 200 mg) to be taken once per day. As there are currently no data available regarding the efficacy of intermittent or event-driven PrEP, it is recommended that TDF/FTC should be prescribed and taken on a regular daily basis.
- Prescribe a 30-day supply initially, then reassess for adherence and tolerability. Prescriptions should be renewed only after repeat HIV testing confirms that the patient remains HIV-negative and eligibility criteria persist. Repeat prescriptions should be provided and reassessment performed at intervals not longer than 90

days.

- For women, ensure that pregnancy test is negative or, if pregnant, that the patient has been informed about the potential risks and benefits of PrEP during pregnancy.
- Provide additional HIV risk-reduction and PrEP medication-adherence counseling and condoms.
 - Adherence counseling should emphasize that efficacy of PrEP was greatly reduced amongst individuals who did not take the medication as prescribed, i.e. one pill once-a-day.
 - The time from initiation of daily oral doses of TDF/FTC to maximal protection against HIV infection is unknown. However, pharmacokinetic data from HIV-infected individuals suggest that steady-state level in the rectal mucosa is reached after 7 days and in the cervico-vaginal mucosa after 20 days of initiating therapy [15, 16].

Follow-up while PrEP is being prescribed

- **After first month, then at least every 3 months thereafter:**
- Monitor HIV antibody status using the 4th generation HIV Antibody/Antigen EIA and document negative status.
- Assess for symptoms of acute HIV since last visit. If symptoms present, perform a pooled HIV RNA NAAT and consult with an expert physician regarding ongoing TDF/FTC use while awaiting test results.
- Check serum creatinine and urinalysis and/or UACR. If there are signs of new persistent or worsening renal dysfunction, additional work up and consultation with a nephrologist are recommended.

- 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.
- Assess risk behaviours and provide risk-reduction counseling and condoms.
- **At least every 6 months:**
- Test for STIs and hepatitis C even if asymptomatic, and treat as needed.

Stopping PrEP

- Order HIV antibody tests as above to document current HIV status.
- If HIV positive, order and document results of HIV resistance testing, and establish linkage to HIV care.
- If HIV negative, establish linkage to risk reduction support services as indicated.
- If patient is being treated for active hepatitis B, ensure appropriate specialist referral prior to stopping PrEP. If patient was receiving treatment for active hepatitis B prior to PrEP, these medications will need to be re-initiated for hepatitis B management following withdrawal of TDF/FTC.
- If pregnant, inform prenatal care provider of TDF/FTC use in early pregnancy and coordinate care to maintain HIV prevention during pregnancy and breastfeeding. Perform HIV testing in each trimester and prior to delivery to ensure seroconversion during pregnancy has not occurred.

(Guidelines are for information purposes only, and do not imply BC-CfE endorsement or recommendations regarding provincial funding of PrEP in British Columbia)

Table 1: SUMMARY OF GUIDANCE FOR PREP USE IN BRITISH COLUMBIA (Adapted from Reference 8)

	Men who have sex with men	Heterosexual men and women	People who use injection drugs
Detecting substantial risk of acquiring HIV infection	HIV-positive sexual partner ¹ Recent STI Multiple sex partners History of inconsistent or no condom use Commercial sex work	HIV-positive sexual partner ¹ Recent STI Multiple sex partners History of inconsistent or no condom use Commercial sex work	HIV-positive injecting partner ¹ Sharing injection equipment
Clinically eligible	Documented negative HIV test result before prescribing PrEP No signs/symptoms of acute HIV infection Normal renal function; no contraindicated medications Documented hepatitis B virus infection status and vaccination status		
Prescription	Daily, continuing, oral doses of tenofovir /emtricitabine (Truvada); 30-day supply initially, then ≤90-day supply on a continuing basis if adherence, tolerability, and eligibility confirmed		
Other services	Follow-up visits after 1 month and at least every 3 months thereafter , to provide the following: HIV test, assess renal function, medication adherence counseling, behavioural risk reduction support, side effect assessment, STI symptom assessment Every 6 months, test for STIs		
	Do oral/rectal STI testing	Assess pregnancy intent Pregnancy test every 3 months	Access to clean needles/syringes and drug treatment services

¹ For individuals in a stable, monogamous relationship with an HIV positive individual, the use of effective antiretroviral therapy by the HIV positive individual as demonstrated by a sustained undetectable HIV viral load has been shown to significantly reduce the risk of HIV transmission by 96% [10]. The added value of PrEP in this setting has not been evaluated.

Table 2: Summary of testing recommendations during PrEP

Assay Type	Baseline	After first month then Q3 months	Q 6 months
HIV Serology (4 th Generation Antibody/Antigen Assay)	X	X	
HIV RNA Pooled NAAT Test - for those with symptoms of acute HIV	X	X	
Hepatitis B Screen (Hepatitis B Surface Antigen, surface antibody, core antibody)*	X*		
Hepatitis C Screen (Hepatitis C Antibody)	X		X
Gonorrhea screen [^] (urine GC NAT test, throat and rectal swabs for GC depending on type of sexual activity reported)	X		X
Chlamydia Screen [^] (Chlamydia urine NAT test)	X		X
Syphilis Screen [^] (T. pallidum EIA)	X		X
Creatinine and urinalysis	X	X	

* Hepatitis B Vaccine should be initiated in unvaccinated individuals. [^] Individuals diagnosed with concurrent STI should be offered standard therapy following Provincial Guidelines

(Guidelines are for information purposes only, and do not imply BC-CfE endorsement or recommendations regarding provincial funding of PrEP in British Columbia)

References

1. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, *et al.* Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men. *The New England Journal Of Medicine* 2010,**363**:2587-2599.
2. Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, *et al.* Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *The New England Journal Of Medicine* 2012,**367**:423-434.
3. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, *et al.* Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *The New England Journal Of Medicine* 2012,**367**:399-410.
4. Choopanya K, Martin M, Suntharasamai P, Sangkum U, Mock PA, Leethochawalit M, *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. *Lancet* 2013,**381**:2083-2090.
5. US Food and Drug Administration. Truvada approved to reduce the risk of sexually transmitted HIV in people who are not infected with the virus. Washington, D.C.: US Food and Drug Administration; 2012.
6. US Centers for Disease Control and Prevention. Interim Guidance: Preexposure Prophylaxis for the Prevention of HIV Infection in Men Who Have Sex with Men. *MMWR* 2011,**60**:65-68.
7. US Centers for Disease Control and Prevention. Update to Interim Guidance for Preexposure Prophylaxis (PrEP) for the Prevention of HIV Infection: PrEP for Injecting Drug Users. *MMWR* 2013,**62**:463-465.
8. US Public Health Service. Preexposure Prophylaxis for the Prevention of HIV Infection in the United States – 2014 Clinical Practice Guideline. In: US Centers for Disease Control and Prevention; US Department of Health and Human Services; 2014. www.cdc.gov/hiv/pdf/prepguidelines2014.pdf
9. World Health Organisation. Guidance on oral pre-exposure prophylaxis (PrEP) for serodiscordant couples, men and transgender women who have sex with men at high risk of HIV: recommendations for use in the context of demonstration projects. In. Geneva, CH: World Health Organisation; 2012. http://apps.who.int/iris/bitstream/10665/75188/1/9789241503884_eng.pdf
10. Cohen MS, Chen YQ, McCauley M, *et al.* Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* 2011;**365**:493-505.
11. Gilead Sciences Canada, Inc. Truvada Product Monograph. Sept. 5, 2013.
12. McComsey GA, Tebas P, Shane E, *et al.* Bone disease in HIV infection: A practical review and recommendations for HIV care providers. *Clin Infect Dis.* 2010;**51**:937-946.

13. Mulligan K, Glidden D, Gonzales P, et al. Effects of emtricitabine/tenofovir on bone mineral density in seronegative men from 4 continents: DEXA results of the global iPrEx study. Paper presented at:18th Conference on Retroviruses and Opportunistic Infections 2011; Boston, Massachusetts. Abstract 94LB.
14. Liu AY, Vittinghoff E, Sellmeyer DE, et al. Bone mineral density in HIV-negative men participating in a tenofovir pre-exposure prophylaxis randomized clinical trial in San Francisco. *PloS One*. 2011;6(8):e23688. doi:23610.21371/journal.pone.0023688.
15. Anderson PL KJ, Gardner EM, Rower JE, Meditz A, Grant RM. Pharmacological considerations for tenofovir and emtricitabine to prevent HIV infection. *Journal of Antimicrob Chemother*. 2011,66:240-250.
16. Patterson KB PH, Kraft E, et al. Penetration of tenofovir and emtricitabine in mucosal tissues: implications for prevention of HIV-1 transmission. *Sci Transl Med*. 2011,3:112 - 114.