BRITISH COLUMBIA
CENTRE *for* EXCELLENCE
in HIV/AIDS

GUIDANCE FOR THE USE OF PRE-EXPOSURE PROPHYLAXIS (PREP) FOR THE PREVENTION OF HIV ACQUISITION IN BRITISH COLUMBIA

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Providence HEALTH CARE
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I 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 post-exposure prophylaxis (PEP) where a short course of ART is used following a high-risk exposure event. Since 2010, six 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 that tenofovir DF based PrEP (in combination with emtricitabine, or in two studies as tenofovir DF alone) is effective as part of an HIV prevention package in individuals with high levels of adherence to medication (1-6). Tenofovir DF/emtricitabine (TDF/FTC; Truvada®) was approved by the US Food and Drug Administration for use as PrEP in July 2012 (7). In 2014, the United States (US) Centers for Disease Control and Prevention (CDC) released comprehensive clinical practice guidelines for the use of PrEP in the US (8). In 2015, the World Health Organization (WHO) released updated guidance on the use of PrEP for HIV prevention in populations at risk for HIV (9).

II PrEP IN BC

Emtricitabine-tenofovir DF was licensed for use as HIV PrEP by Health Canada in February 2016. Effective January 1, 2018, access to PrEP in BC is available through the BC-CfE at no cost to qualifying individuals deemed clinically at risk of HIV infection.

The Committee for Drug Evaluation and Therapy at the BC Centre for Excellence in HIV/AIDS has been tasked to provide guidance to BC clinicians for the use of TDF/FTC in the context of PrEP. This information is provided to assist clinicians in determining when and how to prescribe PrEP and how to appropriately monitor patients who are receiving PrEP.

These updated clinical practice guidelines reflect a detailed assessment of the epidemiology of new HIV infections and diagnoses within BC, and where PrEP may have maximal impact at reducing HIV transmission. Note that for each recommendation, a level of evidence is noted based on the GRADE criteria (10).

Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Code	Quality of Evidence	Definition
A	High	Further research is very unlikely to change our confidence in the estimate of effect. • Several high-quality studies with consistent results • In special cases: one large, high-quality multi-centre trial

Code	Quality of Evidence	Definition
B	Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. • One high-quality study • Several studies with some limitations
C	Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. • One or more studies with severe limitations
D	Very Low	Any estimate of effect is very uncertain. • Expert opinion • No direct research evidence • One or more studies with very severe limitations

It is important to note that these Guidelines are for information purposes only, and do not imply recommendations regarding provincial funding of PrEP in British Columbia.

III GUIDANCE ON THE USE OF HIV PRE-EXPOSURE PROPHYLAXIS (PrEP)

1. Recommendations for PrEP in Men Who Have Sex With Men (MSM) and Transgender Women (TGW):

PrEP is recommended for MSM and TGW at high risk of acquiring HIV infection (GRADE A recommendation for MSM; GRADE B recommendation for TGW).

High risk is defined as reporting condomless anal sex **and** having **any** of the following:

a. Infectious syphilis or rectal bacterial sexually transmitted infection (STI), particularly if diagnosed in the preceding 12 months.

b. Use of non-occupational post-exposure prophylaxis (nPEP) on more than one occasion.

c. Ongoing sexual relationship with an HIV-positive partner who is not receiving stable ART and/or does not have an HIV viral load <200 copies/ mL.

d. HIV Incidence Risk Index for men who have sex with men (HIRI-MSM) score ≥10 (See Table 1)

PrEP should be part of a combination prevention strategy that includes behavioural interventions such as condoms and risk reduction counseling. All HIV-negative MSM and TGW reporting condomless anal sex within the last 6 months should be counselled about PrEP.

Rationale for use of PrEP in MSM and TGW in BC:

1. MSM constitute the largest at-risk population in BC, making up over 50% of all new HIV diagnoses in the province (11).
2. The overall HIV incidence for MSM attending STI clinics in BC from 2003 – 2013 was 1.0 per 100 person-years (12). Among MSM in the Momentum Study in Vancouver from 2012-2015, HIV incidence was also 1.1 per 100 person-years (13). A number of factors have been demonstrated to increase HIV risk. Prior diagnosis of bacterial STIs such as syphilis and rectal gonorrhea have been demonstrated to impart a higher risk for HIV infection (11). This finding has been validated in the STI clinic analysis in BC where risk of HIV following a diagnosis of syphilis was 3.6 per 100 person-years, and following rectal gonorrhea was 4.5 per 100 person-years. Following a dual diagnosis of rectal gonorrhea and syphilis, the HIV risk was 17.0 per 100 person-years (12). In the Momentum study, a history of any previous STI diagnosis was associated with an HIV incidence rate of 4.8 per 100 person-years (13).
3. Non-occupational post-exposure prophylaxis (nPEP) has been used to prevent HIV following high risk consensual sexual and needle sharing encounters. Individuals who access nPEP more than once have been found to have a high risk of HIV infection, with repeat users initiating nPEP for receptive condomless anal sex in Vancouver demonstrating an HIV incidence of 7.1 per 100 person-years (14).
4. The risk of HIV transmission is greater with increasing plasma HIV viral load in HIV-positive individuals (15-18). HIV-positive individuals who have had documented suppressed viral load (<200 copies/mL) have negligible risk of transmitting HIV through sexual exposure. The PARTNERS cohort study followed 340 HIV serodiscordant MSM couples and reported 22,000 episodes of condomless sex, during which the HIV-positive partner had an HIV viral load <200 copies/mL on ART (19). In a median of 1.4 years of follow-up, no genetically linked transmissions were documented (with an upper limit to the 95% confidence interval 0.71 per 100 couple-years for anal sex) (19).
5. Use of validated clinical assessment tools such as the HIRI-MSM (Table 1) is a clinically useful strategy that can identify MSM at higher risk of seroconversion. A HIRI-MSM score ≥10 has high sensitivity to detect incident HIV infection (20). Use of HIRI-MSM has been validated in the Momentum study where risk of HIV infection among individuals with a HIRI-MSM score of ≥10 was approximately 2.0 per 100 person-years of follow-up. For those with score >25 the risk was 7.0 per 100 person-years (13), in comparison to an overall HIV incidence rate of 1.1 per 100 person years among all MSM in the study(12). Among those with HIRI-MSM score of <10, there were no HIV incident cases in a median of 2.23 years of follow-up (13).

6. Only one randomized trial, iPrex(1) included TGW and then only 1% of participants were TGW. As such the evidence for effectiveness for PrEP is less certain for TGW who have sex with men than for cis-gendered MSM.

2. Recommendations for PrEP in Heterosexual Men and Women

PrEP is recommended for heterosexual men and women at high risk of acquiring HIV infection (GRADE B recommendation).

High risk is defined as reporting condomless vaginal or anal sex and meeting the following additional criteria:

a. Ongoing sexual relationship with an HIV-positive partner who is not receiving stable ART and/or does not have an HIV viral load <200 copies/mL.

Rationale for use of PrEP in heterosexual men and women in BC:

1. For heterosexual men or women in BC, new HIV infections are extremely rare (approximately 65 cases per year)(11) relative to the size of the heterosexual population of approximately 4 million. Among individuals newly diagnosed with HIV in the province from 2008-2015 who reported only heterosexual exposures, approximately 48% reported that they had a sexual partner who was known to be HIV-positive (21).

2. In the HPTN052 randomized trial of 1763 serodiscordant couples (97% of whom were heterosexual), early initiation of ART was associated with a 96% reduction in transmission (hazard ratio [HR]: 0.04; 95% confidence interval [CI]: 0.01-0.27); only one of 28 linked transmission events occurred in those randomized to early ART, three months after the person's HIV-positive partner initiated ART (22). No infections were seen in those who had been receiving treatment for greater than three months (23). The PARTNERS cohort study evaluated HIV transmission in 548 HIV serodiscordant heterosexual couples reporting 36,000 episodes of condomless sex, during which the HIV-positive partner had an HIV viral load <200 copies/mL on ART (19). In a median of 1.9 years of follow-up, no genetically linked transmissions were documented.

3. Among individuals newly diagnosed with HIV from 2008-2015 in BC who reported only heterosexual exposures, only 5% reported participating in sex work. Sex work is more commonly reported (11%) among individuals newly diagnosed with HIV who report injection drug use as a potential route of HIV exposure (21). A recent analysis from the VIDUS study also found that sex work itself was not associated with HIV incidence when adjusting for other risk factors among individuals who use injection drugs (24). As such sex work itself is not sufficient to warrant a separate consideration for PrEP to prevent heterosexual transmission unless the above criteria are met.

4. Heterosexual exposure to partners who have other risk factors for HIV are reported relatively rarely. Of individuals newly diagnosed with HIV from 2008 - 2015 whose only exposure was through heterosexual sex, 6% reported having a sexual partner who was MSM, another 6% reported that their partner had a history of injection drug use, and 13% were from countries with high HIV prevalence (21). As such, having a sexual partner with

additional risk factors or being from an endemic country are not sufficient to warrant specific consideration for PrEP unless the above criteria are met.

3. Recommendations for PrEP in Persons who Inject Drugs (PWID)

PrEP is recommended for PWID who are at high risk of acquiring HIV infection (GRADE B recommendation).

High risk is defined as reporting sharing of injection equipment **and** meeting the following additional criteria:

a. Having an HIV-positive injecting partner who is not receiving stable ART **and/or** does not have an HIV viral load <200 copies/mL.

b. All PWID who report these risk behaviours should be actively referred to harm reduction services.

Rationale for use of PrEP in PWID in BC:

1. BC has seen a dramatic decrease in new HIV diagnoses among people who use injection drugs, from 125 per year in 2005 to 25 in 2015 (11). Furthermore, in the VIDUS and ARYS cohorts of PWID in Vancouver, the incidence of HIV infection since 2008 has been 0.28 per 100 person-years (25). While risk factors for HIV transmission among PWID through VIDUS have been identified (24), none of them would impart an expected risk of HIV acquisition of >1 per 100 person-years.
2. Among PWID newly diagnosed with HIV from 2008-2015, 43% reported have an injecting partner who is HIV-positive and 48% reported sharing injection equipment (21).
3. While the effectiveness of HIV treatment in reducing transmission risk among PWID has not been well studied, it is assumed to be similar in magnitude to the effectiveness of treatment in reducing HIV transmission through vaginal or anal intercourse. An observational study of PWID in Vancouver from 1996-2007 found large decreases in HIV incidence from a peak of 12 per 100 person-years to a low of <1 per 100 person years, which paralleled decreases in the median viral load due to expanded use of ART among HIV-positive PWID during the same period (26).

IV ASSESMENT FOR PrEP

1. Confirm negative HIV antigen/antibody (Ag/Ab) test immediately before starting PrEP medication, using a 4th generation HIV Ag/Ab enzyme immunoassay (EIA).
    - » If symptoms suggestive of acute HIV infection within the previous 6 weeks are present, and/or history of high-risk condomless 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.

2. 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 PrEP[1].

3. Confirm adequate renal function: calculated creatinine clearance or estimated glomerular filtration rate (eGFR) ≥60 mL per minute, and absence of proteinuria 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 TDF/FTC PrEP is to be prescribed for a person with chronic hepatitis B virus (HBV) infection, appropriate HBV monitoring should be performed in accordance with HBV treatment guidelines, and referral to a qualified practitioner with HBV treatment experience is recommended.**

4. Screen and treat for other STIs (gonorrhea, chlamydia, syphilis) following Canadian Guidelines (27).

5. Review current medications for overlapping toxicities with TDF/FTC. Since TDF and FTC are primarily renally eliminated, there is a potential for increased nephrotoxicity with other agents that can affect renal function or compete for active tubular secretion, i.e. acyclovir, valacyclovir, and non-steroidal anti-inflammatory drugs (NSAIDS) (28).

6. As TDF has been associated with decreases in bone mineral density in both HIV treatment and PrEP settings (12, 29-32), it should be used with caution in persons with a history of osteoporosis or osteomalacia, fragility fractures, or significant risk factors or secondary causes (long-term glucocorticoid therapy, androgen deprivation therapy for prostate cancer, hypogonadism, primary hyperparathyroidism, and intestinal disorders) for osteoporosis. At present, no specific bone mineral density screening is recommended before or during PrEP use.

7. Counsel regarding adherence, risk reduction, and need to seek immediate medical attention if symptoms of acute HIV develop.

V PRESCRIBING PrEP MEDICATION

- Prescribe 1 tablet of tenofovir disoproxil fumarate (TDF) 300 mg/emtricitabine (FTC) 200 mg to be taken once per day. As there are currently data available regarding the efficacy of intermittent or event-driven PrEP from only one clinical trial (IPERGAY) (5), it is recommended that TDF/FTC should be prescribed and taken on a daily basis.
- 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

1 For 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 and Health Centre (604-875-2212; 1-888- 711-3030) for more detailed information.

after 20 days of initiating therapy (31, 33). Individuals should be counselled to continue safer sex practices during this period.

- 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.
- Regularly review ongoing HIV risk exposures and need for ongoing PrEP.
- Review additional HIV risk reduction counselling and PrEP medication-adherence counseling.
    - » Adherence counselling 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.

VI 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 Ag/Ab EIA and document negative status.
    - » Assess for symptoms of acute HIV since last visit (34). If symptoms are present, consider requesting a HIV RNA NAAT by consulting the medical microbiologist on call at the BCCDC Public Health Laboratory (604-661-7033) and consult with a physician with expertise in acute HIV infection regarding ongoing TDF/FTC use while awaiting test results.
    - » Check serum creatinine and urinalysis and/or UACR. If there are signs of new or worsening renal dysfunction, additional work up and consultation with a nephrologist are recommended. Also consider PrEP discontinuation to prevent further renal impairment.
    - » At each follow-up visit perform full STI screens for syphilis, gonorrhea, and chlamydia from all appropriate body sites. Quarterly monitoring was performed in most PrEP studies, and a recent analysis in the US found that 20-40% of STIs would have been missed if screening was conducted only twice yearly in MSM (35).
    - » 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, and more often if inconsistent adherence is identified.
    - » Assess risk behaviours and need for ongoing PrEP; provide risk-reduction counselling and condoms.
    - » Assess for syndemic mental health issues and addictions which might be contributing to HIV risk and refer to appropriate management services.

- **At least every 6-12 months:**
    - » Test for hepatitis C (unless already known to be hepatitis C positive), particularly in PWID and in MSM reporting use of crystal methamphetamine (36).

VII STOPPING PrEP

- Individuals may stop PrEP for multiple reasons, including a change in HIV risk status, financial coverage concerns, or personal choice.
- If PrEP is to be halted, the optimal duration of PrEP continuation after a recent sexual exposure is unclear. PrEP should be continued for at least 48 hours after a high risk exposure (based on data derived from the IPERGAY trial (5)); however, continued use for as long as 28 days after a high risk exposure is recommended by some groups (37).
- Order HIV Ag/Ab 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 PrEP is to be resumed in the future, baseline assessment for HIV Ag/Ab status should be performed before resuming (see Assessment for PrEP).
- 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.

TABLE 1: HIV INCIDENCE RISK INDEX FOR MEN WHO HAVE SEX WITH MEN (HIRI-MSM).

MSM Risk Index		
1. How old are you today?	If <18 years, score 0 If 18-28 years, score 8 If 29-40 years, score 5 If 41-48 years, score 2 If 49 years or more, score 0	
2. In the last 6 months, how many men have you had sex with?	If >10 male partners, score 7 If 6-10 male partners, score 4 If 0-5 male partners, score 0	
3. In the last 6 months, how many times did you have receptive anal sex (you were the bottom) with a man without a condom?	If 1 or more times, score 10 If 0 times, score 0	
4. In the last 6 months, how many of your male sex partners were HIV-positive?	If >1 positive partner, score 8 If 1 positive partner, score 4 If 0 positive partner, score 0	
5. In the last 6 months, how many times did you have insertive anal sex (you were the top) without a condom with a man who was HIV-positive?	If 5 or more times, score 6 If 0-4 times, score 0	

MSM Risk Index		
6. In the last 6 months, have you used meth-amphetamines such as crystal or speed?	If yes, score 6 If no, score 0	_____
Add down entries in right to calculate total score		_____ **Total Score***

***If score is 10 or greater, evaluate for intensive HIV prevention services including PrEP.**
If score is below 10, provide indicated standard HIV prevention services.

TABLE 2: SUMMARY OF GUIDANCE FOR PREP USE IN BC (ADAPTED FROM US FOOD AND DRUG ADMINISTRATION (7))

	Men who have sex with men	Heterosexual men and women	People who use injection drugs
Detecting substantial risk of acquiring HIV infection	Reports condomless sex and at least one of: • Diagnosis of syphilis or rectal gonorrhea or chlamydia within last 12 month; or • Ongoing sexual relationship with an HIV-positive partner who is not receiving stable ART and/or does not have a viral load consistently <200 copies/mL; or • Repeated courses of nPEP; or • HIRI-MSM score ≥10	Reports condomless vaginal or anal sex **and** HIV-positive sexual partner not receiving stable ART **and/or** does not have a viral load consistently <200 copies/mL*	Reports sharing injection equipment **and** HIV-positive injecting partner not receiving stable ART **and/or** does not have a viral load consistently <200 copies/mL*
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 Avoid in patients with documented osteoporosis or osteomalacia		
Prescription	Daily, continuing, oral doses of tenofovir DF/emtricitabine; 30-day supply initially, then ≤90-day supply on a continuing basis if adherence, tolerability, and eligibility confirmed		

<table>
<tr><th></th><th>Men who have sex with men</th><th>Heterosexual men and women</th><th>People who use injection drugs</th></tr>
<tr><td rowspan="2">Other services</td><td colspan="3">Follow-up visits after 1 month and at least every 3 months thereafter, to provide the following:
HIV test, assess renal function, medication adherence counselling, behavioural risk reduction support, side effect assessment, STI symptom assessment.</td></tr>
<tr><td>Do urethral/oral/rectal STI testing every 3 months</td><td>Assess pregnancy intent
Pregnancy test every 3 months</td><td>Access to clean needles/syringes and drug treatment services</td></tr>
</table>

*For 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 and Health Centre (604-875-2212; 1-888- 711-3030) for more detailed information.

TABLE 3: SUMMARY OF TESTING RECOMMENDATIONS DURING PrEP.

Assay Type	Baseline	After first month then Q3 months	Q 6 months
HIV Serology (4th Generation Ab/Ag 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, if not known to be hepatitis C positive)	X		X (for PWID and MSM)

Assay Type	Baseline	After first month then Q3 months	Q 6 months
Gonorrhea screen^ (urine NAAT test, throat and rectal swabs for gonorrhea depending on type of sexual activity reported)	X	X (for MSM)	X
Chlamydia Screen ^ (Chlamydia urine NAAT test; throat and rectal swabs for chlamydia depending on type of sexual activity reported)	X	X (for MSM)	X
Syphilis Screen^ (T. pallidum EIA)	X	X (for MSM)	X
Creatinine and urinalysis or Urine albumin to creatinine ratio	X	X	
Pregnancy test (for women of child-bearing potential)	X	X	

*Hepatitis B Vaccine should be initiated in unvaccinated individuals who are anti-HBs Ab negative. ^ Individuals diagnosed with concurrent STI should be offered standard therapy following Canadian Guidelines (27).

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