Canadian HIV Pre-exposure Prophylaxis and Non-Occupational Post Exposure Prophylaxis DRAFT Guidelines – Executive Summary May 12, 2016 Preliminary Version

Background

Populations including men who have sex with men, persons who inject drugs, women and men engaged in survival sex trade work, certain Canadian aboriginal populations and other groups have an elevated incidence of HIV. Individuals in these communities remain at risk for HIV infection (Tables 1 and 2), and biomedical prevention strategies including pre-exposure prophylaxis (PrEP) and non-occupational post-exposure prophylaxis (nPEP) should be considered a key potential component of combination prevention strategies.

Definitions: Throughout this document, we distinguish between three categories for the risk of HIV transmission per act from an HIV-positive source: high, moderate, and low (Table 6a). These categories apply to the behaviour. We also distinguish between three categories for the likelihood that a given person (eg. patient's sexual partner) has transmissible HIV infection: significant, non-negligible and negligible/none (Table 6b). These categories apply to the person and timepoint.

A) General recommendations

1. PrEP and nPEP should be part of a combination prevention strategy that includes behavioural interventions such as condoms and risk reduction counseling [Grade 1A].

2. Health systems should strive to engage a broad number and range of qualified clinical providers in prescribing and providing follow-up for PrEP and nPEP, including family and specialist physicians, nurses, nurse practitioners, and pharmacists, where provincial scope of practice allows, or under appropriate delegation of responsibility [Grade 1D].

3. Non-prescribing healthcare and service providers should be encouraged to play roles in PrEP and nPEP delivery including clinical monitoring, STI screening and management, risk reduction counseling and adherence support [Grade 2D].

4. Linkages to PrEP prescribers should be readily accessible from multiple access points, including HIV counselling/testing centres; STI, prenatal and family planning clinics [Grade 1C].

5. Mechanisms for formal consultation within institutions, regionally and provincially regarding PrEP and nPEP should be readily available to support health care providers [Grade 1C].

6. PrEP and nPEP providers should be prepared to provide rapid linkage to HIV care for those who test HIV+ during follow-up for PrEP/nPEP [Grade 1C].

B) Recommendations regarding the use of HIV pre-exposure prophylaxis (PrEP) in Canada

B1) ELIGIBILITY FOR PrEP

Gay, bisexual and other men who have sex with men (MSM), and transgender women (TGW)

7. HIV-negative MSM and TGW reporting condomless anal sex within the last 6 months should be counselled and evaluated for the appropriateness of PrEP [Grade 1D]. PrEP is not recommended in the context of a stable closed relationship with a single partner with no/negligible risk of having transmissible HIV [Grade 1C]. PrEP is strongly recommended for MSM [Grade 1A] and TGW [Grade 1B] reporting condomless anal sex within the last 6 months who have any of the following:

    a) Bacterial STI diagnosed or reported in last 12 months
    b) HIRI-MSM risk score ≥11 (*Table to be added*)
    c) Ongoing sexual relationship with HIV positive partner with significant risk of transmissible HIV
    d) Prior use of nPEP

Heterosexual men and women

8. We recommend PrEP for heterosexual serodiscordant couples reporting condomless vaginal or anal sex where the HIV-positive partner has a significant risk of having transmissible HIV [Grade 1A].

9. PrEP may be considered for heterosexual serodiscordant couples reporting condomless vaginal or anal sex where the HIV-positive partner has a non-negligible risk of having transmissible HIV [Grade 1B]. This includes HIV-negative women attempting to conceive with an HIV-positive partner who has a non-negligible risk of having transmissible HIV infection [Grade 2D].

Injection drug use

10. PrEP may be considered for people who inject drugs in whom other harm reduction interventions (eg. needle exchange, opioid substitution therapy) have already been implemented [Grade 2B].

B2) PROVISION OF PrEP

11. PrEP clinical encounters should include patient counseling on risk reduction strategies [Grade 1A], medication adherence [Grade 1B], potential drug toxicities [Grade 1D] and strategies to minimize those risks [Grade 2D].

Recommended PrEP Regimens

12. Daily tenofovir DF/emtricitabine 200/300mg, is recommended for PrEP [Grade 1A].

13. As an alternative, in MSM, tenofovir DF/emtricitabine 200/300 mg administered “on demand” (2 pills at once 2-24 hours before 1st sexual exposure, followed by one pill daily until 48 hours after last sexual activity) may be considered [Grade 2A].

14. Upon PrEP discontinuation, we recommend that PrEP be continued for at least 48 hours after the last risk exposure [Grade 1B].

Evaluation and monitoring before, during and after PrEP

15. As a component of a complete medical history and physical examination (see guideline for full recommendations) we recommend that individuals seeking PrEP be evaluated for signs or symptoms suggestive of acute HIV infection (see Table 4) within the last 12 weeks [Grade 1D].

16. Baseline HIV status should be determined using a laboratory-based 4th generation assay when available, or alternative (see Table 3) for all people in whom PrEP is being considered [Grade 1C].

17. If acute HIV infection is suspected (See table 4) then additional laboratory evaluation with HIV RNA NAAT test (if available) or repeat 4th generation assay 7-21d later is recommended, and PrEP initiation should be deferred [Grade 1C].

18. A serum creatinine (with eGFR >60 mL/min) is recommended for use of tenofovir- based PrEP [Grade 1C].

19. Routine DXA to assess bone mineral density is not recommended unless otherwise indicated according to Osteoporosis Canada guidelines at baseline or during PrEP use [Grade 1B]. TDF/FTC PrEP may be considered in persons with low bone mass or osteoporosis after discussion of the risks and benefits [Grade 2D].

20. Additional laboratory monitoring of baseline hepatic and renal function, STI and hepatitis co-infection is recommended for patients on PrEP (See full guidelines & Table 5 for details), with appropriate therapy and vaccination for non-immune individuals [Grade 1C].

21. We recommend follow-up clinical and laboratory evaluation for HIV infection, medication toxicity (after 30 days and every 3 months thereafter) and incident STI/hepatitis infections (every 3 and 12 months respectively thereafter as indicated by ongoing risk exposures) for patients on PrEP (See Table 5) [Grade 1C].

22. Pregnancy screening in women of child-bearing potential using PrEP is recommended every 3 months [Grade 1D].

23. Upon PrEP discontinuation, we recommend HIV testing using a laboratory-based 4th generation assay when available, or alternative (see Table 3) [Grade 1C].

PrEP use in special populations – hepatitis B infection

24. If TDF/FTC PrEP is prescribed in a person infected with hepatitis B, appropriate HBV monitoring should be performed in accordance with Hepatitis B treatment guidelines in consultation with a qualified practitioner with HBV treatment experience [Grade 1D]

25. When considering PrEP discontinuation, assessment of the need for ongoing HBV therapy should be undertaken. If PrEP is discontinued and no other HBV therapy is used, monitoring for a flare of HBV is recommended [Grade 1D].

PrEP use in special populations – pregnancy and breastfeeding

26. TDF/FTC PrEP may be considered during pregnancy and breastfeeding after discussion of the risks and benefits with the mother [Grade 2D].

C) Recommendations regarding the use of non-occupational HIV post-exposure prophylaxis (nPEP) in Canada

27. We recommend that health care providers who undertake initial assessment for nPEP distinguish between consensual and non-consensual exposures, and provide or refer to sexual assault services when appropriate [Grade 1C].

28. Medications for nPEP should be readily available in emergency departments, clinics and pharmacies where they are likely to be needed urgently [Grade 1D].

C1) ELIGIBILITY FOR nPEP

29. We recommend nPEP for HIV-negative individuals who, within the last 72 hours, have had an exposure that is moderate- or high-risk for HIV transmission with a person who has a significant risk of having transmissible HIV (See Table 6 for definitions) [Grade 1C].

30. nPEP can be considered for HIV-negative individuals who, within the last 72 hours, had an exposure that is moderate- or high-risk for HIV transmission with a person who has a low but non-negligible risk of having transmissible HIV [Grade 2C].

31. We recommend initiating nPEP as soon as possible after exposure, up to a maximum of 72 hours after a potential exposure or exposures to HIV [Grade 1D].

32. Symptoms suggestive of acute HIV infection should not preclude initiation of nPEP [Grade 1C], however additional laboratory evaluation for acute HIV infection is recommended in this circumstance (see Table 3).

33. If the exposed individual is subsequently found to be HIV-positive and has started on nPEP, the antiretroviral regimen should be continued and consultation with an HIV expert as soon as possible is recommended [Grade 1C].

34. We recommend that individuals who are taking PrEP as prescribed (whether as continuous or on-demand use) do not require nPEP after potential HIV exposures [Grade 1B].

35. In a person who is not using PrEP as prescribed, initiation of nPEP may be considered as per the recommendations above. [Grade 2C].

C2) PROVISION OF nPEP

Recommended nPEP Regimens

36. A standard regimen containing three antiretroviral agents should be used whenever nPEP is indicated [Grade 1C].

37. The following regimens are recommended as first-line regimens for nPEP (see Table 7 for comparison of regimens):

    a) INSTI-based regimen: TDF/FTC 1 tablet PO daily and raltegravir 400mg PO BID [Grade 1A], or
    b) PI-based regimen: TDF/FTC 1 tablet PO daily and darunavir/ritonavir 800/100 mg PO daily [Grade 1A]

38. Alternative regimens for nPEP can be considered based on clinical judgement and availability of agents (see Table 7 for details and grading).

39. If the source individual is known/suspected to have HIV drug resistance, a PI-based regimen should be initiated, and consultation with an HIV specialist is recommended. [Grade 1D].

40. Use of a PI-based regimen should be considered when the source or exposed individual is suspected to have increased risk of acute HIV infection at time of nPEP assessment [Grade 2D].

41. When the indication for nPEP is clearly established, the full course of PEP may be dispensed from the outset, rather than using a starter pack [Grade 2A].

Duration of nPEP

42. nPEP should be prescribed to complete a 28-day course [Grade 1D].

43. nPEP can be extended for an additional 48 hours after a repeat high-risk exposure occurring on day 27 or 28 of nPEP [Grade 2B].

44. If ≥72 hours of nPEP have been missed, discontinuation of nPEP should be considered [Grade 2D].

Evaluation of the Source:

Source: HIV status unknown:

45. If the source is available and provides consent, HIV testing with a 4th generation assay is recommended [Grade 1C].

46. If the source is suspected of having acute HIV infection (See table 4) then additional laboratory evaluation with an HIV RNA NAAT test (if available) or repeat 4th generation assay 7-21d later is recommended [Grade 1C].

Source: known HIV-positive

47. If the source is known to be HIV-positive, is available, and provides consent, a detailed ART history and HIV viral load test should be obtained to guide decisions about the need for and type of nPEP to be provided. nPEP should not be withheld pending the results of these investigations (See Tables 6 & 7) [Grade 1D].

Evaluation and monitoring of the exposed individual before, during and after nPEP:

48. We recommend that baseline HIV-status be determined using a laboratory-based 4th generation assay when available, or alternative (see Table 3) for all people in whom nPEP is being considered. Where available, an HIV point-of-care test should be used for initial screening. nPEP should not be withheld pending the results of these investigations [Grade 1C].

49. If acute HIV infection is suspected (See Table 4) then additional laboratory evaluation with HIV RNA NAAT test (if available) or repeat 4th generation assay 7-21d later is recommended. nPEP should not be withheld pending the results of these investigations [Grade 1C].

50. Baseline evaluation of individuals initiating nPEP should include laboratory assessment of hepatic and renal function, and evaluation for STI and hepatitis co-infection, with appropriate subsequent management (see Table 8) [Grade 1D].

51. Ongoing laboratory monitoring of biochemistry during nPEP is recommended only for those with baseline laboratory abnormalities, or in those who develop signs or symptoms of organ dysfunction or medication-related adverse effects during therapy [Grade 1C].

52. HIV serology with a 4th generation assay is recommended at 12 weeks following exposure (8 weeks following completion of nPEP) [Grade 1C].

Recommendations for early discontinuation of nPEP:

53. nPEP should be discontinued early if the source tests HIV-negative using a 4th generation assay [Grade 1C]. However, continuation of nPEP may be considered despite this result where acute HIV infection ("window period") of the source is strongly suspected based on clinical history (Table 4), and pending additional laboratory testing as previously described [Grade 2C].

54. nPEP may be discontinued early if the source is HIV-positive and determined to have had a viral load below the limit of detection (<40 copies/mL) for ≥6 months with no evidence of concurrent STI at the time of the exposure[Grade 1C].

D) Recommendations to support PrEP / nPEP adherence

55. Interventions to support medication adherence should be discussed at the time of PrEP/nPEP initiation, actively monitored at every follow-up patient encounter, and tailored to the individual patient. Interventions may include patient counselling, education, medication reminders, behavioural feedback and reinforcement, peer supporters, follow up telephone calls/text message (SMS) and minimization of out-of-pocket expenses [Grade 1B].

56. For patients with low adherence (i.e. < 80%), intensified counselling using principles of cognitive behavioural therapy and problem solving therapy may be beneficial [Grade 2C].

57. Intensive adherence counselling may be considered in individuals at highest risk of non-adherence (eg. sexual assault survivors receiving nPEP) [Grade 1D].

E) Recommendations for the assessment of syndemic conditions which impact populations at risk for HIV and may impact PrEP/nPEP uptake and adherence

58. Conduct a baseline assessment for substance use and provide referral to harm reduction services and/or addictions services where appropriate. Consider ongoing assessments for substance use [Grade 2D].

59. Conduct a baseline assessment for mental health problems and provide referral to counseling and/or psychiatry services where appropriate [Grade 2C].

Canadian HIV Pre-exposure Prophylaxis and Non-Occupational Post Exposure Prophylaxis DRAFT Guidelines – Tables
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Table 1. HIV prevalence in priority populations in Canada

Classification	2011			2008		
	Point estimate	Range, n	Percentage %	Point estimate	Range, n	Percentage %
Exposure category						
MSM	33,330	28,160-38,500	46.7	30,000	25,000-35,000	46.9
MSM-IDU	2,160	1,520-2,800	3.0	2,030	1,460-2,600	3.2
IDU	12,040	9,580-14,500	16.9	11,150	9,000-13,300	17.4
Heterosexual/non-endemic	12,530	10,260-14,800	17.6	10,900	8,900-12,900	17.0
Heterosexual/ endemic	10,640	8,780-12,500	14.9	9,320	7,640-11,000	14.6
Other	600	400-800	0.8	600	400-800	0.9
Sex						
Female	16,600	13,200-20,000	23.3	14,740	11,980-17,500	23.0
Male	54,700	44,400-65,000	76.7	49,260	40,520-58,000	77.0
Ethnicity						
Aboriginal	6,380	5,160-7,600	8.9	5,440	4,380-6,500	8.5
Other ethnicities	64,920	52,840-77,000	91.1	58,560	47,120-70,000	91.5
Total	**71,300**	**58,600-84,000**	**100.0**	**64,000**	**53,000-75,000**	**100.0**

Source: PHAC HIV/AIDS Epi Update October 2014

Table 2. HIV incidence in key populations in Canada

Classification	2011			2008		
	Point estimate	Range, n	Percentage, %	Point estimate	Range, n	Percentage, %
Exposure category						
MSM	1,480	1,060 - 1,900	46.6	1,470	1,040 - 1,900	44.1
MSM-IDU	80	50 - 110	2.5	90	50 - 130	2.7
IDU	435	300 - 570	13.7	565	400 - 730	16.9
Heterosexual/ non-endemic	645	450 - 840	20.3	670	470 - 870	20.1
Heterosexual/ endemic	535	370 - 700	16.9	540	380 - 700	16.2
Other	<20			<20		
Sex						
Female	755	510 - 1,000	23.8	865	630 - 1,100	25.9
Male	2,420	1,740 - 3,100	76.2	2,470	1,740 - 3,200	74.1
Ethnicity						
Aboriginal	390	280 - 500	12.2	420	290 - 550	12.6
Other ethnicities	2,785	1,970 - 3,600	87.8	2,915	2,030 - 3,800	87.4
Total	**3,175**	**2,250 - 4,100**	**100.0**	**3,335**	**2,370 - 4,300**	**100.0**

Source: PHAC HIV/AIDS Epi Update October 2014

Table 3. Current Diagnostic Assays for detection and monitoring of HIV infection

Diagnostic Test	Target Detected	Window Period[a]	Comments
3rd generation assay	HIV IgG, IgM antibodies	22 (19, 25) days	
3rd generation point of care assay	HIV IgG, IgM antibodies	32 (28, 38) days	Recommended for initial screening when available
4th generation assay	HIV IgG, IgM antibodies HIV p24 antigen	18 (16, 24) days	Recommended as baseline assay for individuals seeking PrEP or nPEP. Repeat test in 7-21 days may help identify acute HIV infection if HIV RNA test unavailable
HIV pooled NAAT	HIV RNA – qualitative	7-10 days	Use pooled or individual HIV RNA for evaluation of suspected acute HIV infection in the setting of PrEP nPEP when available
HIV viral load	HIV RNA – quantitative	10 days	

[a] Median (Interquartile range, if known)

Table 4. Signs and Symptoms of Acute HIV Infection[a]

Sign or symptom	Likelihood of presentation (%)
Fever	53-90
Weight loss / anorexia	46-76
Fatigue	26-90
GI upset	31-68
Rash	9-80
Headache	32-70
Lymphadenopathy	7-75
Pharyngitis	15-70
Myalgia or arthralgia	18-70
Aseptic meningitis	24
Oral ulcers	10-20
Leukopenia	40

[a] Adapted from Richey, L. Am J Med Sci 2013;345:136.

Table 5. Baseline and on-treatment PrEP evaluations:

Assay Type	Baseline	30 days	Q3 months	Q 12 months
HIV Serology (4th Generation Antibody/Antigen Assay)	X	X	X	
HIV RNA or pooled NAAT test (only for those with symptoms of acute HIV)	X	X	X	
Hepatitis A IgG antibody[a]	X			
Hepatitis B Screen (Hepatitis B Surface Antigen, surface antibody, core antibody)[ab]	X			
Hepatitis C Screen (Hepatitis C Antibody)	X			X
Gonorrhea screen[c] (urine GC NAAT test, throat and rectal swabs for GC depending on type of sexual activity reported)	X		X	
Chlamydia Screen[c] (Chlamydia urine NAAT test)	X		X	
Syphilis Screen[c] (T. pallidum EIA)	X		X	
Complete Blood Count	X			
ALT, AST	X			
Creatinine and urinalysis	X	X	X	

[a] Hepatitis A and/or B vaccine should be initiated in unvaccinated individuals.
[b] Individuals with chronic active hepatitis B should be managed in consultation with an HBV expert according to local guidelines.
[c] Individuals diagnosed with concurrent STI should be offered standard therapy and follow-up as per local guidelines.

Table 6. A-C. Risk assessment for nPEP initiation

Table 6A. Exposure Type and risk of HIV transmission per act from an HIV-positive source

Level	Exposure (Unprotected)	Average Risk of Transmission per Act	
High	Anal (receptive)	0.5-3.38%	1 in 30 to 1 in 200
	Needle sharing	0.7-0.8%	1 in 125 to 1 in 143
	Vaginal (receptive)	0.08-0.19	1 in 526 to 1 in 1250
	Anal (penetrative, uncircumcised)	0.62%	1 in 161
Moderate	Anal (penetrative, circumcised)	0.06-0.16%	1 in 625 to 1 in 1667
	Vaginal (penetrative)[a]	0.05-0.1%	1 in 1000 to 1 in 2000
Low	Oral sex (give)	0.01%	1 in 10000
	Oral sex (receive)	0.005%	1 in 20000
	Oral-anal contact	Rare	Rare
	Biting	Rare	Rare
	Sharing sex toys	Rare	Rare
	Blood on compromised skin	Rare	Rare

[a] Circumcision reduces this risk by 60%

Table 6B. Likelihood source has transmissible HIV

Risk	Source Groups
Significant	HIV+ viremic HIV status unknown but source from a priority population with high HIV prevalence compared to the general population: Men who have sex with men Persons who inject drugs Sex trade workers
Low but non-negligible	HIV+ VL<40 but not criteria below
Negligible / none	Confirmed HIV negative HIV+ with VL confirmed to be below limits of detection x6 months and no STIs present at time of exposure HIV status unknown, general population

Table 6C. When to initiate nPEP: Combining risk arising from exposure type, and probability the source has transmissible HIV

		Risk from the exposure type (Table 6a)	
		High / Moderate	**Low**
Likelihood that source person has transmissible HIV (from Table 6b)	**Significant**	Initiate nPEP	nPEP not required
	Low	Consider nPEP	nPEP not required
	Negligible / none	nPEP not required	nPEP not required

Table 7. Preferred and Alternative regimens for nPEP[a]

Preferred		**Alternate**
NRTI backbone	tenofovir disoproxil fumarate / emtricitabine (TDF/FTC) [Grade 1B]	Zidovudine/lamivudine [Grade 2C] Tenofovir disoproxil fumarate + lamivudine [Grade 2C]
3rd drug	INSTI-based regimen: raltegravir [Grade 1B]	dolutegravir [Grade 2D] elvitegravir/cobicistat (coformulated with TDF/FTC) [Grade 2D]
	PI-based regimen: darunavir/ritonavir [Grade 1B]	Lopinavir/ritonavir [Grade 2B] Atazanavir/ritonavir [Grade 2C]
NOT Recommended		
Abacavir, didanosine, efavirenz, nevirapine, stavudine [Grade 1C]		

[a] A complete nPEP regimen includes a two-drug NRTI backbone plus a third drug

Table 8. Monitoring and evaluation of exposed individual at baseline, during and after nPEP initiation

Test	**Baseline**	**Week 2**	**Week 12**
HIV Serology (4th generation Ag/Ab assay)	X		X[a]
HIV RNA or pooled NAAT (only if patient from a high incidence population with symptoms of acute HIV)	X		
Hepatitis A immunity (hepatitis A IgG)[b]	X		
Hepatitis B Screen[bc] (surface antigen, surface antibody, core antibody)	X		
Hepatitis C Screen (Hepatitis C antibody)	X		X
Gonorrhea screen (urine GC NAAT test, throat/rectal swabs for GC depending on type of sexual activity reported)	X[d]		X
Chlamydia screen (urine Chlamydia NAAT test, throat/rectal swabs for Chlamydia depending on type of sexual activity reported)	X[d]		X
Syphilis Screen (serology)	X[d]		X
Complete Blood Count	X		
ALT	X	X[e]	
Serum creatinine	X	X[e]	
β-hcg (if appropriate)	X		

[a] HIV serology should be repeated at 6 months after exposure if hepatitis C infection was acquired from the exposure.
[b] Hepatitis A and/or B vaccine should be initiated in unvaccinated individuals.
[c] Individuals with chronic active hepatitis B should be referred for HBV care as per local guidelines.
[d] Individuals diagnosed with concurrent STI during nPEP should be offered standard therapy and follow-up as per local guidelines.
[e] Recommended if abnormal at baseline or symptomatic