COMMENTARY

Setting the stage for expanding HIV pre-exposure prophylaxis use in Canada

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Abstract

Human immunodeficiency virus (HIV) infection continues to disproportionately affect vulnerable populations in Canada; particularly men who have sex with men (MSM). Novel HIV prevention strategies have recently expanded from the use of non-occupational post-exposure prophylaxis (nPEP) after high risk exposures to the use of pre-exposure prophylaxis (PrEP) in which individuals reduce risk of HIV infection through use of combination antiretrovirals taken prior to risk exposure. With approval of tenofovir/emtricitabine (TDF/FTC) for use as PrEP only in early 2016, and with limited public funding to date, uptake in Canada is in its preliminary stages. These biomedical prevention strategies have proven efficacy for MSM, and they may have potential for other at-risk populations. With generic formulations of TDF/FTC now available in Canada, there is an opportunity for widespread implementation. Expanding knowledge of health care providers across Canada on how best to assess, refer for or prescribe and monitor PrEP will contribute to the current efforts to reach the global goal of eliminating new HIV infections.

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Introduction

It has been over 40 years since the HIV epidemic first drew clinical attention, with reports of opportunistic infections and cancers occurring in young, otherwise healthy gay, bisexual and other men who have sex with men (MSM) (1,2). Despite tremendous advances in HIV diagnostics, HIV care and management and three decades of educational campaigns, MSM continue to bear the brunt of the HIV epidemic in Canada (3). MSM in Canada are now 171 times more likely to acquire HIV infection than men in the general population. The bulk of these infections are now concentrated in urban areas where, in cities such as Vancouver and Toronto, MSM consistently constitute approximately 70% of all new HIV diagnoses each year (4). In addition, Canada has witnessed a dramatic rise in new HIV diagnoses amongst Indigenous individuals living in the Prairie provinces, attributed to injection drug use (IDU) and heterosexual transmission (5).

In countries such as England that have begun to roll out biomedical prevention strategies such as pre-exposure prophylaxis (PrEP), there have been substantial decreases in new infections, with most of this experience to date being amongst MSM (6). The evidence of efficacy and the promising results from early uptake of both pre- and post-prophylaxis medication to prevent the transmission of HIV marks an important new opportunity for HIV prevention strategies in Canada.

Context

HIV prevention strategies have traditionally relied on individual level behavioural interventions, such as improved condom use or sexual health counselling, as well as community level interventions to decreasing risk for marginalized populations, such as needle exchange or harm reduction services for those who inject drugs (7). The emergence of improved HIV testing strategies, including assays with shorter window periods or point-of-care delivery, have led to more HIV infections being diagnosed earlier in the course of disease, with the potential to limit onward transmission of the virus. Suppressive antiretroviral therapy (ART) has been shown to prevent the transmission of HIV from an HIV-positive individual to an uninfected sexual partner (8,9). Expansion of ART programs, in combination with harm reduction programming, has significantly reduced HIV infections amongst those who inject drugs in Vancouver's inner city, with a drop in new diagnoses from over 350 in 1996 to below 30 in 2012 (10).

Despite the significant expansion of ART in Canada, sexual transmission prior to diagnosis, particularly amongst MSM individuals experiencing acute seroconversion, contributes to Canada's ongoing epidemic (11-14). There is emerging global consensus that a combination approach that packages current prevention strategies with emerging biomedical prevention interventions offers the best hope of reducing new HIV infections (15). The objective of this article is to describe the PrEP and non-occupational post-exposure prophylaxis (nPEP) treatments, and the challenges and opportunities for these biomedical

HIV prevention strategies that have the potential to alter the trajectory of the HIV epidemic in Canada and around the world.

Pre- and post-prophylaxis medication strategies

Use of antiretroviral medications for post-exposure prophylaxis has been the standard of care for several decades for high risk exposures occurring in occupational settings (such as hospitals). Use for non-occupational high risk exposures, such as consensual sexual exposure or needle sharing (nPEP), has been endorsed by guidelines in the United States beginning in 2005 (16), and is now standard of care in most jurisdictions in the developed world. Individuals with potential risk exposure are assessed based on the likelihood the source of the exposure could be HIV-positive and the risk of the nature of the exposure itself. If the source is not known to be HIV-positive, local epidemiology of HIV prevalence amongst at-risk populations, such as MSM or people who inject drugs (PWID), is important to assess risk. High risk exposures would include needle sharing and condomless receptive anal sex; moderate risk exposure includes condomless insertive anal or vaginal sex and condomless receptive vaginal intercourse. Individuals found to have had a high or moderate risk exposure from a source with significant likelihood of being HIV-positive are eligible for nPEP. In this setting, individuals receive a 28-day course of standard combination antiretroviral medications to decrease likelihood of infection. Medications must be started as soon as possible after exposure and no later than 72 hours after exposure (17). Individuals should undergo HIV testing at 12 weeks post-exposure to ensure they remain HIV-negative, and should be offered immediate referral for HIV therapy if found to be HIV-positive.

In contrast, PrEP refers to the daily use of the fixed-dose combination of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) in conjunction with ongoing safer sex practices in HIV-negative individuals. Here, therapy is used on an ongoing basis, prior to a potential HIV exposure and continued afterwards to prevent infection. Individuals at potential risk for HIV acquisition should undergo a baseline assessment to ensure they are HIV-negative. Use of a fourth generation HIV assay is recommended for screening due to its reduced window period. Individuals with signs or symptoms of acute HIV infection, or with exposure within the window period (up to 21 days following exposure) of the assay, should be tested with other modalities such as the HIV (RNA) nucleic acid amplification test (NAAT) or be retested 14–21 days later to be sure of an accurate result. Individuals with undiagnosed HIV infection who are started on PrEP may be at risk for development of HIV drug resistance since they do not receive a standard triple antiretroviral regimen. Individuals should be counselled regarding the need for complete adherence to have full protective benefit, and that protective levels are reached after seven days of daily use. PrEP is very well tolerated, with a small risk of gastrointestinal side effects in the first few weeks, and a potential risk of reversible renal and bone toxicity. A meta-analysis of ten placebo-controlled trials has shown that the frequency of adverse events is similar to placebo (OR=1.01, 95%CI=0.99-1.03)(18). Individuals using PrEP undergo regular monitoring every three months with updated HIV testing, renal function testing and screens for sexually transmitted infections. See **Table 1** for a summary of pre- and post-exposure prophylaxis treatments for HIV.

Table 1: Summary of pre- and post-exposure prophylaxis treatments for HIV

Description	Pre-exposure prophylaxis (PrEP)	Non-occupational post-exposure prophylaxis (nPEP)
Labelled indication	Yes	No
Population	Individual at high risk of HIV exposure through sex or needle sharing	Individual who has experienced a high or moderate risk exposure from an individual at significant risk for having transmissible HIV within the preceding 72 hours
Medications used	Tenofovir DF/ emtricitabine	Variable, but current data support the combination of, 1) tenofovir DF, 2) emtricitabine or lamivudine and 3) either an integrase strand transfer inhibitor (raltegravir or dolutegravir) or a boosted protease inhibitor (darunavir/ ritonavir)
Duration	Indefinite while risk of exposure continues Medication is taken daily	Daily for 28 days
Common side-effects	Nausea, GI upset, small risk of reversible nephrotoxicity and decreases in bone density	Regimen-specific, but may include nausea, GI upset, headache, rare risk of renal or liver toxicity, risk of drug interactions if boosted protease inhibitors are used
Monitoring	Baseline HIV, liver, renal and STI screens Followup testing one month after use and quarterly thereafter	Baseline HIV, liver, renal and STI screens Followup testing at two and four weeks after initiation if symptoms arise or if baseline abnormalities detected HIV testing 12 weeks after exposure

Abbreviations: GI, gastrointestinal; STI, sexually transmitted infections; Tenofovir DF, tenofovir disoproxil fumarate

Evidence for PrEP

Use of TDF/FTC for PrEP in HIV-negative individuals at high ongoing risk of HIV acquisition has been rigorously evaluated in randomized clinical trials and has been found to be highly effective, particularly in MSM (**Table 2**). Daily use has been evaluated in two trials, while the Ipergay trial studied "on-demand" PrEP, where TDF/FTC was used 2–24 hours prior to exposure (loading dose of two tablets) followed by daily use until 48 hours after last sexual exposure (19).

Table 2: Summary of HIV pre-exposure prophylaxis trials in men who have sex with men (MSM)

Study	Inclusion criteria	Intervention	HIV incidence rate (Control arm)	Risk reduction	Number needed to treat per year
iPrEx (20,21)	High risk for HIV: Anal sex with >4 partners UAI with HIV+/ unknown partner Prior STI Transactional Sex	Daily tenofovir/ emtricitabine vs. placebo	3.9/100 person-years (95% CI 3.17 – 4.87)	Intention to treat: 44% (95%CI 15 – 63) On treatment with detectable drug: 92% (95% CI 40 – 99)	Overall: 62 (95% CI 44 – 147) With UAI: 36 With STI: 41
PROUD (22)	UAI last 90 days	Immediate vs. deferred daily tenofovir/ emtricitabine	8.9/100 PY 95% CI 6 – 12.7)	Overall: 86% (95% CI 58 – 96)	Overall:13 (95% CI 9 – 25)
Ipergay (19)	UAI with >2 partners in last 6 months	On-demand tenofovir/ emtricitabine vs. placebo	6.6/100 PY	Overall: 86% (95% CI 40 – 99)	Overall: 18

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; PY, person years; STI, sexually transmitted infection; UAI, unprotected anal intercourse

Use of both TDF alone and TDF/FTC has been evaluated for use in preventing HIV transmission amongst heterosexual serodiscordant couples and in other heterosexuals in highly endemic areas (23-26). Findings of these studies are conflicting, with some studies showing protective benefit and others not. This seems to be largely driven by poor adherence to the study drug(s) (26).

Use of TDF alone as PrEP in PWID demonstrated a 48.9% decrease in HIV incidence overall in a study conducted in Bangkok (27). A limitation of that study is that under Thai law, sterile needles could not be provided to study participants, meaning that the incremental benefit of PrEP when a full package of evidence-based prevention strategies for PWID is also implemented remains unknown.

Challenges and opportunities for biomedical prevention

Identifying populations for PrEP

Mathematical modelling studies have clearly shown that PrEP is most cost-effective when given to those at greatest HIV risk (28,29). To date, PrEP scale-up in Canada has focused primarily on MSM because of the availability of clear data on how to identify high-incidence subpopulations and on the feasibility of PrEP implementation. The use of clinical markers, such as antecedent sexually transmitted infection or use of validated risk calculators (30-34) allows for the identification of Canadian MSM with HIV incidence rates well over internationally-recommended thresholds of 2–3% per year (35,36). Awareness of PrEP amongst MSM in urban areas has climbed substantially over the last few years. Recent studies have shown 91.3% of MSM undergoing anonymous HIV testing at a sexual health clinic in Toronto and 80% of MSM engaged in a cohort study in Vancouver were aware of PrEP (37).

Demonstration projects have shown the feasibility of achieving high adherence and 'real-world' implementation data suggest the potential for considerable impact on the HIV epidemic. Daily use of TDF/FTC eliminated new HIV infections amongst MSM receiving PrEP in a health maintenance organization in San Francisco (38,39). Similarly, use of PrEP as a component of comprehensive HIV services led to a 32% reduction in new diagnoses in clinics providing MSM services in London (6). In New South Wales, Australia, a 40% reduction in recent HIV infections in MSM has been ascribed to increased PrEP use (40).

Use in PWID or settings of heterosexual transmission also has potential, but presents different challenges. For instance it would require real-time integration with surveillance programs to identify communities with active transmission, and practical new strategies will be needed for identifying those who are most at-risk. Integrating biomedical prevention into harm reduction strategies for PWID where clear impact on HIV transmission has already been demonstrated has not yet been evaluated. An intriguing possibility evaluated in the Partner Demonstration Project in Africa is to offer PrEP to HIV-negative partners of newly diagnosed individuals initiating ART, serving as a short-term bridge while viral load suppression is achieved in the HIV-positive partner (41). This strategy may be useful in localized communities with ongoing HIV transmission. Similar implementation science initiatives are needed in Canada to better understand the acceptability, feasibility and real-world health outcomes as PrEP is rolled out in high risk populations.

Expanding access to PrEP

Currently, PrEP is prescribed primarily by specialist physicians, but this practice creates a bottleneck. Expanding access to PrEP could be done through building capacity with primary care providers. Given that primary care providers already offer other evidence-based primary prevention strategies for chronic diseases, PrEP prescribing is a logical extension of this role.

Physician surveys support the concept of primary care as an appropriate setting for PrEP delivery (42). Primary care providers give longitudinal care to large numbers of at-risk, HIV-negative persons and have expertise in other components of HIV prevention, such as counselling, substance use and mental health.

Recent studies in the United States (US) have found that awareness of PrEP amongst primary care providers has grown in the years following publication of clinical guidelines by the US Centers for Disease Control and Prevention (76–93% aware), with 17–34% of those surveyed now prescribing PrEP (43-45). Unlike the United States, Australia and the United Kingdom, which have regularly updated national guidelines for HIV treatment and nPEP, Canada has neither. This is in part because health care is a provincial/territorial jurisdiction. Currently only British Columbia and Quebec have issued clinical guidance for physicians prescribing PrEP (46,47). In British Columbia, there are no provincial restrictions regarding type of physician who can prescribe PrEP, while in Quebec, current guidance suggests PrEP should be prescribed only by physicians who already have experience prescribing antiretroviral therapy.

A lack of overall PrEP knowledge has been identified by physicians as a potential barrier to prescribing (44). Other

barriers that may prevent physician uptake of PrEP could include misperceptions regarding potential side effects of PrEP, concerns regarding risk compensation (the notion that individuals may increase risky behaviour if they believe they are being protected against HIV, and thus may overcome protective benefits) and increased sexually transmitted infections amongst PrEP users. These barriers can be readily addressed (48) or are amenable to screening interventions (49).

Increasing physician education and engaging primary care physicians to either prescribe or refer for PrEP will help to expand the reach of this primary prevention strategy.

What about public reimbursement?

Health Canada authorized the use of TDF/FTC in conjunction with ongoing safer sex practises for HIV prevention only in 2016. Until recently, only Quebec had offered public re-imbursement for PrEP. Elsewhere, individuals wishing to use PrEP had been limited to coverage via private third-party insurance, or through use of so-called "buyers clubs", which promote access via online pharmacies (50). In August 2016, as part of the Common Drug Review process of the Canadian Agency for Drugs and Technology in Health (CADTH), the Canadian Drug Expert Committee (CDEC) provided a formal recommendation to participating Canadian federal, provincial and territorial public drug plans that TDF/FTC be listed on their formularies for a PrEP indication according to the Health Canada indication if the following two conditions were met:

- it is provided in the context of a sexual health program by a prescriber experienced in the treatment and prevention of HIV-1 infection
- the price is reduced (51)

However, the first condition is itself a barrier to expanding PrEP uptake, as it implies that only prescribers experienced in HIV prevention or management should prescribe PrEP.

With the very recent entrance of generic TDF/FTC onto the Canadian market, options for lower drug pricing and expanded access are already in place in some areas. In September 2017, Ontario announced coverage of PrEP via the Ontario Drug Benefit Program, with no restrictions on who might prescribe. British Columbia is currently reviewing PrEP coverage in light of new generic pricing (52).

Next steps

We are entering a new era in HIV elimination efforts with access to biomedical prevention strategies. These strategies have proven effectiveness in MSM who continue to be over-represented in the Canadian HIV epidemic, and may also have a role in decreasing transmission in other at-risk populations.

To realize the full benefits of biomedical prevention, a number of steps are needed. The publication of clinical guidelines would increase health care provider comfort levels with PrEP prescribing. Continuing medical education, summarizing the evidence on PrEP and increasing awareness of the guidelines, will improve health care provider knowledge, and transition PrEP into the repertoire of services offered by primary care providers.

In those provinces where PrEP initially may be provided only by those experienced in the treatment and prevention of HIV-1 infection, other primary care clinicians can still identify at-risk individuals, inform them of PrEP and provide opportunities for referral. PrEP referral could also be integrated into existing STI programs, public health partner notification programs or linking to existing programs that see at-risk individuals presenting for assessment for post exposure prophylaxis. Closer linkage of public health programs and clinical services for HIV prevention and care could also enhance knowledge of and acceptance of PrEP.

Conclusion

Biomedical prevention strategies have the potential to alter the trajectory of the HIV epidemic in Canada and around the world. The successful integration of PrEP into existing HIV screening and prevention practices will undoubtedly contribute to the global goal of eliminating new HIV infections.

Authors' statement

MH and DT jointly conceived and contributed to the writing of this article.

Conflict of interest

MH: has received honoraria for delivering educational lectures of his own design (Gilead, Merck and Janssen) or attending advisory boards from BMS, Gilead, Merck, Janssen and Viiv Healthcare. All monies were paid to his institution.

DT: has received honoraria from Viiv Healthcare and Merck for delivering educational lectures of his own design; DT's institution has received support from Gilead and Viiv Healthcare for investigator-initiated research grants; DT is a site Principal Investigator for clinical trials sponsored by GSK.

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