Appendix 1 (as supplied by the authors): Canadian Guidelines on HIV Pre-exposure Prophylaxis and Non-Occupational Post Exposure Prophylaxis

Darrell H. S. Tan MD PhD,[1]* Mark W. Hull MD MHSc,[2] Deborah Yoong BScPhm PharmD,[3] Cécile Tremblay MD,[4] Patrick O'Byrne RN-EC PhD,[5] Réjean Thomas MD,[6] Julie Kille RN,[7] Jean-Guy Baril MD,[8] Joseph Cox MD MSc,[9] Pierre Giguere BPharm MSc,[10] Marianne Harris MD,[2] Christine Hughes BScPharm PharmD,[11] Paul MacPherson MD PhD,[12] Shannon O'Donnell MD MPH,[13] Joss Reimer MD MPH,[14] Ameeta Singh BMBS MSc,[15] Lisa Barrett MD PhD,[16] Isaac Bogoch MD MSc,[17] Jody Jollimore MPP,[18] Gilles Lambert MD,[19] Bertrand Lebouche MD PhD,[20] Gila Metz MD CCFP,[21] Tim Rogers PhD,[22] Stephen Shafran MD[15]

1. Division of Infectious Diseases, St. Michael's Hospital, Toronto;
2. BC Centre for Excellence in HIV/AIDS, Vancouver;
3. Department of Pharmacy, St. Michael's Hospital, Toronto;
4. Centre de Recherche du Centre Hospitalier de l'Université de Montréal, Montréal;
5. School of Nursing, University of Ottawa, Ottawa;
6. Clinique L'Actuel, Montréal;
7. Canadian Association of Nurses in HIV/AIDS Care;
8. Clinique du Quartier Latin, Montréal;
9. Direction régionale de santé publique, Centre intégré universitaire de santé et de services sociaux du Centre-Sud-de-l'Île-de-Montréal, Montréal;
10. Department of Pharmacy, The Ottawa Hospital, Ottawa;
11. Faculty of Pharmacy & Pharmaceutical Sciences, University of Alberta, Edmonton;
12. Division of Infectious Diseases, The Ottawa Hospital, Ottawa;
13. Department of Emergency Medicine, St. Paul's Hospital, Vancouver;
14. Winnipeg Regional Health Authority, Winnipeg;
15. Division of Infectious Diseases, Department of Medicine, University of Alberta, Edmonton;
16. Dalhousie University, Halifax;
17. Divisions of Internal Medicine and Infectious Diseases, Toronto General Hospital, Toronto;
18. Health Initiative for Men, Vancouver;
19. Institut national de santé publique du Québec, Montréal;
20. Research Institute of the McGill University Health Centre, Montréal;
21. Department of Family Medicine, University of Ottawa, Ottawa;
22. CATIE (Canadian AIDS Treatment Information Exchange), Toronto;

***Correspondence to:**
30 Bond St., 4CC – Room 4-179
Toronto ON, M5B 1W8
Tel: (416) 864-5568, Fax: (416) 864-5310
darrell.tan@gmail.com

These guidelines have been endorsed by:

Association of Medical Microbiology and Infectious Disease (AMMI) Canada
Canadian Association of Emergency Physicians (CAEP)
Canadian Association of Nurses in AIDS Care (CANAC)
Canadian HIV and Viral Hepatitis Pharmacists Network (CHAP)

Appendix to: Tan DHS, Hull MW, Yoong D, et al. Canadian guideline on HIV pre-exposure prophylaxis and nonoccupational postexposure prophylaxis. CMAJ 2017. doi: 10.1503/cmaj.170494. *CMAJ* 2017. doi: 10.1503/cmaj.161485.

CANADIAN GUIDELINES ON HIV PrEP & nPEP

Canadian Guidelines on HIV Pre-exposure Prophylaxis and Non-Occupational Post Exposure Prophylaxis

Table of Contents

Background

New HIV infections occur every year in Canada, highlighting the need for integrated prevention programs. Pre-exposure prophylaxis (PrEP) and non-occupational post-exposure prophylaxis (nPEP) are two important HIV prevention strategies that should now be considered standard of care and implemented as key components of a comprehensive response to the epidemic. PrEP is the use of certain antiretroviral medications (ARVs) by HIV-uninfected persons at high, ongoing risk of HIV acquisition, beginning before and continuing after potential HIV exposures. PEP involves the short-term (28 days) use of ARVs immediately after a specific HIV exposure, and is referred to as "non-occupational" (nPEP) when used after sexual and injection drug use exposures, rather than accidental exposures occurring in work contexts (eg. healthcare). Because PrEP and nPEP harness biomedical tools, yet are critically dependent on behavioural factors such as medication adherence, participation in clinical follow-up, and integration with other HIV prevention strategies (eg. condom use, safer injection equipment, etc.), they are best conceived of as 'biobehavioural' strategies nested within a comprehensive program of preventive care.

PEP has been a standard of care intervention for many years, and Health Canada has granted regulatory approval for the use of a single combination ARV as PrEP for the first time in 2016. Nonetheless, several challenges have limited their clinical and public health impact in Canada, including financial barriers to accessing the medications for HIV prevention purposes in most Canadian jurisdictions, inadequate familiarity with relevant evidence guiding nPEP and PrEP use among front-line health care providers, and variability in clinical practice nationwide.

These guidelines were developed by the Biomedical HIV Prevention Working Group of the CIHR Canadian HIV Trials Network (CTN) in order to address these gaps. To our knowledge, there are no existing Canadian national guidelines for clinicians on when and how to use ARVs as nPEP and PrEP. We adopted a client perspective, as our primary intended audience is clinicians working in primary care, infectious diseases, emergency medicine, nursing, pharmacy and related disciplines. In addition, policy-makers, community organizations and other stakeholders may find these guidelines useful for informing policy and programming.

BIOLOGY OF HIV TRANSMISSION

There are three predominant modes of transmission for HIV infection: sexual, blood-borne, and vertical (ie. from mother-to-child during pregnancy, childbirth and/or breastfeeding). Sexual activity accounts for the vast majority of new infections in Canada, followed by injection drug use. While a full account of the molecular events leading to a new HIV infection is beyond the scope of this document, a brief overview is important for understanding how PrEP and nPEP can act to prevent infection.

To initiate infection, HIV virions and/or infected cells must gain access to a mucosal surface or to the bloodstream of a susceptible individual. During sexual transmission, the virus must first cross the mucosal barrier, before being taken up by dendritic cells and being rapidly transported to regional lymph nodes within approximately two days after exposure.[1,2] Further dissemination of virus to lymphoid organs throughout the body occurs via the bloodstream within three days, and represents the establishment of irreversible infection.[1] This 72-hour period is thought to provide a critical window of opportunity for PrEP and nPEP, during which inhibition of viral replication using ARVs can prevent infection.

The risk of HIV acquisition from a given exposure depends on two factors: the likelihood the source has transmissible HIV infection, and the biological risk of HIV transmission based on the type of exposure that has occurred. We distinguish between three categories for the likelihood that a person has transmissible HIV infection: substantial, low but non-zero, and negligible/none (Table 1). These categories apply to the source person, only at that particular time, and depend on the person's HIV treatment status if known to be HIV-positive, or on the probability of the person being HIV-positive if the HIV status is unknown (See Epidemiology of HIV below).

The classification of HIV-infected persons with undetectable viral load (<40 copies/mL) and no known sexually transmitted infections (STIs) as having negligible/no risk of transmissible HIV is based on several lines of evidence, and is now widely accepted within the HIV scientific community. First, HIV transmission has long been known to be associated with higher viral load,[3-7] and ART suppresses HIV viral load in blood and in genital secretions.[8] A meta-analysis of studies evaluating heterosexual transmission found no documented HIV transmission in those with HIV viral load <400 copies/mL on ART,[9] but was unable to account for condom use in the analysis. Second, in the HPTN052 randomized trial of 1763 serodiscordant couples, early initiation of ART was associated with a 96% reduction in transmission (hazard ratio [HR]=0.04; 95%CI=0.01-0.27);[10] 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, with no infections seen in those suppressed for greater than six months.[10] However, reported rates of condom use in that trial were high. Further, the PARTNER cohort study evaluated phylogenetically linked transmission events among 548 heterosexual and 340 gay, bisexual or other men who have sex with men (hereafter abbreviated MSM) serodiscordant couples reporting 36,000 and 22,000 episodes of condomless sex respectively, during which the HIV-positive partner had an HIV viral load below 200 copies/mL on ART.[11] Over 1238 couple-years of follow-up, no linked transmissions were documented (upper bound of the 95%CI=0.3/100 couple-years, and 0.71/100 couple-years for anal sex).[11] Data from the Opposites Attract study, also show no HIV transmissions among serodiscordant MSM couples over 236.2 couple-years of follow-up when the HIV-positive partner had a viral load below 200 copies/mL.[12] Finally, although recent studies have suggested no clear increase in seminal fluid or cervical HIV shedding in virologically suppressed patients with urethritis and genital ulcerative disease,[13,14] previous work, including a meta-analysis have suggested that the genital inflammation and mucosal breakdown associated with STIs increases overall per-sex act infectivity 5-fold in heterosexual settings (95%CI=1.4-19.5), and that the presence of STIs may increase risk of vertical transmission.[15,16]

We further distinguish between three categories of exposures, for which the risk of HIV transmission per exposure to HIV is either high, moderate, or low. The per-act risk of transmission differs based on the type of exposure (anal, vaginal or oral sex, or percutaneous; Table 2). Exposures classified as being at higher risk for HIV transmission include condomless receptive anal sex and needle sharing, while exposures conferring moderate risk include condomless insertive anal sex and vaginal sex.[15,17-19] Additional factors may modulate the per sex-act transmission risk and may be helpful during patient counseling. For example, for both anal and vaginal intercourse, risk to the receptive partner is higher if ejaculation occurs inside the receptive partner; in a cohort of Australian MSM, risk was estimated at 1.43% (95%CI=0.48–2.85%) per receptive anal sex act with ejaculation versus 0.65% (95%CI=0.15-1.53%) without, when the partner was known to be HIV-positive.[20] Also, risk to the insertive partner from a known HIV-positive partner is decreased if the insertive partner is circumcised; among MSM, the odds ratio for HIV acquisition is 0.27 (95%CI=0.17-0.44) based on a meta-analysis of observational studies,[21] while among heterosexual males, the incidence risk ratio is 0.50 (95%CI=0.34-0.72 at one year) based on meta-analysis of three randomized trials.[22]

EPIDEMIOLOGY OF HIV IN CANADA

Although estimated HIV incidence has been slowly decreasing in Canada over the past decade, the number of new infections each year remains substantial, at 2,044 in 2014 (Supplementary Table 1).[23] HIV incidence remains disproportionately concentrated in several priority populations. More than half of new infections (54.3%) occur in MSM, in whom HIV risk is estimated to be 131 times higher than in other Canadian men, and in whom incidence has been relatively stable, in contrast to the decreases seen in other priority groups.[24] Similarly, HIV incidence among people who inject drugs (PWID), people from HIV-endemic countries, and Indigenous people is estimated to be 59, 6.4 and 2.7 times higher than in other Canadians respectively.[24] National data on HIV incidence among people for sex workers and their clients are scarce, perhaps in part because sex work is criminalized in Canada; as such these guidelines should be applied to these individuals as for other MSM or heterosexuals.

There were 2,044 HIV cases reported in Canada in 2014, giving a national HIV diagnosis rate of 5.8 per 100,000 population.[25] Geographically, the highest rate (per 100,000 population) was in Saskatchewan (10.8) followed by Yukon (8.2), Alberta (6.7), Manitoba (6.6) and Ontario (6.1).[25] In all provinces except Saskatchewan, the 2014 rate remained relatively similar to recent years.[25] In Saskatchewan, the all-age HIV diagnosis rate reached a high of 19.2 per 100,000 population in 2009, with annual decreases thereafter to a rate of 10.8 per 100,000 population in 2014.[25]

Estimated annual HIV incidence is greater than the annual number of reported cases because a sizeable proportion of HIV infections are undiagnosed. The Public Health Agency of Canada estimated that by the end of 2014, roughly 21% of all HIV-infected people in Canada were unaware of their infection, highlighting the ongoing need to expand HIV testing strategies nationwide.[23]

HIV prevalence in Canada has risen steadily since the 1980s as a function of both continued HIV incidence, and the success of antiretroviral therapy (ART), which has transformed HIV from an invariably life-threatening condition into a chronic disease with near-normal life expectancy.[26,27] Prevalent cases remain concentrated in the same priority populations mentioned above. Clinicians are advised to be familiar with local HIV epidemiology, given the variability in the HIV epidemic across Canada.

Importantly, the Panel recognizes that these epidemiologic constructs may contribute to stigma and discrimination, and thus advises appropriate caution when applying them to individuals. In addition, individuals in these groups may be at risk for syndemic mental health disorders, substance use, and other challenging social/structural settings, which often lead to an elevated risk of infection, and which are important to address as a component of comprehensive HIV prevention strategies.[28]

Methods

We followed the GRADE (Grading of Recommendation, Assessment, Development and Evaluation) system, a rigorous and widely accepted methodology for the development of clinical practice guidelines. We first assembled a panel of 25 experts from across Canada representing diverse disciplines (infectious diseases, primary care, emergency medicine, public health, pharmacy, nursing, community) and varying views on biomedical HIV prevention, with invitations from the co-chairs (DHST, MWH) on the basis of expertise in the subject area; the rationale for selecting each member was circulated within the panel. We then convened an initial series of teleconferences among panel members to establish consensus on the core issues to be addressed by the guideline. The panel was then subdivided into five working groups, striving for geographic and disciplinary balance within each group, each focusing on one of the

following topics: 1) indications for PrEP, 2) provision of PrEP, 3) indications for nPEP, 4) provision of nPEP, and 5) additional issues that warrant attention during PrEP and nPEP clinical encounters.

Box 1. GRADE System for recommendations

These guidelines were developed using the GRADE (Grading of Recommendation, Assessment, Development and Evaluation) system, which specifies two categories of strength of recommendation, and four categories of quality of evidence on which recommendations are based.

Strength of recommendations

1. These are strong recommendations, those for which the Panel is confident that the desirable effects of an intervention outweigh undesirable effects (or vice versa), across the range of patients for whom the recommendation is intended.

2. These recommendations are actions that should be considered, for which the Panel is less confident of the balance between desirable and undesirable consequences. While the majority of individuals in this situation would want the suggested course of action, many would not, and clinicians must recognize that different choices will be appropriate for different individuals.

Quality of evidence

A. High quality evidence (starting point for randomized controlled trials)
B = Moderate
C = Low (starting point for observational studies)
D = Very low

Each working group articulated specific questions to be addressed through teleconferences and electronic communications; these were refined with feedback from the entire panel. Of these, we identified four key questions of interest, regarding specific clinical indications and specific drug regimens for PrEP and nPEP respectively, and we specified key outcomes of interest in rank order of importance for each key question (Appendix 2).

We then engaged the assistance of an information specialist to conduct structured searches of Medline, Embase and CINAHL to address each question, combining terms for PrEP and nPEP with terms for our study designs of interest (clinical trials and cohort studies). Our initial search included indexed literature up to January 8 2016; these searches were later repeated using the same search terms in November 2016 and September 2017. Each retrieved abstract was reviewed for relevance by at least two panel members; articles were then selected for retrieval by consensus of the two reviewers if they were clinical trials or cohort studies of PrEP or nPEP reporting on our outcomes of interest. Each retrieved article was first reviewed by at least two panel members for evidence relevant to the guideline questions. Findings were extracted onto standardized electronic forms and discussed in the working groups, with critical appraisal of the quality of the evidence according to the GRADE system (which recommends considering study design, study limitations, consistency of findings across studies, indirectness of evidence, imprecision, publication bias, magnitude of effect, confounding, and dose-response gradients).[29-31] The study selection diagrams for our key questions are presented in Appendix 3. Summary of findings tables are presented in Appendix 4.

Working groups then formulated the preliminary wording and grading for each recommendation, using GRADE terminology (Box 1), after consideration of the overall certainty of the evidence, desirable and undesirable outcomes, patient values, resource requirements and feasibility. To agree upon the wording and grading, we held an in-person panel meeting in Toronto on April 15-16, 2016, followed by a series of teleconferences and electronic discussions. The final statements were approved through consensus rather than through a formal voting process. Working groups then summarized the evidence supporting each statement in the body of the guideline text.

Consultation on draft recommendations with representatives of the HIV community (physicians, researchers and community members) was held during and following an open forum held at the 2016 Canadian Association for HIV Research Conference. The final statements were approved through consensus rather than through a formal voting process. Formal endorsements were then sought from several relevant national organizations, each of which had the opportunity to review and comment on the draft version before agreeing to endorse it. The final resulting document was approved by all panel members prior to submission for publication.

MANAGEMENT OF COMPETING INTERESTS

All panel members agreed to Terms of Reference that included public disclosure of all perceived and actual conflicts of interest at the beginning and end of the guideline development process. To manage potential competing interests, conflict of interest statements were posted on a shared drive accessible to all Panel members. Panelists with competing interests were permitted to participate in panel discussions without restriction.

Overview of recommendations

A summary of the recommendations is provided in Box 2. These are discussed in full below.

Box 2. Recommendations for the use of PrEP and nPEP in Canada

Indications for PrEP

1. PrEP is recommended for MSM [Grade 1A; strong recommendation, high quality of evidence] and TGW [Grade 1B; strong recommendation, moderate quality of evidence] who report condomless anal sex within the last 6 months and who have any of the following:
    a. Infectious syphilis or rectal bacterial STI, particularly if diagnosed in the preceding 12 months
    b. Recurrent use of nPEP (more than once)
    c. Ongoing sexual relationship with HIV positive partner with substantial risk* of transmissible HIV (*See Table 1 for risk definitions)
    d. High-incidence risk index (HIRI-MSM) risk score ≥11 (Supplementary Table 2)

    PrEP is not recommended in the context of a stable closed relationship with a single partner with no or negligible risk of having transmissible HIV [Grade 1B; strong recommendation, moderate quality of evidence].
2. We recommend PrEP for the HIV-negative partner in heterosexual serodiscordant relationships reporting condomless vaginal or anal sex where the HIV-positive partner has a substantial risk* of having transmissible HIV [Grade 1A; strong recommendation, high quality of evidence]. PrEP may be considered for the HIV-negative partner in heterosexual serodiscordant relationships reporting condomless vaginal or anal sex, where the HIV-positive

partner has a low but non-negligible risk* of having transmissible HIV [Grade 2B; weak recommendation, moderate quality of evidence]. (*See Table 1 for risk definitions)

3. PrEP may be considered for people who inject drugs if they are sharing injection drug use paraphernalia with a person with a non-negligible risk* of HIV infection [Grade 2B; weak recommendation, moderate quality of evidence]. (*See Table 1 for risk definitions)

Recommended PrEP regimens

4. The regimen recommended for use as PrEP is tenofovir DF/emtricitabine 300/200mg taken orally once daily [Grade 1A; strong recommendation, high quality of evidence].
5. As an alternative, in MSM, tenofovir DF/emtricitabine 300/200 mg administered "on demand" (2 pills taken together 2-24 hours before 1st sexual exposure, followed by one pill daily until 48 hours after last sexual activity) may be considered [Grade 2A; weak recommendation, high quality of evidence].

Indications for nPEP

6. We recommend nPEP for HIV-negative individuals who present no later than 72 hours after an exposure that is moderate- or high-risk* for HIV transmission with a person who has a substantial risk* of having transmissible HIV [Grade 1C; strong recommendation, low quality of evidence]. (*See Tables 1-2 for definitions)
7. nPEP can be considered for HIV-negative individuals who present no later than 72 hours after 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; weak recommendation, low quality of evidence]. (*See Tables 1-2 for definitions)
8. We recommend initiating nPEP as soon as possible after an exposure, up to a maximum of 72 hours afterwards [Grade 1D; strong recommendation, very low quality of evidence].

Recommended nPEP Regimens

9. The following are recommended as first-line regimens for nPEP (Tables 5 and A5):
    a. TDF/FTC 1 tablet PO daily and raltegravir 400mg PO BID for 28 days [Grade 1A; strong recommendation, high quality of evidence], or
    b. TDF/FTC 1 tablet PO daily and dolutegravir 50mg PO daily for 28 days [Grade 1C; strong recommendation, low quality of evidence], or
    c. TDF/FTC 1 tablet PO daily and darunavir 800mg PO daily + ritonavir 100mg PO daily for 28 days [Grade 1A; strong recommendation, high quality of evidence].
10. 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; weak recommendation, high quality of evidence].

Box 3 outlines factors that should be part of a health systems approach to PrEP and nPEP.

COMBINATION HIV PREVENTION

Clinical trials of PrEP and nPEP have nested these interventions within a comprehensive package of HIV prevention services, including risk reduction counseling, condoms, regular HIV testing, and STI testing. Because it would be unethical to withhold such services in clinical practice and in interventional studies on HIV prevention, we advise that they be integrated into all clinical PrEP and nPEP delivery. In many parts of Canada, other proven harm reduction strategies such as needle and syringe programs as well as opiate substitution treatment, have not yet been implemented to their full potential, despite prior evidence of their efficacy.[32-34] Additional effort to implement these interventions is warranted.

'Syndemic conditions' are defined as multiple concurrent epidemics that interact and worsen the effects of one another.[35] Increased vulnerability to HIV has been associated with syndemic conditions such as substance use, partner violence, depression and childhood sexual abuse among MSM,[36] and conditions such as substance abuse and violence in women.[37]

Box 3. A health systems approach to the use of PrEP and nPEP in Canada

- PrEP and nPEP should be part of a combination prevention strategy that includes behavioural interventions (eg. condoms, counseling on risk reduction, partner reduction), biomedical interventions (eg. treatment of HIV-positive partners, testing and treatment of sexually transmitted infections) and attention to syndemic conditions that may predispose people to increased risk-taking behaviour (eg. depression, substance use).
- Health systems should ensure the availability of other harm reduction interventions for PWID including programs that distribute sterile equipment for drug use and medication-assisted treatments for substance use disorders.
- Health systems should strive to engage a broad number and range of qualified clinical providers in initiating 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. Non-prescribing healthcare and service providers should be encouraged to play roles in PrEP and nPEP delivery including clinical monitoring, screening and management of sexually transmitted infections, counselling on risk reduction and adherence support.
- Medications for nPEP should be readily available in emergency departments, and certain clinics (eg. STI clinics and those serving at-risk populations) and pharmacies where they are likely to be needed urgently.
- PrEP and nPEP providers should be prepared to provide rapid referrals to HIV care for those who test HIV positive during initial assessment or follow-up for PrEP or nPEP
- HIV-negative people at risk of HIV acquisition, including those who have condomless vaginal or anal sex and people who inject drugs, should be counselled about and considered for PrEP.

Several studies have noted specific associations between the presence of syndemic issues and use of PrEP or nPEP. In two studies of Toronto MSM seeking or using PrEP, rates of depression, problem alcohol use and problem drug use were as high as 42%, 37.5% and 34.5% respectively using standardized psychometric tools.[38,39] In a behavioural HIV prevention trial among 4295 MSM in the United States, nPEP use was associated with both injection (aOR=2.44, 95%CI=1.69-3.51) and non-injection drug use (aOR=1.5, 95%CI=1.1-1.9).[40] Among 788 MSM seeking nPEP in Boston, 7.4% had chronic crystal methamphetamine use disorder at first nPEP use, and crystal methamphetamine use was in turn associated with major depressive disorder, anxiety disorder, attention deficit disorder, homelessness/unstable housing, as well as increased HIV incidence (aOR=3.61, 95%CI=1.51-8.60).[41] Among 145 adolescents presenting to emergency departments for nPEP in the context of sexual assault, 47% had a pre-existing psychiatric diagnosis.[42] PrEP and nPEP patient encounters may thus be important opportunities to identify and address these underlying psychosocial issues, as they are risk factors for HIV acquisition and are associated with poorer PrEP/nPEP adherence.[42] However, evidence regarding specific strategies for screening patients for these conditions was lacking.

ORGANIZATION OF HEALTH SERVICES FOR PrEP AND nPEP DELIVERY

Data explicitly comparing clinical outcomes and quality of care according to provider type and setting are lacking. However, given the diversity of activities involved in offering holistic PrEP/nPEP care, including risk-reduction counseling, medication counseling, adherence support and clinical care, there may be advantages to engaging a variety of clinical and social service providers in PrEP/nPEP delivery, such as improvements in efficiency, cost-effectiveness, patient satisfaction, and quality of care.[43-46] In addition, referrals to PrEP and nPEP prescribers should be readily accessible from multiple access points, including emergency rooms, HIV/STI counselling/testing centres, student health facilities, prenatal and family planning clinics and pharmacies. Limited data show similarly high enrollment into PrEP demonstration projects from different access points (eg. STI clinics, reproductive health programs),[47] suggesting that a variety of practice settings may be suitable for reaching at-risk individuals. As a broader variety of providers becomes engaged in providing PrEP/nPEP, it is also important that experts be available for consultation, to support health care providers in the assessment, initiation and follow-up of PrEP and nPEP.

Because timely access to antiretroviral medications is critical to the success of nPEP, clinical settings where nPEP is likely to be prescribed or accessed should ensure an adequate supply of medication on site. Efforts to eliminate administrative barriers to nPEP access are also advised.[48]

If a patient being assessed for, or during use of PrEP or nPEP acquires HIV infection, it is essential that they be rapidly linked to HIV care, as early treatment of HIV is associated with decreased morbidity/mortality[49,50] and decreased onwards HIV transmission.[9,10,51] Early linkage to care may facilitate initiation of ARV therapy, rapid virologic suppression and may minimize loss-to-follow-up.[52]

RAISING AWARENESS ABOUT PrEP AND nPEP AMONG AT-RISK PEOPLE

The decision to initiate PrEP or nPEP should be jointly made by patients and their healthcare providers. However, patients can only participate in such decision-making if they are informed about the existence, risks and benefits of these interventions. Knowledge of PrEP and nPEP among at-risk Canadian populations is variable. Efforts to raise awareness about these interventions are therefore needed at the community level, and providers should counsel at-risk individuals about PrEP and nPEP in the context of routine care.

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

INDICATIONS FOR PrEP

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

1. **PrEP is recommended for MSM [Grade 1A; strong recommendation, high quality of evidence] and TGW [Grade 1B; strong recommendation, moderate quality of evidence] who report condomless anal sex within the last 6 months and who have any of the following:**
    a. **Infectious syphilis or rectal bacterial STI, particularly if diagnosed in the preceding 12 months**
    b. **Recurrent use of nPEP (more than once)**
    c. **Ongoing sexual relationship with HIV positive partner with substantial risk* of transmissible HIV (*See Table 1 for risk definitions)**
    d. **High-incidence risk index (HIRI-MSM) risk score ≥11 (Supplementary Table 2)**

PrEP is not recommended in the context of a stable closed relationship with a single partner with no or negligible risk of having transmissible HIV [Grade 1B; strong recommendation, moderate quality of evidence].

Evidence for PrEP use in MSM

There is high quality evidence that PrEP is effective at preventing HIV among MSM (Appendix 4). In the randomized controlled trial (RCT) iPrEx, daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) reduced HIV incidence by 44% by intention-to-treat analysis,[53] and in the open-label randomized PROUD trial, it reduced acquisition of HIV by 86%.[54] Even higher reduction approaching 100% (95%CI=86%-100%) was achieved among MSM with high adherence in the iPrEx open-label extension cohort study,[55] emphasizing the importance of strategies to support medication adherence (see below). Outcomes of the US PrEP Demonstration Project conducted in 3 US cities have demonstrated only 2 cases of HIV infection (incidence=0.43; 95%CI=0.05–1.54) amongst 557 MSM and transgender women, both of whom had levels of tenofovir suggestive of poor adherence.[56] Similarly, real-world observational data from a cohort of 667 MSM engaged in PrEP care in a managed health care plan in San Francisco has demonstrated no HIV infections over a two year follow-up period.[57]

The evidence in TGW was downgraded to moderate quality because it is primarily extrapolated from data on MSM. Although the iPrEx trial enrolled transgender women, and although subgroup analyses that control for medication adherence suggest similar levels of protection in TGW to that in MSM,[58] the total volume of data available on PrEP efficacy in this population remains low.[59]

Risk assessment for PrEP

To define which MSM/TGW are at "high risk", the Panel first considered that condomless anal sex (CAS) is the key risk behaviour driving the high incidence of HIV infection in these populations. PrEP can be considered in all HIV-uninfected MSM and TGW reporting CAS, except in the setting of a monogamous relationship with a partner who has no, or negligible risk of having transmissible HIV.[51]

Identifying additional risk factors that predict an elevated risk for HIV infection amongst MSM is an important component of PrEP assessment. The listed criteria were selected because well-conducted observational studies show that these specific risk factors are associated with a high incidence of subsequent HIV infection among MSM. First, certain bacterial STIs are strong predictors of subsequent HIV risk. In a New York City cohort, the relative risk of HIV infection was 2.58 (95%CI=1.33-5.03) among MSM with rectal gonorrhea and/or chlamydia, and 1 in 15 such individuals were diagnosed with HIV within just one year of STI diagnosis;[60] comparable findings have been reported from Washington State.[61] A similarly high HIV incidence is seen after syphilis infection.[61-63] Of note, both syphilis and rectal STIs can commonly be asymptomatic, underscoring the importance of regular STI screening in sexually active MSM, in accordance with existing Canadian guidelines.[64] Prior use of nPEP is another potential indication for PrEP,[65,66] with an HIV incidence rate ratio of 4.8 (95%CI=2.0-11.5) compared to a general cohort of MSM in a report from Amsterdam,[67] and data from British Columbia suggesting that recurrent use of nPEP is associated with an incidence of 7.14/100 person-years among MSM.[68] Having an ongoing HIV-infected sexual partner who has a substantial risk of transmissible HIV (see Table 1 for definitions) is another appropriate indication for PrEP; this should be re-evaluated if the risk of transmissible HIV in the HIV-infected partner changes (eg. due to virologic suppression following initiation of antiretroviral therapy).

Use of a validated assessment tool that predicts HIV incidence such as the HIRI-MSM risk index is also a useful clinical means of identifying higher-risk MSM This index was developed for the express purpose of identifying MSM who may warrant PrEP, with the authors suggesting that PrEP be considered in men scoring 10 or higher.[69] Because the panel's recommendations for PrEP in MSM are based on a history of condomless anal sex *plus* additional risk, and because condomless anal sex is itself associated with 10 points on this scale, scores of 11 or higher are suggested. In the Momentum cohort of Vancouver MSM, scoring 10 or higher was associated with an HIV incidence of 2.04/100 person-years; scoring 25 or greater was associated with an incidence of 7.04/100 person-years.[70]

The recommendations are strong because PrEP has good acceptability,[71] excellent safety and high effectiveness in this population, because these criteria are readily identifiable by both patients and providers, and because the high risk of HIV infection associated with these criteria implies high cost-effectiveness. Although PrEP is associated with a small risk of renal and bone toxicities, these changes are generally reversible,[72,73] and the panel did not feel that the magnitude of these risks warranted a weak recommendation.

Heterosexuals

2. **We recommend PrEP for the HIV-negative partner in heterosexual serodiscordant relationships reporting condomless vaginal or anal sex where the HIV-positive partner has a substantial risk* of having transmissible HIV [Grade 1A; strong recommendation, high quality of evidence]. PrEP may be considered for the HIV-negative partner in heterosexual serodiscordant relationships reporting condomless vaginal or anal sex, where the HIV-positive partner has a low but non-negligible risk* of having transmissible HIV [Grade 2B; weak recommendation, moderate quality of evidence]. (*See Table 1 for risk definitions)**

High quality evidence has demonstrated high PrEP efficacy in heterosexual men and women (Appendix 4). Specifically, daily oral TDF/FTC was effective for preventing HIV in heterosexual people in Sub-Saharan Africa, while two additional studies did not find protective benefit of PrEP in this setting (FEMPrEP and VOICE trials), likely due to adherence issues.[74,75] Partners PrEP was a randomized trial showing a 75% (95%CI=55-87%) reduction in HIV acquisition among those in heterosexual sero-discordant couples (ie. among HIV-uninfected persons in a relationship with an HIV-infected partner).[76] The TDF2 study was a randomized trial that found 62.2% (95%CI=21.5%-83.4%) efficacy among sexually active heterosexual adults in a high prevalence setting (Botswana).[77] Targeting PrEP for those whose partners potentially have a substantial or non-negligible risk of transmissible HIV is supported by the eligibility criteria for the Partners PrEP trial,[78] as well as data from the Partners Demonstration Project, which found that providing PrEP to HIV-negative adults in serodiscordant relationships until six months after their HIV-positive partner initiated antiretroviral therapy was associated with a 96% (95%CI=81-99%) reduction in HIV incidence compared to the expected rate for the population if ART and PrEP were not available.[79]

Nested analyses within the Partners PrEP trial suggest no adverse impact of PrEP on the efficacy of oral, injectable and implantable hormonal contraception,[80] nor any impact of depot medroxyprogesterone acetate on PrEP efficacy in women or their male partners.[81]

Data on peri-conception PrEP use remains limited. Case series suggest that PrEP is a safe and effective option for HIV-uninfected women seeking pregnancy with an HIV-infected partner, in combination with additional strategies including suppressive antiretroviral therapy in the seropositive partner, confirmed

absence of concurrent STIs and timed ovulatory intercourse.[82-84] A nested substudy within the Partners PrEP trial found that PrEP does not affect male fertility, as evidenced by similar frequencies of live births and pregnancy losses among partners of men using PrEP versus placebo.[85] Results of a modelling study suggest that PrEP adds little benefit if the male partner is fully suppressed on ART.[86]

Our recommendations focus on heterosexuals in known serodiscordant relationships, because the risk of HIV acquisition can be readily identified in this setting, and because HIV prevalence in the general Canadian heterosexual population is low.[23,25] When considering PrEP for heterosexual adults on the basis of having multiple or unknown-status partners, practitioners must make decisions on a case-by-case basis, using local epidemiologic data and patient-reported risk behaviours/exposures in the partner. The panel did not identify any validated assessment tools for predicting incident infection in heterosexual adults in industrialized world setting such as Canada.

People who inject drugs

3. **PrEP may be considered for people who inject drugs if they are sharing injection drug use paraphernalia with a person with a non-negligible risk* of HIV infection [Grade 2B; weak recommendation, moderate quality of evidence]. (*See Table 1 for risk definitions)**

The Bangkok Tenofovir Study, the only RCT of PrEP in PWID, showed that daily oral TDF (without emtricitabine) conferred a 48.9% (95%CI=9.6-72.2%) reduction in HIV infection.[87] Higher efficacy of 74% was observed among those with detectable concentrations of tenofovir.[87] This evidence was graded as moderate quality because of two main limitations. First, 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. Second, in this trial and in general, it was not possible to distinguish PrEP efficacy attributable to the prevention of sexual versus parenteral HIV transmission, though sexual risk may also be an indication for PrEP as described above. There are also relatively few data on the feasibility, cost-effectiveness and acceptability of PrEP in this population. Thus the recommendation to use PrEP in PWID is weak.

The ARCH-IDU risk assessment tool may be helpful to clinicians considering PWID patients for PrEP,[88] but it has not been as rigorously validated as the HIRI-MSM.[69] PrEP for prevention of injection drug use-related HIV infection is an off-label use of TDF/FTC in Canada. The panel emphasizes that health systems should ensure full access to other proven harm reduction strategies,[32-34] as stated above.

PROVISION OF PrEP

Recommended PrEP Regimens

4. **The regimen recommended for use as PrEP is tenofovir DF/emtricitabine 300/200mg taken orally once daily [Grade 1A; strong recommendation, high quality of evidence].**

Daily TDF/FTC is the regimen of choice because it has been the most widely evaluated in high-quality studies among various at-risk populations.[53,55,76,77,89] Of note, although this regimen failed to show preventive efficacy in two large trials among women in Africa, FEM-PrEP and VOICE, there is consensus that these negative results were driven by poor adherence to the study drugs in these placebo-controlled trials.[74,75,90]

Pharmacokinetic data suggest that drug concentrations consistent with high levels of protection are achieved within 4-7 days in rectal tissue among MSM using this regimen.[91,92] Data regarding time to

protection for cervicovaginal exposures are fewer but suggest that steady state concentrations may be achieved after only 7 days, while no data are available for penile exposures.[92] PrEP users should be made aware of these principles to avoid the mistaken impression that protection is immediate.

Overall, daily oral TDF/FTC was well tolerated in clinical trials, with few discontinuations due to adverse events, although gastrointestinal symptoms such as nausea or abdominal pain has been associated with temporary PrEP interruptions in two studies.[55,89] 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).[93]

Daily TDF alone reduced HIV incidence by 67% among heterosexual men and women in the Partners PrEP study,[76] and 49% among people who inject drugs in the Bangkok Tenofovir Study,[87] but did not prevent HIV among women in the VOICE study, although adherence was poor[75]. Although this regimen met criteria for non-inferior efficacy compared to daily TDF/FTC in Partners PrEP (HR=0.67, 95%CI=0.39-1.17),[76] the larger body of evidence for daily TDF/FTC, and the lack of a major safety[94] or cost advantage (given the availability of generic TDF/FTC in Canada) over TDF/FTC mean that TDF alone is not recommended for PrEP at this stage. Importantly, there are no human data on the use of tenofovir alafenamide/emtricitabine (TAF/FTC) as PrEP at this time, and neither this regimen nor any other available antiretroviral drug can be recommended as PrEP until results of clinical trials become available.

5. **As an alternative, in MSM, tenofovir DF/emtricitabine 300/200 mg administered "on demand" (2 pills taken together 2-24 hours before 1st sexual exposure, followed by one pill daily until 48 hours after last sexual activity) may be considered [Grade 2A; weak recommendation, high quality of evidence].**

"On-demand" PrEP has been studied in one randomized placebo-controlled trial among MSM, IPERGAY, and showed 86% efficacy.[95] This study used a loading dose (two tablets) of TDF/FTC taken 2-24 hours prior to sex, followed by one tablet daily for 48 hrs after the last act of sexual intercourse. If sexual activity resumed within a week, a single dose prior to sex was recommended. If sexual activity resumed more than a week later, then the loading dose schedule (two tablets) was re-initiated. This regimen was designed to facilitate adherence among individuals who may have difficulty with a daily regimen, and who can predict periods of sexual activity where they would be at risk for HIV acquisition. Of note, participants in this study used a mean of 15 tablets per month, such that the reported efficacy is consistent with the iPrEx open-label extension (iPrEx-OLE) finding of very high efficacy even in those who managed to take daily PrEP only four days per week.[55] The recommendation is weak because there is uncertainty in the effectiveness of more sporadic sexual exposures (ie. less than once weekly) among MSM, and no clear data to guide recommendations for other populations. In contrast to daily PrEP, on-demand dosing is an off-label use of TDF/FTC in Canada.

Practical advice for providing PrEP

Suggestions on how to monitor patients using PrEP are provided in Boxes 4.1-4.2 and are explained in detail below.

HIV testing at baseline and follow-up

Because undiagnosed HIV is common in populations where PrEP may be indicated,[96] and because TDF/FTC alone is inadequate to achieve full virologic suppression in HIV-positive persons, it is critical to rule out chronic or acute HIV infection prior to PrEP initiation and prior to each follow-up prescription.

Though rare, initiation of PrEP by persons with undiagnosed acute HIV has been shown to be the key driver of drug resistance in PrEP clinical trials.[93,97]

Documentation of HIV seronegativity using the most sensitive locally available assay is thus essential shortly before PrEP initiation (eg. 14 days, or depending on the timing of recent exposures to ensure appropriate consideration of the test window period). A 4th generation HIV antigen/antibody combination test is preferred, as it offers a shorter window period compared to older assays.[98] In addition, a complete medical history and physical examination should be performed, with particular attention to signs and symptoms of acute HIV infection (AHI; Supplementary Box 1),[99] recognizing that both the positive and negative predictive value of these findings in limited.

Box 4.1 Practical advice for providing HIV pre-exposure prophylaxis (PrEP)

- ***HIV testing at baseline and follow-up:*** For all people in whom PrEP is being considered or continued, HIV-negative status should be confirmed shortly before every initial or follow-up prescription is provided. This confirmation should involve a laboratory-based 4th generation assay (or alternative if this is unavailable; see Supplementary Table 3). Confirmation of HIV status should further include evaluation for signs or symptoms suggestive of acute HIV infection (Supplementary Box 1) within the last 12 weeks. If acute HIV infection is suspected, additional laboratory evaluation with an HIV RNA NAAT test (if available) or repeat 4th generation assay 7-21 days later is suggested, and PrEP should be deferred or suspended until results are received.
- ***Renal monitoring:*** Underlying kidney disease should be ruled out before PrEP is started, using a urinalysis and serum creatinine. The eGFR should be >60 mL/min for use of PrEP.
- ***Bone health:*** Routine DXA to assess bone mineral density is not advised unless otherwise indicated according to Osteoporosis Canada guidelines at baseline or during PrEP use. PrEP may be considered in people with low bone mass or osteoporosis after the risks and benefits have been discussed with them.
- ***Sexually transmitted infections and viral hepatitis:*** Laboratory screening for STIs is suggested at baseline and at each quarterly follow-up visit, with appropriate therapy for any identified infections. Hepatitis A, B and C serologies should be performed at baseline, with vaccination for Hepatitis A and/or B for non-immune individuals and repeat serologic screening every 12 months for those who remain hepatitis B unvaccinated and hepatitis C uninfected.
- ***Frequency of follow-up:*** We suggest follow-up clinical and laboratory evaluation after 30 days and every 3 months thereafter (Table 3), and each PrEP prescription should be for no more than 3 months with no automatic refills.
- ***Pregnancy screening:*** We suggest pregnancy screening in people of child-bearing potential using PrEP every 3 months.
- ***Counseling:*** PrEP clinical encounters should include assessments and counseling regarding strategies for reducing risk of HIV infection, syndemic conditions, potential drug toxicities and adherence to medication.
- ***Adherence support:*** Interventions to support adherence to medication should be discussed at the time that PrEP is begun, actively monitored at every follow-up patient encounter, and tailored to the individual patient. Specific interventions may include patient counselling, education, medication reminders, behavioural feedback and reinforcement, peer support, follow up telephone calls or text messages, and minimization of out-of-pocket expenses.
- ***PrEP discontinuation:*** We suggest that PrEP be continued for 2-28 days after the last HIV exposure. Upon PrEP discontinuation, we advise subsequent follow-up HIV testing using a

laboratory-based 4th generation assay when available, or alternative (see Supplementary Table 3), at up to 8 weeks afterwards.

Although 50-90% of persons with a new HIV infection may experience acute retroviral syndrome symptoms, the predictive value of these symptoms in isolation or combination is poor.[100,101] In patients with AHI signs/symptoms within the previous 12 weeks, but negative HIV serology, more sensitive testing (RNA nucleic acid amplification testing [NAAT]) should be conducted, if possible, to rule out AHI prior to starting PrEP.[102-104] In high risk populations, 4th generation testing increased overall HIV detection rates by 2-4% compared to 3rd generation tests, whereas NAAT resulted in a 6% increase.[103] If nucleic acid testing is unavailable, the 4th generation test should be repeated in 7-21 days and PrEP initiation deferred until results are confirmed to be negative.[102]

Routine quarterly testing for HIV is advised during PrEP use, to ensure continued HIV seronegativity is documented before PrEP prescriptions are renewed. The optimal approach to a seropositive result is unclear. Possible interventions include i) discontinuing PrEP while awaiting confirmation of HIV status using an HIV nucleic acid test; ii) addition of antiretroviral medications to the PrEP regimen as empiric treatment intensification for suspected drug resistant HIV infection (eg. addition of boosted darunavir and an integrase inhibitor); or iii) continuing PrEP under the assumption of a false positive result (which occurred with both rapid 3rd generation EIA and 4th generation assays in the US PrEP Demonstration Project[105]). In the absence of definitive data, the Panel advises that such results be considered true positive results, and that PrEP be discontinued. These individuals should be rapidly referred to a provider experienced in HIV care, and tests for HIV resistance (ie HIV genotype) should be ordered.

Supplementary Box 1. Signs and Symptoms of Acute HIV Infectiona

Fever (53-90%)
Weight loss / anorexia (46-76%)
Fatigue (26-90%)
Gastrointestinal 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 [99]

HIV drug resistance

PrEP can lead to HIV drug resistance only if a person initiates or continues PrEP when already HIV seropositive. As stated above, this most commonly arises when PrEP is initiated by persons with undiagnosed acute HIV,[93,97] emphasizing the importance of screening for acute HIV at baseline. Resistance arising during PrEP use is rare, but was seen in the FEM-PrEP and VOICE trials in which medication adherence was questionable.[74,75]

Two cases have now been reported of PrEP failure in MSM who likely experienced primary HIV infection with strains resistant to TDF/FTC.[106,107] The risk of such transmitted drug resistance depends on the

population-level prevalence of these mutations in HIV-infected individuals and varies geographically, but is generally felt to be rare.

Renal monitoring

TDF is known to be associated with glomerular and tubular nephrotoxicity in HIV-infected[108-111] and HBV-infected individuals.[112] In HIV-negative adults, PrEP is associated with subclinical decreases in estimated glomerular filtration rate of roughly 1 mL/min/year greater than placebo, that are generally reversible.[113-116] PrEP is not significantly associated with renal tubulopathy.[117] In the US PrEP Demonstration Project, PrEP-related decline in estimated glomerular filtration rate (eGFR) was non-progressive through Week 48, and decline to eGFR<70 mL/min was more common in older patients with baseline eGFR <90 mL/min.[118] A recent meta-analysis found that PrEP was associated with more grade 1 or higher creatinine changes (pooled OR=1.36; 95%CI=1.09–1.72), but the absolute risk increase was only 0.6% (95%CI=0.1–1.2%).[72] Underlying kidney disease should be ruled out before starting PrEP using a urinalysis and serum creatinine, and caution should be exercised in those with additional risk factors for renal disease. TDF-based PrEP is not advised for those with creatinine clearance (CrCl) or eGFR below 60 mL/min.[119] Creatinine should be repeated after one month, as TDF-related changes in renal function were seen as early as 4 weeks in PrEP studies.[113-115] Progressive declines in eGFR should be investigated and managed according to Canadian Society of Nephrology Guidelines.[120,121] Urinalysis is therefore not advised on a routine basis for patients receiving PrEP, because no trials have found significant differences in serum phosphate or renal tubular function among PrEP users.[113] There are no data on specific interventions for reducing PrEP-related renal toxicity, but the panel suggests minimizing concomitant nephrotoxins, avoiding volume depletion, management of hypertension and control of blood glucose as per guidance from the Canadian Society of Nephrology.[120,121]

Bone Health

PrEP is also associated with modest decreases in bone mineral density (BMD), mirroring the known effects of TDF on bone in HIV-infected patients.[122,123] In iPrEx, BMD differences were -0.61% to -0.91% compared to placebo by 24 weeks but stabilized after that point.[124] Changes recover upon cessation of drug.[73,125] Differences measured -0.7% to -1.1% over 15-24 months in another MSM study,[126] and -0.84% to -1.62% over 30 months among men and women in a Botswanan study.[127] No increase in fracture rates has been observed thus far in PrEP studies, but follow-up times have been short. Bone densitometry is not routinely advised unless clinically indicated according to Osteoporosis Canada guidelines.[128] PrEP could be considered in persons with low bone mass or osteoporosis, after a full discussion of the potential risks and benefits. As a primary preventive measure, all patients receiving PrEP should be counselled regarding appropriate calcium and vitamin D intake, and exercise recommendations as for the general population.[128]

Sexually transmitted infections (STIs) and viral hepatitis

Because STIs and viral hepatitides are prevalent in PrEP target populations, thorough and regular screening (every three months for STIs) is indicated.[129-131] Of particular importance is screening for hepatitis B virus (HBV) infection, since the medications used for HIV PrEP (TDF and FTC) are also active against HBV. Individuals who are not immune to HAV and/or HBV should be offered vaccination according to Canadian Immunization Guidelines.[132] Those who remain susceptible to HBV and HCV should undergo annual screening, or more frequently depending on symptoms and ongoing risk exposures,[131,133] although TDF/FTC use may itself protect against HBV acquisition.[134]

Frequency of follow-up

The suggested follow-up schedule is one month after PrEP initiation followed by a 3-monthly basis, which is the routine followed in most studies to date.[53,55,56,76,79,95] Longer intervals between STI screens have been shown to be associated with missed or delayed STI diagnoses in PrEP-using populations.[129,130] Each visit should address medication tolerability and adherence, symptoms of acute HIV and STIs, pregnancy (by history and laboratory testing as appropriate), and the ongoing need for PrEP, and should include counseling regarding HIV risk reduction and medication adherence.

Specific components of effective risk reduction counseling interventions include education about HIV transmission and risk, assessment of patient motivations, and skills training regarding self-management, partner negotiation and condom usage.[135] Five principles underlying effective counseling interventions include: framing the desired behaviour change as part of a new social role; conveying issue- and population-specific information; teaching cognitive, affective and behavioural self-management skills; addressing environmental barriers to implementing the desired change; and providing tools for ongoing support.[136] Of note, PrEP trials have generally shown either no or minimal increases in risk-taking behaviour among study participants.[54,137-140] Specific adherence support interventions are discussed below.

Pregnancy screening

Routine testing for pregnancy is warranted as applicable, because there is relatively less data on PrEP use in this setting, and patients should be made aware of the potential risks and benefits (see below).

Counselling

Risk reduction and syndemic conditions: PrEP users should be educated about additional HIV prevention strategies from which they could benefit. These include condom use, seropositioning (engaging in anal sex as the insertive rather than receptive partner due to the lower risk of HIV acquisition), nPEP, antiretroviral therapy for HIV-positive partners, needle and syringe programs as well as opiate substitution treatment. Because of the high burden of syndemic conditions among PrEP users,[38,39] providers should actively screen for mental health and substance use problems, and provide onward referrals as needed.

Drug toxicities: Patients' experiences using PrEP should be discussed in light of their impact on medication adherence as well as published data on safety and tolerability (see above).

Adherence: A direct relationship between adherence and HIV prevention efficacy has been clearly demonstrated in the original PrEP trials. The iPrEx trial found that HIV acquisition was reduced by 92% among participants in the active arm with detectable drug concentrations, compared to 44% in intent-to-treat analyses.[53] In the Partners PrEP trial, efficacy increased from 75% overall to 90% in the TDF/FTC arm when drug was detectable in the blood.[76] Among Thai people who inject drugs, PrEP efficacy was only 49% overall, but was 74% among those with detectable tenofovir concentrations.[87] Further, in the iPrEx open-label extension (OLE) study among MSM, HIV incidence was reduced by 44% in participants taking less than two doses per week, by 84% in those taking 2-3 doses per week, and by 100% (95%CI=86%-100%) in those taking 4-7 doses per week.[55] These data also suggest that PrEP is considerably more "forgiving" of imperfect adherence among MSM than is antiretroviral therapy of established HIV infection, but it is unclear if this is also the case for other populations, notably women. Given this importance, providers should actively discuss and monitor adherence at every encounter. When monitoring adherence, it may be helpful to combine multiple strategies (eg. self-report, pill count,

pharmacy refill records), since self-report has often been shown to overestimate adherence in PrEP clinical trials.[141,142]

Adherence support

Additional adherence support interventions may be warranted for some patients, and should be tailored to the individual. However, there are only limited data on specific interventions that improve PrEP and nPEP adherence. In a single-arm Ugandan substudy among participants with low (<80%) adherence in the Partners PrEP trial, intensified counselling using principles of cognitive behavioural therapy and problem-solving improved adherence from 75.7% to 84.1% in the month after the first intervention session ($p<0.001$).[143,144] A systematic review of adherence support interventions across other prevention fields found that multi-modal interventions were most effective.[145] Specific interventions that should be considered are listed in Supplementary Box 2.

Supplementary Box 2. Interventions to support PrEP / nPEP adherence

Counseling interventions
Education about the importance of medication adherence
Ensuring accurate knowledge about medication risks and benefits
Preparing for and managing side effects
Screening for depression and substance use
Feedback on medication adherence

Patient-initiated strategies
Self-efficacy based interventions (e.g. pill boxes, phone apps)
Integration into daily routine

Additional interventions
Short text message reminders or check-ins
Peer / social support

PrEP Discontinuation

If a decision is made that PrEP is no longer indicated, an HIV test should be performed and the patient provided with linkage to ongoing care and counselling as appropriate. The optimal timing for conducting the HIV test is unclear but could be considered at up to 8 weeks after stopping PrEP, depending on the timing of the most recent exposure and the degree of PrEP adherence, because of the possibility that PrEP may delay the development of HIV antibodies. For those discontinuing daily PrEP, it remains unclear for exactly how long PrEP should be taken after the last exposure. The efficacy of "on-demand" PrEP as studied in the IPERGAY trial suggests that a minimum of two daily doses is required,[95] but insufficient data are available to be confident that more is not needed. Pharmacokinetic models suggest that drug levels consistent with >90% risk reduction persists for seven days after PrEP discontinuation in MSM,[91] but this finding does not indicate when it is clinically appropriate to stop PrEP. In the absence of definitive data, the panel suggests a conservative approach of continuing PrEP for up to 28 days after the last exposure (based on standard recommendations for PEP, below). MSM with a long duration of PrEP adherence may require as little as two days.

PrEP use in special populations

Box 4.2 Additional considerations when using PrEP in special populations

- ***Hepatitis B infection:*** If TDF/FTC PrEP is prescribed in a person infected with chronic hepatitis B, appropriate monitoring for hepatitis B virus should be performed in accordance with hepatitis B treatment guidelines, if necessary in consultation with a qualified practitioner with experience in treating the virus. When considering PrEP discontinuation, the need for ongoing therapy for hepatitis B virus should be assessed. If PrEP is discontinued and no other therapy for hepatitis B virus is used, monitoring for a flare of the condition is advised.
- ***Pregnancy and breastfeeding:*** TDF/FTC PrEP may be considered during pregnancy and breastfeeding after the benefits and risks have been discussed with the patient.

Hepatitis B virus (HBV) infection

Because TDF and FTC both have antiviral activity against hepatitis B virus (HBV), PrEP use in an HBV-infected person would also function as HBV therapy. Care must thus be taken to ensure the proper monitoring of TDF/FTC for both clinical indications, and providers should follow existing Canadian guidelines for the additional management of HBV in such individuals.[146] Discontinuation of TDF/FTC could potentially trigger a hepatitis flare in HBV-infected persons, and should be monitored accordingly, although data on the absolute risk of a flare is scarce. The only published report in this population found that among 2499 participants in iPrEx, five of those randomized to receive TDF/FTC had chronic HBV infection (defined on the basis of positive HBV surface antigen) and were followed after PrEP discontinuation; none met criteria for hepatitis flares, although one had a grade 1 elevation in transminases at 12 weeks post-discontinuation.[147]

Pregnancy and breastfeeding

Data on 1785 heterosexual couples in the Partners PrEP trial found no differences in pregnancy loss, preterm birth, congenital malformations, infant mortality or infant growth outcomes with TDF/FTC or TDF alone as PrEP compared to placebo, but confidence intervals were wide, so a small risk of harm could not be completely excluded.[148] Data on HIV-infected women from the antiretroviral pregnancy registry suggest no difference in birth defects with TDF/FTC-containing HIV treatment regimens.[119] Both TDF and FTC are reported to be secreted in breast milk at low-moderate levels.[119] One study of 50 breastfeeding women taking PrEP as directly observed therapy showed that 6% and 96% of infant plasma samples had detectable tenofovir and emtricitabine levels, respectively, and that the overall amounts of drug ingested by breastfed infants were estimated to be <0.01% and 0.5% of the therapeutic pediatric daily doses.[149]

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

INDICATIONS FOR nPEP

6. **We recommend nPEP for HIV-negative individuals who present no later than 72 hours after an exposure that is moderate- or high-risk* for HIV transmission with a person who has a substantial risk* of having transmissible HIV [Grade 1C; strong recommendation, low quality of evidence]. (*See Tables 1-2 for definitions)**

7. **nPEP can be considered for HIV-negative individuals who present no later than 72 hours after 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; weak recommendation, low quality of evidence]. (*See Tables 1-2 for definitions)

Rationale

Data drawn from animal models,[150] studies of mother-to-child transmission,[151] as well as case-control[152] and cohort studies[153] in the occupational setting suggest that HIV medications can be given to HIV-negative persons after potential HIV exposure to prevent seroconversion. In the occupational setting, the observed magnitude of risk reduction with zidovudine monotherapy as PEP was 81%;[152] modern PEP regimens are believed to offer considerably greater efficacy. Nevertheless, complete protection against infection cannot be guaranteed, with reported cases of PEP failure related to delayed initiation, poor adherence, transmission of drug-resistant virus, and other factors.[154-156] Although the quality of this evidence regarding PEP efficacy is low, being based on observational studies only, ethical constraints preclude the potential for higher quality data in humans.

Assessment of transmission risk

The risk of HIV acquisition depends on two factors: the likelihood the source has transmissible HIV infection (Table 1 and Epidemiology of HIV section), and the biological risk of HIV transmission based on the exposure type (Table 2). Among those who present within the 72-hour window during which intervention is possible, nPEP is recommended if the exposure type was moderate-to-high risk and the source individual has a substantial risk of having transmissible HIV infection (Table 4). nPEP may be considered for individuals who present within 72 hours of 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. The use of post-exposure prophylaxis is not recommended for individuals who have had a low-risk exposure, regardless of source HIV status. The Panel does not recommend nPEP for those who have had a moderate-to-high risk exposure from a source individual who is known to be HIV-positive but is documented to be virologically suppressed on ART, and who does not have a known concomitant STI. Of note, all PEP use is off-label in Canada.

Timing of initiating nPEP

8. **We recommend initiating nPEP as soon as possible after an exposure, up to a maximum of 72 hours afterwards [Grade 1D; strong recommendation, very low quality of evidence].**

Although there are no data on adult humans regarding the maximum time threshold after which nPEP no longer offers protective benefit, in animal models, a gradient of prevention benefit was observed with no transmission events among animals treated within 24 hours of exposure, only partial protection among those treated at 72 hours, and no benefit if initiation was delayed beyond 72 hours, in keeping with the biology of HIV infection.[157-159] In the perinatal setting, greater protection is associated with initiation of antiretroviral prophylaxis intra-partum versus 48 hours postpartum versus 72 hours postpartum.[160] This recommendation is strong despite the very low quality of evidence because of its sound basis in the biology of HIV transmission, and because feasibility and ethical constraints preclude the potential for higher quality human studies.

The urgency of nPEP initiation suggests that emergency departments are an optimal setting in which nPEP can be prescribed, and observational data show that prescribing by emergency physicians is safe and appropriate.[161]

Evaluation of the Source

If possible, assessment of the relevant sexual or injection drug use partners is warranted, because ascertainment of their HIV status is key to determining whether nPEP is indicated. The preferred assay for HIV testing of source patients of unknown status is a 4th generation combination antigen/antibody

Box 5.1 Evaluating the source person

- If the source person is of unknown HIV status, is available and provides consent, HIV testing with a 4th generation assay should be performed. If the source person is suspected clinically of having acute HIV infection (Supplementary Box 1) then additional laboratory evaluation with an HIV RNA NAAT test (if available) or repeat 4th generation assay 7-21 days later is advised.
- If the source person is known to be HIV-positive, is available, and provides consent, a detailed history of antiretroviral therapy and HIV viral load test should be obtained to guide decisions about the need for and type of nPEP to be provided.
- If the source person is of unknown HIV status but at high epidemiologic risk, or is HIV-positive and unavailable or does not provide consent for additional viral load testing (or verification of undetectable status), there should be an assumption of substantial risk for transmissible HIV infection.

assay due to its window period of 14 -21 days (Supplementary Table 3). If the source has clinical signs or history suggesting acute HIV infection (Supplementary Box 1), then an HIV RNA NAAT test should also be performed to further reduce the window period to 7-15 days;[162] if this assay is unavailable, a follow-up 4th generation assay should be repeated 14-21 days later (ie. after the window period of the first test). If the source is found to be HIV negative, then nPEP may be discontinued. Data from an nPEP program in Switzerland found that in situations where the source could be tested (43% of unknown status cases), nPEP could be avoided or discontinued in all but 6% of cases, leading to a 30% reduction in costs for those exposed individuals.[163]

If the source individual is known to be HIV-positive, and is available for assessment, an updated viral load test, viral resistance data and detailed ART history should be obtained to guide decisions regarding the need for nPEP (Tables 1 and 4) and choice of nPEP regimen, though initiation of nPEP should not be delayed pending this information.

PROVISION OF nPEP

Recommended nPEP Regimens

9. **The following are recommended as first-line regimens for nPEP (Tables 5 and A5):**
    a. **TDF/FTC 1 tablet PO daily and raltegravir 400mg PO BID for 28 days [Grade 1A; strong recommendation, high quality of evidence], or**
    b. **TDF/FTC 1 tablet PO daily and dolutegravir 50mg PO daily for 28 days [Grade 1C; strong recommendation, low quality of evidence], or**
    c. **TDF/FTC 1 tablet PO daily and darunavir 800mg PO daily + ritonavir 100mg PO daily for 28 days [Grade 1A; strong recommendation, high quality of evidence].**

Because PEP is highly effective, clinical trials cannot feasibly establish the superiority of any specific nPEP regimen over another for preventing HIV seroconversion. Our recommendations are therefore based primarily on moderate-to-high quality data on rates of regimen completion and adverse events associated with various nPEP regimens (Appendix 4). The panel recommendations are strong for all three potential regimens because they each have generally favourable risk/benefit profiles,

acceptability, costs and feasibility, though the best choice may vary depending on patient characteristics (Table 5 and Supplementary Table 4). All contain the NRTI backbone TDF/FTC, which has been associated with higher rates of PEP completion.[164]

Observational studies have shown that the integrase strand transfer inhibitor (INSTI) raltegravir with TDF/FTC is well tolerated, results in reasonable adherence, and has a low propensity for drug-drug interactions.[165-168] One RCT comparing raltegravir to twice daily use of the PI lopinavir/ritonavir (LPV/r), both used with TDF/FTC, found raltegravir to have fewer adverse events (60.8% versus 74.3%, p=0.04), fewer premature discontinuation (23.7% versus 36.6%, p=0.04) and improved adherence (30.8% versus 49.2%, p=0.03), though it is uncertain if prescribing LPV/r once daily could have improved the latter outcome.[169] The protease inhibitor (PI) ritonavir-boosted darunavir (DRV/r) with TDF/FTC is also a recommended option, on the basis of an RCT in occupational and non-occupational PEP showing fewer grade 2 or higher adverse drug reactions (16.1% versus 29.3%, p=0.006) particularly diarrhea and nausea, and similarly high completion rates (93.5% versus 90%), compared to LPV/r.[170] Dolutegravir once daily along with TDF/FTC was also recently studied in nPEP users and 90% were able to complete the 28 day regimen as prescribed, with 98% reporting complete adherence and adverse events primarily being grade 1-2.[171]

The choice between these three options should be based on patient factors (Supplementary Table 4). Raltegravir with TDF/FTC may be preferred in patients using multiple medications,[168] since raltegravir is neither a substrate, inducer nor inhibitor of the cytochrome P450 enzyme system. Dolutegravir also has limited drug interactions while in contrast, ritonavir-boosted darunavir has substantial risk of drug interactions through its effects at cytochrome P450. However, adherence to raltegravir may be challenging due to its twice daily dosing schedule, while dolutegravir or darunavir+ritonavir with TDF/FTC are dosed once daily.

Conversely, darunavir+ritonavir with TDF/FTC is recommended if the source is known or suspected to harbour drug-resistant virus (eg. documented prior drug resistance, found to be viremic despite antiretroviral therapy at the time of exposure), or if the exposed individual is suspected to have acute HIV infection at the time of assessment, due to its potency against viruses harbouring a wide range of resistance mutations.[172,173] Consultation with an HIV specialist is recommended in such scenarios, but nPEP initiation should not be delayed pending expert advice.

Administration of dolutegravir or raltegravir should be separated from oral medications containing polyvalent cations (eg. cation-containing antacids, iron, or calcium supplements) to avoid chelation and reduced oral absorption of the integrase inhibitor.

Rationale for three-drug regimens

The recommended nPEP regimens all involve three active antiretroviral drugs. Indirect evidence for three-drug nPEP regimens, containing two nucleoside reverse transcriptase inhibitors (NRTIs) plus a third drug from another class such as a protease inhibitor (PI) or integrase strand transfer inhibitor (INSTI), comes from clinical trials in HIV- infected patients, where randomized trials clearly established the superiority of triple over dual therapy.[174,175] However, no randomized trials have directly compared dual versus triple therapy for nPEP. Prior iterations of some international guidelines have recommended two-drug nPEP for lower risk exposures, based primarily on better tolerability and nPEP completion rates compared to triple therapy regimens.[176,177] However, given that currently available antiretrovirals are much better tolerated, the relevance of this consideration to modern nPEP is limited. While three-

drug nPEP may increase costs, it eliminates the need for additional risk stratification at the time of initial assessment, and increases the likelihood that individuals with undiagnosed baseline HIV infection receive a fully active regimen.

Alternative nPEP regimens

Alternative nPEP regimens may be considered in certain clinical settings, or if side effects emerge while using a preferred regimen (see below and Table 5).

NRTI alternatives: Zidovudine/lamivudine is an alternative to TDF/FTC in those with renal dysfunction (eGFR<50mL/min; TDF requires dosage adjustment in this situation and may increase the risk of renal toxicity) but is associated with more frequent side effects and greater risk of non-adherence. Use of TDF with lamivudine is another alternative to TDF/FTC but imposes a slightly greater pill burden. Tenofovir alafenamide/emtricitabine has not been evaluated for use in PEP, but its success in preventing simian/human immunodeficiency virus (SHIV) infection in 6/6 rhesus macaques when used as PrEP is encouraging.[178]

INSTI alternatives: Elvitegravir (co-formulated with cobicistat/tenofovir DF/emtricitabine) is an alternate INSTI to raltegravir and dolutegravir that has the advantage of being a one pill, once daily regimen with proven excellent tolerability in the HIV-positive population.[179-181] Elvitegravir with TDF/FTC has been shown to have good nPEP completion rates and tolerability,[182,183] but a disadvantage is its potential risk for drug interactions due to cytochrome P450 inhibition by cobicistat, and it lacks the high genetic barrier to resistance that characterizes darunavir- and dolutegravir-based regimens. Raltegravir HD 1200 mg once daily may also be a reasonable alternative INSTI, based on extrapolation from the twice daily regimen in PEP together with the once daily regimen in established HIV infection,[184] although there is no published experience with the use of this formulation in PEP.

PI alternatives: Lopinavir/ritonavir and atazanavir-ritonavir are alternate PIs to darunavir+ritonavir, supported by prospective clinical data.[167,170,185,186] However, lopinavir/ritonavir imposes a high pill burden and risk of gastrointestinal side effects compared to darunavir,[170] while sub-therapeutic drug levels of atazanavir may occur if used with acid-suppressing agents such as proton pump inhibitors. Darunavir boosted by cobicistat can also be considered as an alternative, based on the similar pharmacokinetic profile achieved compared to ritonavir-boosted darunavir,[187] although there are limited clinical data on its efficacy even in the setting of established HIV infection. Drug interactions may be a challenge with all PI-based regimens due to their co-administration of the cytochrome P450 enzyme inhibitors ritonavir, or cobicistat.

Regimens not recommended for use in nPEP: Abacavir is not recommended, given the impracticality of screening nPEP candidates for the HLA-B*5701 allele that predicts life-threatening hypersensitivity reactions to that drug.[188] The Panel does not recommend any non-nucleoside reverse transcriptase inhibitor-based regimen for nPEP use; nevirapine-based PEP has been associated with hepatotoxicity, skin reactions and death,[189] efavirenz-based PEP is associated with central nervous system intolerance and PEP non-completion,[190] and all NNRTI regimens including rilpivirine-based PEP may have compromised effectiveness due to the prevalence of NNRTI resistance in the community (although tolerability and completion rates with rilpivirine co-formulated with TDF/FTC were high in an Australian open-label study[191]).

Duration of nPEP

The panel did not identify any human data comparing various durations of PEP. However, a seminal macaque study observed a significantly decreased risk of seroconversion when PEP was administered for 28 compared to 10 days or 3 days.[192] Clinical trials comparing the efficacy of different durations of nPEP are unlikely to be conducted in the future, and a 28-day course of medications remains the standard of care.

The duration of nPEP may need to be extended in the event that a repeat high-risk exposure before the 28-day course is completed. Among MSM, nPEP should be extended for an additional 48 hours after a repeat high-risk exposure occurring on day 27 or 28 of nPEP, provided that the regimen included TDF/FTC and adherence was high. Although exposures on day 27 and 28 have not been studied directly, results from the IPERGAY study of "on-demand" PrEP can be extrapolated to recommend two further days of therapy following exposure under these circumstances.[95] This recommendation is based on the pharmacokinetic argument that four weeks of TDF/FTC-containing nPEP should achieve high tissue concentrations at the time of the additional exposure,[91] analogous to the effect of the loading dose in IPERGAY. Since no such data exist for other populations, consideration should be given for a longer course (additional 2-28 days) if this scenario arises in non-MSM. The duration of additional PEP required if an exposure occurs at other points during PEP use is unclear but could be up to 28 days after the repeat exposure.

Use of Starter Kits

10. **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; weak recommendation, high quality of evidence].**

A common practice when dispensing nPEP medications is to provide only a partial supply initially (also called a starter pack), enabling prescribers to reassess the need for nPEP when baseline laboratory results become available, modify therapy in cases of drug intolerance or concerns about drug resistance, and ultimately, limit drug costs and toxicities by preventing unnecessary use. However, a systematic review showed that dispensing a full course of nPEP rather than a starter kit at initial presentation is associated with fewer PEP refusals and superior PEP completion rates.[193] When the indication for nPEP is clearly established, the full course of PEP may therefore be dispensed from the outset, rather than using a starter pack. This recommendation is weak because variability in who (patients or institutions providing the starter packs) covers the cost of the medication in different contexts may produce differences in which approach is favoured.

Practical advice for providing nPEP

Suggestions on how to provide nPEP are shown in Boxes 5.2-5.3.

Box 5.2 Initial evaluation and monitoring for nPEP

- ***Screening for sexual assault:*** Health care providers who undertake initial assessment for nPEP should distinguish between consensual and non-consensual exposures and should provide or refer to sexual assault services accordingly.
- ***Baseline HIV testing:*** Baseline HIV status should be determined using a laboratory-based 4th generation assay when available, or alternative (see Supplementary Table 3) for all people in whom nPEP is being considered. Where available, an HIV point-of-care test can also be included, but should not replace the standard serology test.

- ***Additional laboratory testing:*** Baseline evaluation of individuals initiating nPEP should include laboratory assessment of hepatic and renal function, and evaluation for STI and hepatitis infection, with appropriate subsequent management (see Table 6). Ongoing laboratory monitoring of biochemistry and hematology during nPEP is advised 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.
- ***Counseling:*** nPEP clinical encounters should include assessments and counseling regarding strategies for reducing risk of HIV infection, syndemic conditions, potential drug toxicities and adherence to medication.
- ***Adherence support:*** Interventions to support adherence to medication should be discussed at the time of nPEP initiation, actively monitored at every follow-up patient encounter, and tailored to the individual patient. Specific interventions may include patient counselling, education, medication reminders, behavioural feedback and reinforcement, peer support, follow-up telephone calls or text messages and minimization of out-of-pocket expenses.
- ***Follow-up HIV testing:*** Final follow-up HIV testing should be performed using a 4th generation assay at 12 weeks following exposure (8 weeks following completion of nPEP).

Screening for sexual assault

Screening for non-consensual sex is advised in order to ensure patients are offered access to sexual assault services where appropriate, and because sexual assault is a recognized risk factor for challenges with nPEP adherence which may warrant additional support.[194,195]

Baseline HIV testing

Baseline HIV status should be determined for all people in whom nPEP is being considered, using a laboratory-based 4th generation assay when available, supplemented by HIV RNA NAAT test if acute HIV infection is suspected (Supplementary Box 1, Supplementary Table 3; see also section on nPEP in special populations). An HIV point-of-care test can be used in parallel for initial screening, since results become available immediately, but should not replace standard serology testing as it is a third generation assay. Individuals presenting for nPEP often belong to populations with high rates of pre-existing undiagnosed HIV, with studies finding 1.2-6.8% of MSM seeking nPEP to be HIV-positive at baseline.[196,197]

Additional laboratory testing

Because baseline prevalence of STIs is high in nPEP users (up to 16.5% in a Dutch MSM cohort),[198-200] thorough evaluation for bacterial STIs and viral hepatitis is advised at the initial nPEP assessment (Table 6). Baseline assessment of renal and hepatic function is also advised, but because of the excellent toxicity profiles of the recommended nPEP regimens, ongoing monitoring is only needed if baseline abnormalities are identified and in those developing signs or symptoms of organ dysfunction or medication-related adverse effects.[165-167,169,170,201,202]

Counselling

Risk reduction and syndemic conditions: nPEP users should be educated about additional HIV prevention strategies from which they could benefit. These include condom use, seropositioning (engaging in anal sex as the insertive rather than receptive partner due to the lower risk of HIV acquisition), PrEP, antiretroviral therapy for HIV-positive partners, needle and syringe programs as well as opiate substitution treatment. Because of the high burden of syndemic conditions among nPEP users,[40-42]

providers should actively screen for mental health and substance use problems, and provide onward referrals as needed.

Drug toxicities: Patients' experiences using nPEP should be discussed in light of their impact on medication adherence as well as published data on regimen-specific safety and tolerability (see above).

Adherence: Human data on the relationship between adherence and efficacy in the setting of nPEP are lacking, but animal models show increasing efficacy with an increasing number of days of nPEP use, as described above.[192]

Adherence support

A small RCT among nPEP users in France found that an intensive four-session counseling intervention improved adherence to nPEP medications and follow-up care.[203] Two additional RCTs of intensive support interventions (multi-session counseling, telephone support with adherence diary) were unable to show statistically significant improvements in nPEP adherence, although findings were in the direction of benefit.[204,205] Building on findings from a pilot trial,[206] a single RCT found that combining nPEP with contingency management (positive reinforcement in the form of vouchers for goods/services) among methamphetamine-using MSM was associated with increased nPEP completion (aOR=7.2, 95%CI=1.1-47.9).[207] Specific interventions that should be considered are listed in Supplementary Box 2. Intensive adherence support may be particularly important in those with risk factors for poor adherence, such as sexual assault survivors using nPEP.[194,195]

Follow-up HIV testing

The suggestion to conduct follow-up testing with a 4th generation HIV test at 12 weeks following exposure (8 weeks following completion of nPEP) is based on data showing that the probability of a false negative result with this assay reaches 0.01 by 42 days after infection.[208,209] While there is uncertainty about whether nPEP delays HIV seroconversion, there are no data confirming this to be the case. HIV testing beyond the 12 week time-point may be considered in special circumstances. For instance, delayed seroconversion has been seen in an individual who acquired concurrent HIV and HCV,[210] leading U.S. Centers for Disease Control to recommend HIV testing at six months in those with HCV seroconversion during nPEP follow-up.[211] Delaying until 16 weeks may be considered if only 3rd generation HIV testing is available, because of its longer window period; with this assay, the probability of a false negative result reaches 0.01 by 80 days post-infection. Of note, delayed seroconversion has been seen in a cohort of acutely HIV-infected individuals initiating antiretroviral therapy in Thailand a median of 19 days (range=1-62) after infection.[212] HIV test non-reactivity remained as high as 17% and 4% after 24 weeks of ART with 4th and 3rd generation tests respectively (with the third generation having a surprisingly lower rate compared to the more sensitive 4th generation assay), but the impact of four weeks of PEP on seroconversion with these assays remains unclear.[212]

Conversely, early testing at 4-6 weeks post-exposure may be considered if symptoms suggestive of acute HIV infection arise. Further, because most nPEP programs report challenges with high loss to follow-up,[194,196,213] earlier testing may be considered to facilitate retention in care. Earlier testing may help distinguish nPEP failure from HIV seroconversion resulting from additional exposures distal to the index event.[155] However, routinely testing at 4-6 weeks is not advised based on the uncertain reliability of an early test in the context of nPEP use, the additional healthcare costs involved in routinely doing such testing, and the requirement that all patients testing negative at this timepoint would still be advised to repeat a test at 12 weeks.

Early discontinuation of nPEP

In general, nPEP should be discontinued early (before day 28) if the source tests HIV-negative using a 4th generation HIV assay. Continuation may be considered despite this result where acute HIV infection of the source is strongly suspected based on clinical history; additional follow-up with an HIV RNA NAAT test or repeat 4th generation assay should be performed in such situations (see Section on Evaluation of the Source above, Supplementary Table 3 and Supplementary Box 1).

Similarly, nPEP may be discontinued early if the source is HIV-positive but has a negligible risk of transmissible infection (Table 1), as determined by an up-to-date clinical assessment. This assessment should include an updated HIV viral load measurement because self-reported results can be inaccurate;

Box 5.3 Stopping nPEP early

- nPEP should be discontinued early if the source tests HIV-negative using a 4th generation assay. However, continuation of nPEP may be considered despite this result where acute HIV infection of the source is strongly suspected based on clinical history (Supplementary Box 1), and results of additional laboratory testing are pending as previously described.
- nPEP may be discontinued early if the source is HIV-positive and found 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.
- If ≥72 consecutive hours of nPEP have been missed, discontinuation of nPEP should be considered.

in one cohort of MSM from San Francisco, 92% of those on ART believed they had a suppressed viral load at the time of their last clinic visit, but only 62% actually did on the basis of laboratory testing.[214]

Due to the half-lives of the recommended nPEP agents (~9 hours for raltegravir, ~15 hours for ritonavir-boosted darunavir, ~14 hours for dolutegravir), and the known decreased efficacy of initiating nPEP more than 72 hours after an exposure, it is unclear if therapeutic levels will be maintained in the setting of an extended dosing interruption, and nPEP discontinuation should be considered if there as been a 72 hour interruption between scheduled doses. For periods of shorter interruption, nPEP should be resumed to complete the full 28 day original course.

nPEP use in special populations

Suspected acute HIV infection in the exposed individual

Symptoms suggestive of possible acute HIV infection (Supplementary Box 1) should not preclude nPEP initiation, because the predictive value of the clinical examination for acute HIV is poor, as noted above.[100,101] Instead, additional laboratory evaluation for acute HIV infection is advised in this circumstance (Supplementary Table 3). If the exposed individual is subsequently found to be HIV-positive and has already started nPEP, the medications should be continued and consultation with an HIV expert should be urgently arranged to determine optimal further management.

PrEP users

Individuals who are taking PrEP as prescribed (continuously or "on-demand") do not require nPEP after potential HIV exposures due to the protective benefit of PrEP alone.[53,76,77,87,89,95] In contrast, if a patient is not using PrEP exactly as prescribed (ie. doses have been missed), there are limited data to guide clinicians. While observational data suggest that imperfect adherence to PrEP still offers some

protection among MSM (see above),[55] experimental comparisons are lacking, and comparable data in other populations do not exist. Decisions regarding nPEP in PrEP users with imperfect adherence must be individualized, based on how many doses were missed, timing relative to the potential HIV exposure, and the nature of the exposure. Consultation with an expert may be warranted.

Box 5.4 Additional considerations when using nPEP in special populations

- ***Suspected acute HIV infection:*** If acute HIV infection of the exposed individual is suspected (Supplementary Box 1) then additional laboratory evaluation with an HIV RNA NAAT test (if available) or repeat 4th generation assay 7-21 days later should be performed. nPEP should not be withheld pending the results of these investigations. If the exposed individual is subsequently found to be HIV-positive and has started on nPEP, the antiretroviral regimen should be continued and an HIV expert should be consulted as soon as possible.
- ***PrEP users:*** Individuals who are taking PrEP as prescribed (whether as continuous or on-demand use) do not require nPEP after potential HIV exposures. In a person who is not using PrEP as prescribed, initiation of nPEP may be considered as per the guideline recommendations.
- ***Hepatitis B infection:*** Patients with chronic HBV infection who require nPEP may receive a regimen containing TDF/FTC, but close clinical and laboratory monitoring for hepatitis flares should be considered upon completion of nPEP.
- ***Pregnancy and breastfeeding:*** Patients who are pregnant and require nPEP should receive TDF/FTC 1 tablet orally daily, with either raltegravir 400 mg PO twice daily, or darunavir 800 mg orally daily + ritonavir 100 mg orally daily. Breastfeeding during nPEP use is not advised.

Hepatitis B virus (HBV) infection

Because the recommended nPEP backbone (TDF/FTC) is fully active against both HIV and HBV, there have been concerns that completion of nPEP after 28 days (in effect removal of HBV therapy) could result in hepatitis flares; prospective trials of PrEP have excluded HBV-infected individuals for this reason.[89,95] However, given the absence of such flares when TDF/FTC-based PrEP was stopped in a small study of individuals with chronic HBV infection,[147] TDF/FTC may be used for nPEP in HBV-infected patients who have no evidence of severe liver disease. Close clinical and laboratory monitoring for hepatitis flares after nPEP completion should be considered.

Pregnancy and breastfeeding

The raltegravir- and ritonavir-boosted darunavir-based nPEP regimens recommended in this guideline are among the preferred treatment regimens for HIV-infected pregnant women, based on ample safety and treatment efficacy data.[215] While some guidelines suggest BID dosing for darunavir+ritonavir in HIV-infected pregnant women, the Panel supports standard once daily dosing when this agent is selected for nPEP in pregnancy because the viral burden is considerably reduced compared to established HIV infection, and because pharmacokinetic studies in HIV-infected pregnant women in all trimesters confirm adequate darunavir levels using the once daily dose.[216] In contrast, data on dolutegravir use in pregnancy are scarce, such that it is not preferred in this setting.

Of note, a multicentre clinical trial comparing the NRTI backbone TDF/FTC to zidovudine/lamivudine in HIV-positive pregnant women, both in combination with lopinavir/ritonavir, found that TDF/FTC was associated with a higher rate of both early premature delivery at <34 weeks and of infant death through

week 1 of life.[217] This finding has led one[218] but not other[219,220] HIV guideline panels to recommend against TDF/FTC use in pregnancy among HIV-positive women, particularly when combined with lopinavir/ritonavir. Our panel maintains a recommendation to use TDF/FTC with either raltegravir or ritonavir-boosted darunavir as nPEP in the setting of pregnancy because of study limitations, the indirectness of this evidence, and inconsistency with other data.

It is unknown whether raltegravir and darunavir are secreted into human breast milk, whereas both TDF and FTC are secreted at low-moderate levels.[119,221,222] Because of insufficient clinical data in this setting, breastfeeding during nPEP use is not recommended.

Guideline Implementation

While avoidance of HIV infection is highly valued by virtually all HIV-negative people, the panel acknowledges that individuals may have variable preferences regarding the potential for inconveniences, rare drug toxicities and stigma associated with these interventions. To date, medication costs have also restricted the feasibility and acceptability of these strategies. However, the recent introduction of generic TDF/FTC and the increasing availability of public drug coverage for PrEP in Canada may have dramatic effects on their uptake.

The tremendous financial cost of HIV infection and the young age of those newly diagnosed (majority of new cases occur in those aged 30 -39 years of age)[223] underscore the economic and social importance of preventing new infections. Biomedical prevention strategies can reduce the system-level costs associated with HIV infection, but are themselves associated with costs related to the medications themselves and the need for longitudinal follow-up.

Multiple studies from industrialized world settings have found that PrEP is cost-effective using willingness-to-pay thresholds of $50,000-$100,000 USD per quality-adjusted life-year when appropriately targeted to “high-risk” MSM populations, although definitions of “high risk”, model assumptions and time horizons have varied between studies.[224-230] Cost-effectiveness is generally greater in settings with higher baseline HIV prevalence and in populations with higher HIV incidence. The World Health Organization advises that PrEP be considered cost-effective if deployed in populations with annual HIV incidence >3%,[231] a level seen in all MSM PrEP trials and in Canadian MSM with other high risk markers such as bacterial STIs and prior use of nPEP.[68,70]

Limited data exists for the cost-effectiveness of nPEP. A French study found that general use of nPEP was moderately cost-effective with a cost-effectiveness ratio of €88,692 per QALY gained.[232] Other analyses in the US and Australian contexts have found that nPEP is cost-effective when offered to MSM reporting condomless anal sex (particularly if the source was HIV-positive).[233-235] Systematic reviews have found that nPEP is cost-effective among MSM reporting condomless anal sex with any partner, in heterosexuals reporting condomless anal sex with an HIV-positive partner and in PWID reporting needle-sharing with an HIV-positive source.[236,237] In considering these issues together while developing these guidelines, our panel has made strong recommendations for PrEP and nPEP in patient groups at highest risk of HIV infection, and recommendations to consider these interventions for those at more moderate risk.

Canadian physicians’ awareness of PrEP and nPEP has historically been low, although studies on this topic predate Health Canada regulatory approval for PrEP.[238,239] We are currently developing proposals

to monitor awareness of, implementation of and fidelity to these guidelines among key stakeholders, and will seek funding for these knowledge translation activities in the coming year.

Given the rapidly changing HIV prevention landscape, with clinical trials of novel oral, injectable and topical agents in progress, and additional studies of alternative dosing strategies and long-term outcomes underway, updates to the Guidelines are planned when either a new product obtains Health Canada regulatory approval for use as PrEP or nPEP in Canada, or within five years of publication.

Comparison to other guidelines

Our recommendations are broadly consistent with major international and industrialized country guidelines. The WHO recommends PrEP for any risk group with HIV incidence over 3%.[240] More granular recommendations are made for MSM, PWID and heterosexual populations in regional/national guidelines from Europe, the U.K., United States and Australasia, based on additional risk factors.[241-244] For MSM, most recommend PrEP for those with a prior STI, and prior nPEP is also included by the IAS-USA guidelines. In contrast, no other guideline explicitly recommends using the HIRI-MSM for targeting PrEP, but since all guidelines recommend PrEP for MSM with history of condomless anal intercourse, a HIRI-MSM score >11 is consistent with these recommendations. Neither the UK or European guidelines recommend PrEP for PWID, however the UK guidelines explicitly recommends access to harm reduction prevention services. For nPEP, overall clinical indications and requirement for a 28 day course of therapy within 72 hours of exposure are similar across guidelines. For all but the Australian guidelines, a standard three drug regimen is recommended, with minor variations in preferred agents.

Research and policy gaps

Numerous research gaps persist. Clinical instruments for identifying individuals at elevated HIV risk that would benefit most from PrEP are urgently needed in Canada, particularly for populations other than MSM. Additional PrEP-related outcome data are also needed regarding non-MSM populations in industrialized world contexts, outcomes related to pregnancy and breastfeeding, on-demand PrEP and other potential intermittent dosing schedules, long-term toxicities, and long-term behavioural outcomes related to adherence and risk behaviour. Data on the optimal timing of PrEP discontinuation and follow-up HIV testing relative to exposure are also an important gap. For nPEP, key knowledge gaps relate to the use of newer antiretroviral agents, strategies for transitioning individuals at high HIV risk onto PrEP, and the optimal timing of follow-up HIV testing. Finally, implementation research is greatly needed to understand how best to deliver these complex bio-behavioural interventions to at-risk populations as part of a comprehensive HIV prevention strategy.

It is essential that Provincial, Territorial and Federal policy-makers develop funding models to support the use of PrEP and nPEP. This will likely require decisions for targeted applications of PrEP given the current high price of medications, and the need to review and adjust policies when cheaper generic versions become available.

Given the rapidly changing HIV prevention landscape, with clinical trials of novel oral, injectable and topical agents in progress, and additional studies of alternative dosing strategies and long-term outcomes underway, updates to the Guidelines will be conducted when clinical trial data on new PrEP/nPEP regimens become available.

Conclusions

The tremendous financial cost of HIV infection and the young age of those newly diagnosed (majority of new cases occur in those aged 30-39 years of age)[23] underscore the economic and social importance of preventing new infections. It is the Panel's hope that this guideline will contribute to reducing HIV incidence in Canada by improving the quality of care, increasing access to care, reducing inappropriate variation in practice, and promoting the rigorous evaluation of biomedical prevention strategies nationwide.

Tables

Table 1. Categories of risk that a person has transmissible HIV infection

Risk	Examples
Substantial	• HIV+ and viremic (ie. viral load >40 copies/mL) • HIV status unknown but source from a population with high HIV prevalence compared to the general population (eg. men who have sex with men, people who inject drugs)
Low but non-zero	• HIV+ and believed to have a viral load <40 copies/mL, with concomitant STI present at the time of exposure
Negligible or none	• Confirmed HIV negative • HIV+ with confirmed viral load <40 copies/mL and no known sexually transmitted infections present at time of exposure • HIV status unknown, general population

Table 2. Risk of HIV transmission per act by exposure type from an HIV-positive source[a]

Level	Exposure type	Estimated risk per act, %
High	Anal (receptive)	1.38 (1.02-1.86)
	Needle sharing	0.63 (0.41-0.92)
Moderate	Anal (insertive)	0.11 (0.04-0.28)
	Vaginal (receptive)	0.08 (0.06-0.11)
	Vaginal (insertive)	0.04 (0.01-0.14)
Low	Oral sex (giving)	Precise estimates not available
	Oral sex (receiving)	
	Oral-anal contact	
	Sharing sex toys	
	Blood on compromised skin	

[a] Adapted from [18]

Supplementary Table 1. Epidemiology of HIV in Canada, 2014[a]

Classification	Estimated number of incident infections			Estimated number of people living with HIV		
	Point estimate	Range, n	Percentage %	Point estimate	Range, n	Percentage %
Exposure category						
MSM	1396	990-1800	54.3	37230	31000-43500	49.3
MSM-PWID	65	40-90	2.5	2400	1800-3000	3.2
PWID	270	180-360	10.5	11560	9500-13600	15.3
Heterosexual/non-endemic	481	330-630	18.7	12340	10000-14600	16.3
Heterosexual/ endemic	358	250-470	13.9	11360	9300-13400	15.0
Other	<20			610	400-800	0.8
Sex						
Female	595	440-750	23.2	16880	13800-20000	22.4
Male	1975	1550-2400	76.8	58620	48200-69000	77.6
Ethnicity						
Aboriginal	278	200-360	10.8	6850	5500-8200	9.1
Non-Aboriginal	2292	1700-2900	89.2	68650	57000-80300	90.9
Total	2570	1940-3200	100	75500	63400-87600	100

[a] Adapted from[23]

Supplementary Table 2. HIV Incidence Risk Index for MSM (HIRI-MSM)[a]

Question number	Question	Response	Score
1	How old are you today (years)?	<18 years 18-28 years 29-40 years 41-48 years ≥49 years	0 8 5 2 0
2	How many men have you had sex with in the last 6 months?	>10 male partners 6-10 male partners 0-5 male partners	7 4 0
3	How many of your male sex partners were HIV positive?	>1 positive partner 1 positive partner <1 positive partner	8 4 0
4	In the last 6 months, how many times did you have receptive anal sex (you were the bottom) with a man without a condom?	1 or more times 0 times	10 0
5	In the last 6 months, how many times did you have insertive anal sex (you were the top) with a man who was HIV positive?	5 or more times 0-4 times	6 0
6	In the last 6 months, have you used methamphetamines such as crystal or speed?	Yes No	5 0
7	In the last 6 months, have you used poppers (amyl nitrate)?	Yes No	3 0

[a] Reproduced from [69]. Add down entries in right-hand column to calculate total score.

Supplementary Table 3. Current Diagnostic Assays for detection and monitoring of HIV infection[a]

Diagnostic Test	Target Detected	Window Period[b]	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	Optional, additional test for initial screening where available
4th generation assay	HIV IgG, IgM antibodies; HIV p24 antigen	18 (16, 24) days	Recommended 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 the evaluation of suspected acute HIV infection, when available
HIV viral load	HIV RNA (quantitative)	10 days	

[a] Adapted from [162,246,247]

[b] Median (Interquartile range, if known)

Table 3. Baseline and on-treatment PrEP evaluations

Assay Type	Baseline	30 days	Q3 months	Q 12 months
Laboratory evaluation				
HIV testing[a]	X	X	X	
Hepatitis A immunity (hepatitis A IgG)[b]	X			
Hepatitis B screen (surface antigen, surface antibody, core antibody)[bc]	X			X[b]
Hepatitis C antibody	X			X
Screening for gonorrhea and chlamydia[d] (urine nucleic acid amplification test, throat and rectal swabs for culture or nucleic acid amplification; test anatomic sites depending on type of sexual activity reported)	X		X	
Syphilis serology[d]	X		X	
Complete blood count	X			
Creatinine	X	X	X	
Urinalysis	X			
Pregnancy test (as appropriate)	X		X	
Clinical evaluation				
Symptoms of HIV seroconversion	X	X	X	
PrEP adherence		X	X	
Indication for PrEP	X	X	X	
Use of other HIV and STI prevention strategies	X	X	X	
Presence and management of syndemic conditions	X	X	X	

[a] Preferred HIV test is a 4th generation antibody/antigen combo assay. Those with signs or symptoms of acute HIV should also undergo HIV RNA or pooled nucleic acid amplification test.

[b] Hepatitis A or B vaccine should be initiated in unvaccinated individuals. Those who remain non-immune to hepatitis B virus should be rescreened annually.

[c] Individuals with chronic active hepatitis B should be managed in consultation with an expert on hepatitis B virus according to Canadian guidelines.

[d] Individuals diagnosed with STIs should be offered standard therapy and follow-up as per local guidelines.

Table 4. Risk assessment for beginning nPEP

Likelihood that source person has transmissible HIV (from Table 1)	Risk from the exposure type (from Table 2)	
	High / Moderate	**Low**
Substantial	Initiate nPEP	nPEP not required
Low	Consider nPEP	nPEP not required
Negligible / none	nPEP not required	nPEP not required

Table 5. nPEP Regimens: Preferred and Alternative agents[ab]

Preferred		**Alternate**
NRTI backbone	Tenofovir disoproxil fumarate / emtricitabine (TDF/FTC) 300/200 mg PO once daily [Grade 1C]	Zidovudine/lamivudine 300/150mg PO twice daily [Grade 2C] or Tenofovir disoproxil fumarate 300mg PO once daily + lamivudine 300mg PO once daily [Grade 2C]
3rd drug	Darunavir 800 mg PO once daily + ritonavir 100mg PO once daily [Grade 1A] or Dolutegravir 50mg PO once daily [Grade 1C] or Raltegravir 400mg PO twice daily [Grade 1A]	Atazanavir 300mg PO once daily + ritonavir 100mg PO once daily [Grade 2C] or Darunavir/cobicistat 800/150 mg PO once daily [Grade 2D] or Elvitegravir/cobicistat 150/150mg (coformulated with TDF/FTC 300/200mg) PO once daily [Grade 2C] or Lopinavir/ritonavir 800/200 mg PO once daily [Grade 2A] or Raltegravir HD 1200mg PO once daily [Grade 2D]
NOT Recommended		
Abacavir, didanosine, efavirenz, nevirapine, stavudine		

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

[b] A thorough medication history (including prescription drugs, supplements, herbal preparations etc.) should be taken prior to selecting an nPEP regimen due to the potential for drug-drug interactions.

Supplementary Table 4: nPEP Regimens: Advantages and disadvantages of preferred agents[a]

	Advantages	Disadvantages
Darunavir + ritonavir	• Once daily dosing • Higher genetic barrier to resistance than raltegravir • Pregnancy: a preferred PI-based regimen for use in HIV-infected pregnant women • No dosage adjustment required in renal/mild-moderate liver dysfunction	• Gastrointestinal side effects • Rash • Darunavir: substrate and inhibitor of CYP 3A4 • Ritonavir: inhibitor of P450 enzyme system (CYP3A>2D6>2C19>2A6, 2E1); also induces 1A2, 2C9, CYP2C19 and UGT activity
Dolutegravir	• Once daily dosing • No food requirement • Potent against virus harbouring various drug resistance mutations • No dosage adjustment required in renal/mild-moderate liver dysfunction	• UGT substrate and minor substrate of CYP3A4; also inhibits OCT2 renal transporter • Oral absorption reduced by di-/trivalent cations (eg. Ca, Al, Mg)
Raltegravir	• No food requirement • Not involved in CYP450 interactions • Pregnancy: a preferred INSTI-based regimen for use in HIV-infected pregnant women • No dosage adjustment required in renal/mild-moderate liver dysfunction	• Twice daily dosing • Lower genetic barrier to resistance than PI-based regimens • UGT substrate affected by UGT inhibitors and inducers (eg. rifampin) • Oral absorption reduced by di-/trivalent cations (eg. Ca, Al, Mg) • Myopathy, elevated CK and rhabdomyolysis have rarely been reported

[a] A thorough medication history (including prescription drugs, supplements, herbal preparations etc.) should be taken prior to selecting an nPEP regimen due to the potential for drug-drug interactions.

Table 6. Suggested evaluation at baseline, during and after nPEP

Test	Baseline	Week 2	Week 12
HIV testing[a]	X		X[b]
Hepatitis A immunity (hepatitis A IgG)[c]	X		
Hepatitis B screen[cd] (surface antigen, surface antibody, core antibody)	X		
Hepatitis C screen (Hepatitis C antibody)	X		X
Screening for gonorrhea and chlamydia [e] (urine nucleic acid amplification test, throat and rectal swabs for culture or nucleic acid amplification; test anatomic sites depending on type of sexual activity reported)	X		X
Syphilis serology[e]	X		X
Complete Blood Count	X		
ALT	X	X[f]	
Serum creatinine	X	X[f]	
Pregnancy testing (if appropriate)	X		

[a] Preferred HIV test is a 4th generation antibody/antigen assay. Those with signs/symptoms of acute HIV should also undergo HIV RNA or pooled NAAT test.
[b] Consider repeating HIV serology at 6 months after exposure if hepatitis C infection was acquired from the exposure.
[c] Hepatitis A and/or B vaccine should be initiated in unvaccinated individuals.
[d] Individuals with chronic active hepatitis B should be referred for hepatitis B virus care as per local guidelines.
[e] Individuals diagnosed with concurrent STI during nPEP should be offered standard therapy and follow-up as per local guidelines.
[f] Suggested if abnormal at baseline or symptomatic.

References

1. Spira AI, Marx PA, Patterson BK, et al. Cellular targets of infection and route of viral dissemination after an intravaginal inoculation of simian immunodeficiency virus into rhesus macaques. J Exp Med 1996;183:215-25.
2. Hu J, Gardner MB, Miller CJ. Simian immunodeficiency virus rapidly penetrates the cervicovaginal mucosa after intravaginal inoculation and infects intraepithelial dendritic cells. J Virol 2000;74:6087-95.
3. Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. The New England journal of medicine 2000;342:921-9.
4. Wawer MJ, Gray RH, Sewankambo NK, et al. Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. J Infect Dis 2005;191:1403-9.
5. Gray RH, Wawer MJ, Brookmeyer R, et al. Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda. Lancet 2001;357:1149-53.
6. Lingappa JR, Hughes JP, Wang RS, et al. Estimating the impact of plasma HIV-1 RNA reductions on heterosexual HIV-1 transmission risk. PloS one 2010;5:e12598.
7. Baeten JM, Kahle E, Lingappa JR, et al. Genital HIV-1 RNA predicts risk of heterosexual HIV-1 transmission. Sci Transl Med 2011;3:77ra29.
8. Vernazza PL, Troiani L, Flepp MJ, et al. Potent antiretroviral treatment of HIV-infection results in suppression of the seminal shedding of HIV. The Swiss HIV Cohort Study. AIDS 2000;14:117-21.
9. Attia S, Egger M, Muller M, Zwahlen M, Low N. Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. Aids 2009;23:1397-404.
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. Rodger AJ, Cambiano V, Bruun T, et al. Sexual Activity Without Condoms and Risk of HIV Transmission in Serodifferent Couples When the HIV-Positive Partner Is Using Suppressive Antiretroviral Therapy. JAMA 2016;316:171-81.
12. Bavinton B, Grinsztejn B, Phanuphak N, et al. HIV treatment prevents HIV transmission in male serodiscordant couples in Australia, Thailand and Brazil. 9th IAS Conference on HIV Science July 23-26, 2017 Abstract TUAC0506LB; 2017; Paris, France.
13. Sadiq ST, Taylor S, Kaye S, et al. The effects of antiretroviral therapy on HIV-1 RNA loads in seminal plasma in HIV-positive patients with and without urethritis. AIDS 2002;16:219-25.
14. Graham SM, Masese L, Gitau R, et al. Genital ulceration does not increase HIV-1 shedding in cervical or vaginal secretions of women taking antiretroviral therapy. Sex Transm Infect 2011;87:114-7.
15. Boily MC, Baggaley RF, Wang L, et al. Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies. Lancet Infect Dis 2009;9:118-29.
16. Adachi K, Klausner JD, Bristow CC, et al. Chlamydia and Gonorrhea in HIV-Infected Pregnant Women and Infant HIV Transmission. Sex Transm Dis 2015;42:554-65.
17. Baggaley RF, White RG, Boily MC. HIV transmission risk through anal intercourse: systematic review, meta-analysis and implications for HIV prevention. Int J Epidemiol 2010;39:1048-63.
18. Patel P, Borkowf CB, Brooks JT, Lasry A, Lansky A, Mermin J. Estimating per-act HIV transmission risk: a systematic review. AIDS 2014;28:1509-19.
19. Baggaley RF, Boily MC, White RG, Alary M. Risk of HIV-1 transmission for parenteral exposure and blood transfusion: a systematic review and meta-analysis. AIDS 2006;20:805-12.
20. Jin F, Jansson J, Law M, et al. Per-contact probability of HIV transmission in homosexual men in Sydney in the era of HAART. Aids 2010;24:907-13.

21. Wiysonge CS, Kongnyuy EJ, Shey M, et al. Male circumcision for prevention of homosexual acquisition of HIV in men. Cochrane Database Syst Rev 2011:CD007496. doi: 10.1002/14651858.CD007496.pub2.
22. Siegfried N, Muller M, Deeks JJ, Volmink J. Male circumcision for prevention of heterosexual acquisition of HIV in men. Cochrane Database Syst Rev 2009:CD003362. doi: 10.1002/14651858.CD003362.pub2.
23. Summary: Estimates of HIV incidence, prevalence and proportion undiagnosed in Canada, 2014. Ottawa: Public Health Agency of Canada; 2015.
24. Yang Q, Ogunnaike-Cooke S, Halverson J, et al. Estimated national HIV incidence rates among key populations in Canada, 2014. Canadian Conference on HIV/AIDS Research Abstract EPH35; 2016; Winnipeg, Canada.
25. HIV and AIDS in Canada: Surveillance report to December 31, 2014. Ottawa: Public Health Agency of Canada; 2015.
26. Samji H, Cescon A, Hogg RS, et al. Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. PLoS One 2013;8:e81355. doi: 10.1371/journal.pone.0081355. eCollection 2013.
27. Patterson S, Cescon A, Samji H, et al. Life expectancy of HIV-positive individuals on combination antiretroviral therapy in Canada. BMC Infect Dis 2015;15:274.:10.1186/s12879-015-0969-x.
28. Friedman MR, Stall R, Silvestre AJ, et al. Effects of syndemics on HIV viral load and medication adherence in the multicentre AIDS cohort study. AIDS 2015;29:1087-96.
29. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. BMJ 2004;328:1490.
30. Atkins D, Eccles M, Flottorp S, et al. Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches The GRADE Working Group. BMC Health Serv Res 2004;4:38.
31. Atkins D, Briss PA, Eccles M, et al. Systems for grading the quality of evidence and the strength of recommendations II: pilot study of a new system. BMC Health Serv Res 2005;5:25.
32. MacArthur GJ, van Velzen E, Palmateer N, et al. Interventions to prevent HIV and Hepatitis C in people who inject drugs: a review of reviews to assess evidence of effectiveness. Int J Drug Policy 2014;25:34-52. doi: 10.1016/j.drugpo.2013.07.001. Epub Aug 21.
33. Gowing L, Farrell MF, Bornemann R, Sullivan LE, Ali R. Oral substitution treatment of injecting opioid users for prevention of HIV infection. Cochrane Database Syst Rev 2011:CD004145. doi: 10.1002/14651858.CD004145.pub4.
34. Aspinall EJ, Nambiar D, Goldberg DJ, et al. Are needle and syringe programmes associated with a reduction in HIV transmission among people who inject drugs: a systematic review and meta-analysis. Int J Epidemiol 2014;43:235-48. doi: 10.1093/ije/dyt243. Epub 2013 Dec 27.
35. Singer M. Introduction to Syndemics: A Critical Systems Approach to Public and Community Health. San Francisco: Wiley; 2009.
36. Stall R, Mills TC, Williamson J, et al. Association of co-occurring psychosocial health problems and increased vulnerability to HIV/AIDS among urban men who have sex with men. Am J Public Health 2003;93:939-42.
37. Meyer JP, Springer SA, Altice FL. Substance abuse, violence, and HIV in women: a literature review of the syndemic. J Womens Health (Larchmt) 2011;20:991-1006. doi: 10.89/jwh.2010.328. Epub 1 Jun 13.
38. Tan DH, Leon-Carlyle M, Mills R, Moses E, Carvalhal A. Self-Administered Screening for Syndemic Mental Health Problems Should be Routinely Implemented Among MSM PrEP Users. J Gay Lesbian Ment Health 2016;20:13-20.

39. Coleman TA, Hart TA, Noor S, et al. Characteristics of men who have sex with men seeking HIV pre-exposure prophylaxis in a Canadian demonstration project. 24th Annual Canadian Conference on HIV/AIDS Research Poster CS59; 2015; Toronto, Canada.
40. Donnell D, Mimiaga MJ, Mayer K, Chesney M, Koblin B, Coates T. Use of non-occupational post-exposure prophylaxis does not lead to an increase in high risk sex behaviors in men who have sex with men participating in the EXPLORE trial. AIDS Behav 2010;14:1182-9. doi: 10.007/s10461-010-9712-1.
41. Oldenburg CE, Jain S, Mayer KH, Mimiaga MJ. Post-exposure prophylaxis use and recurrent exposure to HIV among men who have sex with men who use crystal methamphetamine. Drug Alcohol Depend 2015;146:75-80.:10.1016/j.drugalcdep.2014.11.010. Epub Nov 26.
42. Olshen E, Hsu K, Woods ER, Harper M, Harnisch B, Samples CL. Use of human immunodeficiency virus postexposure prophylaxis in adolescent sexual assault victims. Arch Pediatr Adolesc Med 2006;160:674-80.
43. Paxton LA. Considerations regarding antiretroviral chemoprophylaxis and heterosexuals in generalized epidemic settings. Curr Opin HIV AIDS 2012;7:557-62. doi: 10.1097/COH.0b013e328359064a.
44. Burns DN, Grossman C, Turpin J, Elharrar V, Veronese F. Role of oral pre-exposure prophylaxis (PrEP) in current and future HIV prevention strategies. Curr HIV/AIDS Rep 2014;11:393-403. doi: 10.1007/s11904-014-0234-8.
45. Bruno C, Saberi P. Pharmacists as providers of HIV pre-exposure prophylaxis. Int J Clin Pharm 2012;34:803-6. doi: 10.1007/s11096-012-9709-0. Epub 2012 Oct 17.
46. Sawkin M, Shah M. Development of a pharmacist-led human immunodeficiency virus pre-exposure prophylaxis clinic at an urban community clinic. J Am Pharm Assoc 2016;56:e48.
47. Liu A, Cohen S, Follansbee S, et al. Early experiences implementing pre-exposure prophylaxis (PrEP) for HIV prevention in San Francisco. PLoS Med 2014;11:e1001613. doi: 10.1371/journal.pmed.. eCollection 2014 Mar.
48. Cohen SE, Liu AY, Bernstein KT, Philip S. Preparing for HIV pre-exposure prophylaxis: lessons learned from post-exposure prophylaxis. Am J Prev Med 2013;44:S80-5.
49. Lundgren JD, Babiker AG, Gordin F, et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. N Engl J Med 2015;373:795-807. doi: 10.1056/NEJMoa1506816. Epub 2015 Jul 20.
50. Danel C, Moh R, Gabillard D, et al. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. N Engl J Med 2015;373:808-22. doi: 10.1056/NEJMoa1507198. Epub 2015 Jul 20.
51. Rodger AJ, Cambiano V, Bruun T, et al. Sexual Activity Without Condoms and Risk of HIV Transmission in Serodifferent Couples When the HIV-Positive Partner Is Using Suppressive Antiretroviral Therapy. JAMA 2016;316:171-81. doi: 10.1001/jama.2016.5148.
52. Pilcher CD, Ospina-Norvell C, Dasgupta A, et al. The Effect of Same-Day Observed Initiation of Antiretroviral Therapy on HIV Viral Load and Treatment Outcomes in a U.S. Public Health Setting. J Acquir Immune Defic Syndr 2016.
53. 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.
54. McCormack S, Dunn DT, Desai M, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. Lancet 2015;9:00056-2.
55. Grant RM, Anderson PL, McMahan V, et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. Lancet Infect Dis 2014;14:820-9. doi: 10.1016/S473-3099(14)70847-3. Epub 2014 Jul 22.

56. Liu AY, Cohen SE, Vittinghoff E, et al. Preexposure Prophylaxis for HIV Infection Integrated With Municipal- and Community-Based Sexual Health Services. JAMA Intern Med 2016;176:75-84.
57. Volk JE, Marcus JL, Phengrasamy T, et al. No New HIV Infections With Increasing Use of HIV Preexposure Prophylaxis in a Clinical Practice Setting. Clin Infect Dis 2015;61:1601-3.
58. Deutsch MB, Glidden DV, Sevelius J, et al. HIV pre-exposure prophylaxis in transgender women: a subgroup analysis of the iPrEx trial. Lancet HIV 2015;2:e512-9. doi: 10.1016/S2352-3018(15)00206-4. Epub 2015 Nov 6.
59. Escudero DJ, Kerr T, Operario D, Socias ME, Sued O, Marshall BD. Inclusion of trans women in pre-exposure prophylaxis trials: a review. AIDS Care 2015;27:637-41. doi: 10.1080/09540121.2014.986051. Epub 2014 Nov 28.
60. Pathela P, Braunstein SL, Blank S, Schillinger JA. HIV incidence among men with and those without sexually transmitted rectal infections: estimates from matching against an HIV case registry. Clin Infect Dis 2013;57:1203-9. doi: 10.093/cid/cit437. Epub 2013 Jun 25.
61. Katz DA, Dombrowski JC, Bell TR, Kerani RP, Golden MR. HIV Incidence Among Men Who Have Sex With Men After Diagnosis With Sexually Transmitted Infections. Sex Transm Dis 2016;43:249-54. doi: 10.1097/OLQ.0000000000000423.
62. Pathela P, Braunstein SL, Blank S, Shepard C, Schillinger JA. The high risk of an HIV diagnosis following a diagnosis of syphilis: a population-level analysis of New York City men. Clin Infect Dis 2015;61:281-7. doi: 10.1093/cid/civ289. Epub 2015 Apr 13.
63. Solomon MM, Mayer KH, Glidden DV, et al. Syphilis predicts HIV incidence among men and transgender women who have sex with men in a preexposure prophylaxis trial. Clin Infect Dis 2014;59:1020-6. doi: 10.93/cid/ciu450. Epub 2014 Jun 13.
64. Canadian Guidelines on Sexually Transmitted Infections: Public Health Association of Canada; 2013.
65. Leal L, Torres B, Leon A, et al. Predictive Factors for HIV Seroconversion Among Individuals Attending a Specialized Center After an HIV Risk Exposure: A Case-Control Study. AIDS Res Hum Retroviruses 2016;32:1016-21. Epub 2016 Aug 30.
66. Whitlock G, McCormack C, Fearnley J, McOwan A. High HIV incidence in men who have sex with men attending for postexposure prophylaxis: a service evaluation. Sex Transm Infect 2016;13:2016-052623.
67. Heuker J, Sonder GJ, Stolte I, Geskus R, van den Hoek A. High HIV incidence among MSM prescribed postexposure prophylaxis, 2000-2009: indications for ongoing sexual risk behaviour. AIDS 2012;26:505-12. doi: 10.1097/QAD.0b013e32834f32d8.
68. Hull M, Lachowsky N, Moore DM, et al. High incidence of subsequent HIV seroconversion amongst MSM accessing recurrent non-occupational post-exposure prophylaxis (NPEP) in Vancouver, BC. 25th Annual Canadian Conference on HIV/AIDS Research Abstract EPH12; 2016; Winnipeg, Canada.
69. Smith DK, Pals SL, Herbst JH, Shinde S, Carey JW. Development of a clinical screening index predictive of incident HIV infection among men who have sex with men in the United States. J Acquir Immune Defic Syndr 2012;60:421-7.
70. Lachowsky N, Cui Z, Sereda P, et al. HIV incidence rate and predictors among gay and other men who have sex with men (MSM) in Vancouver: Additional benefit of administrative health data linkage. 25th Annual Canadian Conference on HIV/AIDS Research Abstract EPHP 504; 2016; Winnipeg, Canada.
71. Peng P, Su S, Fairley CK, et al. A Global Estimate of the Acceptability of Pre-exposure Prophylaxis for HIV Among Men Who have Sex with Men: A Systematic Review and Meta-analysis. AIDS Behav 2017;7:017-1675.

72. Yacoub R, Nadkarni GN, Weikum D, et al. Elevations in Serum Creatinine With Tenofovir-Based HIV Pre-Exposure Prophylaxis: A Meta-Analysis of Randomized Placebo-Controlled Trials. J Acquir Immune Defic Syndr 2016;71:e115-8.
73. Mirembe BG, Kelly CW, Mgodi N, et al. Bone Mineral Density Changes Among Young, Healthy African Women Receiving Oral Tenofovir for HIV Preexposure Prophylaxis. J Acquir Immune Defic Syndr 2016;71:287-94. doi: 10.1097/QAI.0000000000000858.
74. 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.
75. Marrazzo JM, Ramjee G, Richardson BA, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. The New England journal of medicine 2015;372:509-18.
76. Baeten JM, Donnell D, Mugo NR, et al. Single-agent tenofovir versus combination emtricitabine plus tenofovir for pre-exposure prophylaxis for HIV-1 acquisition: an update of data from a randomised, double-blind, phase 3 trial. Lancet Infect Dis 2014;14:1055-64.
77. 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.
78. 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.
79. Baeten JM, Heffron R, Kidoguchi L, et al. Integrated Delivery of Antiretroviral Treatment and Pre-exposure Prophylaxis to HIV-1-Serodiscordant Couples: A Prospective Implementation Study in Kenya and Uganda. PLoS Med 2016;13:e1002099. doi: 10.1371/journal.pmed.. eCollection 2016 Aug.
80. Murnane PM, Heffron R, Ronald A, et al. Pre-exposure prophylaxis for HIV-1 prevention does not diminish the pregnancy prevention effectiveness of hormonal contraception. AIDS 2014;28:1825-30. doi: 10.097/QAD.0000000000000290.
81. Heffron R, Mugo N, Were E, et al. Preexposure prophylaxis is efficacious for HIV-1 prevention among women using depot medroxyprogesterone acetate for contraception. AIDS 2014;28:2771-6. doi: 10.1097/QAD.0000000000000493.
82. Whetham J, Taylor S, Charlwood L, et al. Pre-exposure prophylaxis for conception (PrEP-C) as a risk reduction strategy in HIV-positive men and HIV-negative women in the UK. AIDS Care 2014;26:332-6. doi: 10.1080/09540121.2013.819406. Epub 2013 Jul 22.
83. Vernazza PL, Graf I, Sonnenberg-Schwan U, Geit M, Meurer A. Preexposure prophylaxis and timed intercourse for HIV-discordant couples willing to conceive a child. AIDS (London, England) 2011;25:2005-8.
84. Seidman DL, Weber S, Timoney MT, et al. Use of HIV pre-exposure prophylaxis during the preconception, antepartum and postpartum periods at two United States medical centers. Am J Obstet Gynecol 2016;215:632.e1-.e7. doi: 10.1016/j.ajog.2016.06.020. Epub Jul 19.
85. Were EO, Heffron R, Mugo NR, et al. Pre-exposure prophylaxis does not affect the fertility of HIV-1-uninfected men. AIDS 2014;28:1977-82.
86. Hoffman RM, Jaycocks A, Vardavas R, et al. Benefits of PrEP as an Adjunctive Method of HIV Prevention During Attempted Conception Between HIV-uninfected Women and HIV-infected Male Partners. J Infect Dis 2015;212:1534-43.
87. 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. Lancet 2013;381:2083-90.
88. Smith DK, Pan Y, Rose CE, et al. A Brief Screening Tool to Assess the Risk of Contracting HIV Infection Among Active Injection Drug Users. J Addict Med 2015;9:226-32. doi: 10.1097/ADM.0000000000000123.

89. McCormack S, Dunn DT, Desai M, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. Lancet 2016;387:53-60.
90. Corneli AL, Deese J, Wang M, et al. FEM-PrEP: adherence patterns and factors associated with adherence to a daily oral study product for pre-exposure prophylaxis. J Acquir Immune Defic Syndr 2014;66:324-31. doi: 10.1097/QAI.0000000000000158.
91. Seifert SM, Glidden DV, Meditz AL, et al. Dose response for starting and stopping HIV preexposure prophylaxis for men who have sex with men. Clin Infect Dis 2015;60:804-10. doi: 10.1093/cid/ciu916. Epub 2014 Nov 18.
92. Seifert SM, Chen X, Meditz AL, et al. Intracellular Tenofovir and Emtricitabine Anabolites in Genital, Rectal, and Blood Compartments from First Dose to Steady State. AIDS Res Hum Retroviruses 2016;32:981-91. Epub 2016 Sep 19.
93. Fonner VA, Dalglish SL, Kennedy CE, et al. Effectiveness and safety of oral HIV preexposure prophylaxis for all populations. AIDS 2016;30:1973-83. doi: 10.097/QAD.0000000000001145.
94. Baeten JM, Donnell D, Mugo NR, et al. Single-agent tenofovir versus combination emtricitabine plus tenofovir for pre-exposure prophylaxis for HIV-1 acquisition: an update of data from a randomised, double-blind, phase 3 trial. Lancet Infect Dis 2014;14:1055-64. doi: 10.16/S473-3099(14)70937-5. Epub 2014 Oct 7.
95. Molina JM, Capitant C, Spire B, et al. On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. The New England journal of medicine 2015;373:2237-46.
96. Hosek SG, Siberry G, Bell M, et al. The acceptability and feasibility of an HIV preexposure prophylaxis (PrEP) trial with young men who have sex with men. J Acquir Immune Defic Syndr 2013;62:447-56. doi: 10.1097/QAI.0b013e3182801081.
97. Grant RM, Liegler T. Weighing the risk of drug resistance with the benefits of HIV preexposure prophylaxis. The Journal of infectious diseases 2015;211:1202-4.
98. Taylor D, Durigon M, Davis H, et al. Probability of a false-negative HIV antibody test result during the window period: a tool for pre- and post-test counselling. Int J STD AIDS 2015;26:215-24. doi: 10.1177/0956462414542987. Epub 2014 Jul 16.
99. Richey LE, Halperin J. Acute human immunodeficiency virus infection. Am J Med Sci 2013;345:136-42.
100. Wood E, Kerr T, Rowell G, et al. Does this adult patient have early HIV infection?: The Rational Clinical Examination systematic review. JAMA 2014;312:278-85.
101. Braun DL, Kouyos RD, Balmer B, Grube C, Weber R, Gunthard HF. Frequency and Spectrum of Unexpected Clinical Manifestations of Primary HIV-1 Infection. Clin Infect Dis 2015;61:1013-21.
102. Hoenigl M, Green N, Camacho M, et al. Signs or Symptoms of Acute HIV Infection in a Cohort Undergoing Community-Based Screening. Emerg Infect Dis 2016;22:532-4. doi: 10.3201/eid2203.151607.
103. Krajden M, Cook D, Mak A, et al. Pooled nucleic acid testing increases the diagnostic yield of acute HIV infections in a high-risk population compared to 3rd and 4th generation HIV enzyme immunoassays. J Clin Virol 2014;61:132-7. doi: 10.1016/j.jcv.2014.06.024. Epub Jul 3.
104. Peters PJ, Westheimer E, Cohen S, et al. Screening Yield of HIV Antigen/Antibody Combination and Pooled HIV RNA Testing for Acute HIV Infection in a High-Prevalence Population. JAMA 2016;315:682-90. doi: 10.1001/jama.2016.0286.
105. Bacon O, Vittinghoff E, Cohen S, et al. HIV Testing in the US PrEP Demonstration Project: rEIA vs Antigen/Antibody vs RNA. Conference on Retroviruses and Opportunistic Infections Abstract 524; 2016; Boston, MA.

106. Knox DC, Anderson PL, Harrigan PR, Tan DH. Multidrug-Resistant HIV-1 Infection despite Preexposure Prophylaxis. N Engl J Med 2017;376:501-2. doi: 10.1056/NEJMc1611639.
107. Markowitz M, Grossman H, Anderson PL, et al. Newly Acquired Infection with Multi-Drug Resistant HIV-1 in a Patient Adherent to Pre-Exposure Prophylaxis. J Acquir Immune Defic Syndr 2017;26:0000000000001534.
108. Cooper RD, Wiebe N, Smith N, Keiser P, Naicker S, Tonelli M. Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-infected patients. Clin Infect Dis 2010;51:496-505.
109. Ryom L, Mocroft A, Kirk O, et al. Association between antiretroviral exposure and renal impairment among HIV-positive persons with normal baseline renal function: the D:A:D study. J Infect Dis 2013;207:1359-69. doi: 10.093/infdis/jit043. Epub 2013 Feb 4.
110. Mocroft A, Kirk O, Reiss P, et al. Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients. AIDS 2010;24:1667-78. doi: 10.097/QAD.0b013e328339fe53.
111. Scherzer R, Estrella M, Li Y, et al. Association of tenofovir exposure with kidney disease risk in HIV infection. AIDS 2012;26:867-75. doi: 10.1097/QAD.0b013e328351f68f.
112. Rodriguez-Novoa S, Garcia-Samaniego J, Prieto M, et al. Altered Underlying Renal Tubular Function in Patients With Chronic Hepatitis B Receiving Nucleos(t)ide Analogs in a Real-World Setting: The MENTE Study. J Clin Gastroenterol 2016;50:779-89. doi: 10.1097/MCG.0000000000000569.
113. Solomon MM, Lama JR, Glidden DV, et al. Changes in renal function associated with oral emtricitabine/tenofovir disoproxil fumarate use for HIV pre-exposure prophylaxis. AIDS 2014;28:851-9. doi: 10.1097/QAD.0000000000000156.
114. Martin M, Vanichseni S, Suntharasamai P, et al. Renal function of participants in the Bangkok tenofovir study--Thailand, 2005-2012. Clin Infect Dis 2014;59:716-24. doi: 10.1093/cid/ciu355. Epub 2014 May 14.
115. Mugwanya KK, Wyatt C, Celum C, et al. Changes in glomerular kidney function among HIV-1-uninfected men and women receiving emtricitabine-tenofovir disoproxil fumarate preexposure prophylaxis: a randomized clinical trial. JAMA Intern Med 2015;175:246-54. doi: 10.1001/jamainternmed.2014.6786.
116. Mugwanya KK, Wyatt C, Celum C, et al. Reversibility of Glomerular Renal Function Decline in HIV-Uninfected Men and Women Discontinuing Emtricitabine-Tenofovir Disoproxil Fumarate Pre-Exposure Prophylaxis. J Acquir Immune Defic Syndr 2016;71:374-80. doi: 10.1097/QAI.0000000000000868.
117. Mugwanya K, Baeten J, Celum C, et al. Low Risk of Proximal Tubular Dysfunction Associated With Emtricitabine-Tenofovir Disoproxil Fumarate Preexposure Prophylaxis in Men and Women. J Infect Dis 2016;214:1050-7. doi: 10.93/infdis/jiw125. Epub 2016 Mar 29.
118. Liu AY, Vittinghoff E, Anderson PL, et al. Changes in Renal Function Associated With TDF/FTC PrEP Use in the US Demo Project. Conference on Retroviruses and Opportunistic Infections. Boston, MA. Abstract 867.2016.
119. Gilead Sciences, Inc. Product Monograph: Truvada (Emtricitabine/Tenofovir Disoproxil Fumarate) Tablets (200 mg/300 mg) Antiretroviral Agent. 2016.
120. Levin A, Hemmelgarn B, Culleton B, et al. Guidelines for the management of chronic kidney disease. CMAJ 2008;179:1154-62. doi: 10.503/cmaj.080351.
121. Levin A, Mendelssohn D. Care and referral of adult patients with reduced kidney function: Position paper from the Canadian Society of Nephrology. Canadian Society of Nephrology; 2006.

122. Bedimo R, Maalouf NM, Zhang S, Drechsler H, Tebas P. Osteoporotic fracture risk associated with cumulative exposure to tenofovir and other antiretroviral agents. AIDS 2012;26:825-31. doi: 10.1097/QAD.0b013e32835192ae.
123. 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;51:937-46. doi: 10.1086/656412.
124. Mulligan K, Glidden DV, Anderson PL, et al. Effects of Emtricitabine/Tenofovir on Bone Mineral Density in HIV-Negative Persons in a Randomized, Double-Blind, Placebo-Controlled Trial. Clin Infect Dis 2015;61:572-80. doi: 10.1093/cid/civ324. Epub 2015 Apr 23.
125. Grant R, Mulligan K, McMahan V, et al. Recovery of Bone Mineral Density After Stopping Oral HIV Preexposure Prophylaxis. Conference on Retroviruses and Opportunistic Infections. Boston, MA. Abstract 48LB.2016.
126. 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:e23688. doi: 10.1371/journal.pone.0023688. Epub 2011 Aug 29.
127. Kasonde M, Niska RW, Rose C, et al. Bone mineral density changes among HIV-uninfected young adults in a randomised trial of pre-exposure prophylaxis with tenofovir-emtricitabine or placebo in Botswana. PLoS One 2014;9:e90111. doi: 10.1371/journal.pone.0090111. eCollection 2014.
128. Papaioannou A, Morin S, Cheung AM, et al. 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. CMAJ 2010;182:1864-73. doi: 10.503/cmaj.100771. Epub 2010 Oct 12.
129. Cohen S, Vittinghoff E, Philip SS, et al. Quarterly STI screening optimizes STI detection among PrEP users in the Demo Project. Conference on Retroviruses and Opportunistic Infections Abstract #870. Boston MA.2016.
130. Golub SA, Pena S, Boonrai K, Douglas N, Hunt M, Radix A. STI data from community-based PrEP implementation suggest changes to CDC guidelines. Conference on Retroviruses and Opportunistic Infections Abstract 869. Boston, MA.2016.
131. Richardson D, Fisher M, Sabin CA. Sexual transmission of hepatitis C in MSM may not be confined to those with HIV infection. J Infect Dis 2008;2008 Apr 15;197:1213-4.
132. Canadian Immunization Guide. Public Health Agency of Canada. ; 2016.
133. McFaul K, Maghlaoui A, Nzuruba M, et al. Acute hepatitis C infection in HIV-negative men who have sex with men. J Viral Hepat 2015;22:535-8. doi: 10.1111/jvh.12366. Epub 2014 Nov 21.
134. Shilaih M, Marzel A, Scherrer AU, et al. Dually Active HIV/HBV Antiretrovirals as Protection Against Incident Hepatitis B Infections: Potential for Prophylaxis. J Infect Dis 2016;214:599-606. doi: 10.1093/infdis/jiw195. Epub 2016 May 18.
135. Scott-Sheldon LA, Huedo-Medina TB, Warren MR, Johnson BT, Carey MP. Efficacy of behavioral interventions to increase condom use and reduce sexually transmitted infections: a meta-analysis, 1991 to 2010. J Acquir Immune Defic Syndr 2011;58:489-98. doi: 10.1097/QAI.0b013e31823554d7.
136. Rotheram-Borus MJ, Swendeman D, Flannery D, Rice E, Adamson DM, Ingram B. Common factors in effective HIV prevention programs. AIDS Behav 2009;13:399-408. doi: 10.1007/s10461-008-9464-3. Epub 2008 Oct 2.
137. Marcus JL, Glidden DV, Mayer KH, et al. No evidence of sexual risk compensation in the iPrEx trial of daily oral HIV preexposure prophylaxis. PLoS One 2013;8:e81997. doi: 10.1371/journal.pone.0081997. eCollection 2013.
138. Liu AY, Vittinghoff E, Chillag K, et al. Sexual risk behavior among HIV-uninfected men who have sex with men (MSM) participating in a tenofovir pre-exposure prophylaxis (PrEP) randomized trial in the United States. J Acquir Immune Defic Syndr 2013.

139. Mugwanya KK, Donnell D, Celum C, et al. Sexual behaviour of heterosexual men and women receiving antiretroviral pre-exposure prophylaxis for HIV prevention: a longitudinal analysis. Lancet Infect Dis 2013;13:1021-8. doi: 10.16/S473-3099(13)70226-3. Epub 2013 Oct 17.
140. Gust DA, Soud F, Hardnett FP, et al. Evaluation of Sexual Risk Behavior Among Study Participants in the TDF2 PrEP Study Among Heterosexual Adults in Botswana. J Acquir Immune Defic Syndr 2016;73:556-63.
141. Koenig LJ, Lyles C, Smith DK. Adherence to antiretroviral medications for HIV pre-exposure prophylaxis: lessons learned from trials and treatment studies. Am J Prev Med 2013;44:S91-8. doi: 10.1016/j.amepre.2012.09.047.
142. van der Straten A, Van Damme L, Haberer JE, Bangsberg DR. Unraveling the divergent results of pre-exposure prophylaxis trials for HIV prevention. AIDS 2012;26:F13-9.
143. Haberer JE, Baeten JM, Campbell J, et al. Adherence to antiretroviral prophylaxis for HIV prevention: a substudy cohort within a clinical trial of serodiscordant couples in East Africa. PLoS Med 2013;10:e1001511. doi: 10.1371/journal.pmed.. Epub 2013 Sep 10.
144. Psaros C, Haberer JE, Katabira E, et al. An intervention to support HIV preexposure prophylaxis adherence in HIV-serodiscordant couples in Uganda. J Acquir Immune Defic Syndr 2014;66:522-9. doi: 10.1097/QAI.0000000000000212.
145. Marcus JL, Buisker T, Horvath T, et al. Helping our patients take HIV pre-exposure prophylaxis (PrEP): a systematic review of adherence interventions. HIV Med 2014;15:385-95. doi: 10.1111/hiv.12132. Epub 2014 Feb 24.
146. Coffin CS, Fung SK, Ma MM. Management of chronic hepatitis B: Canadian Association for the Study of the Liver consensus guidelines. Can J Gastroenterol 2012;26:917-38.
147. Solomon MM, Schechter M, Liu AY, et al. The Safety of Tenofovir-Emtricitabine for HIV Pre-Exposure Prophylaxis (PrEP) in Individuals With Active Hepatitis B. J Acquir Immune Defic Syndr 2016;71:281-6. doi: 10.1097/QAI.0000000000000857.
148. Mugo NR, Hong T, Celum C, et al. Pregnancy incidence and outcomes among women receiving preexposure prophylaxis for HIV prevention: a randomized clinical trial. JAMA 2014;312:362-71. doi: 10.1001/jama.2014.8735.
149. Mugwanya KK, Hendrix CW, Mugo NR, et al. Pre-exposure Prophylaxis Use by Breastfeeding HIV-Uninfected Women: A Prospective Short-Term Study of Antiretroviral Excretion in Breast Milk and Infant Absorption. PLoS Med 2016;13:e1002132. doi: 10.1371/journal.pmed.. eCollection 2016 Sep.
150. Irvine C, Egan KJ, Shubber Z, Van Rompay KK, Beanland RL, Ford N. Efficacy of HIV Postexposure Prophylaxis: Systematic Review and Meta-analysis of Nonhuman Primate Studies. Clin Infect Dis 2015;60:S165-9. doi: 10.1093/cid/civ069.
151. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. N Engl J Med 1994;331:1173-80.
152. Cardo DM, Culver DH, Ciesielski CA, et al. A case-control study of HIV seroconversion in health care workers after percutaneous exposure. Centers for Disease Control and Prevention Needlestick Surveillance Group. N Engl J Med 1997;337:1485-90.
153. Joyce MP, Kuhar D, Brooks JT. Notes from the field: occupationally acquired HIV infection among health care workers - United States, 1985-2013. MMWR Morb Mortal Wkly Rep 2015;63:1245-6.
154. Jochimsen EM. Failures of zidovudine postexposure prophylaxis. Am J Med 1997;102:52-5; discussion 6-7.
155. Roland ME, Neilands TB, Krone MR, et al. Seroconversion following nonoccupational postexposure prophylaxis against HIV. Clin Infect Dis 2005;41:1507-13.

156. Borba Brum MC, Dantas Filho FF, Yates ZB, Vercoza Viana MC, Martin Chaves EB, Trindade DM. HIV seroconversion in a health care worker who underwent postexposure prophylaxis following needlestick injury. Am J Infect Control 2013;41:471-2.
157. Tsai CC, Emau P, Follis KE, et al. Effectiveness of postinoculation (R)-9-(2-phosphonylmethoxypropyl) adenine treatment for prevention of persistent simian immunodeficiency virus SIVmne infection depends critically on timing of initiation and duration of treatment. J Virol 1998;72:4265-73.
158. Otten RA, Smith DK, Adams DR, et al. Efficacy of postexposure prophylaxis after intravaginal exposure of pig-tailed macaques to a human-derived retrovirus (human immunodeficiency virus type 2). J Virol 2000;74:9771-5.
159. Whitney JB, Hill AL, Sanisetty S, et al. Rapid seeding of the viral reservoir prior to SIV viraemia in rhesus monkeys. Nature 2014;512:74-7.
160. Wade NA, Birkhead GS, Warren BL, et al. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. N Engl J Med 1998;339:1409-14.
161. Malinverni S, Libois A, Gennotte AF, La Morte C, Mols P. Prescription of Non-Occupational Post-Exposure HIV Prophylaxis by Emergency Physicians: An Analysis on Accuracy of Prescription and Compliance. PLoS One 2016;11:e0153021. doi: 10.1371/journal.pone.. eCollection 2016.
162. Gilbert M, Cook D, Steinberg M, et al. Targeting screening and social marketing to increase detection of acute HIV infection in men who have sex with men in Vancouver, British Columbia. AIDS 2013;27:2649-54.
163. Greub G, Gallant S, Zurn P, et al. Spare non-occupational HIV post-exposure prophylaxis by active contacting and testing of the source person. AIDS 2002;16:1171-6.
164. Ford N, Shubber Z, Calmy A, et al. Choice of antiretroviral drugs for postexposure prophylaxis for adults and adolescents: a systematic review. Clin Infect Dis 2015;60:S170-6. doi: 10.1093/cid/civ092.
165. Mayer KH, Mimiaga MJ, Gelman M, Grasso C. Raltegravir, tenofovir DF, and emtricitabine for postexposure prophylaxis to prevent the sexual transmission of HIV: safety, tolerability, and adherence. J Acquir Immune Defic Syndr 2012;59:354-9.
166. McAllister J, Read P, McNulty A, Tong WW, Ingersoll A, Carr A. Raltegravir-emtricitabine-tenofovir as HIV nonoccupational post-exposure prophylaxis in men who have sex with men: safety, tolerability and adherence. HIV Med 2014;15:13-22.
167. Thomas R, Galanakis C, Vezina S, et al. Adherence to Post-Exposure Prophylaxis (PEP) and Incidence of HIV Seroconversion in a Major North American Cohort. PLoS One 2015;10:e0142534.
168. Mulka L, Annandale D, Richardson C, Fisher M, Richardson D. Raltegravir-based HIV postexposure prophylaxis (PEP) in a real-life clinical setting: fewer drug-drug interactions (DDIs) with improved adherence and tolerability. Sex Transm Infect 2016;92:107.
169. Leal L, Leon A, Torres B, et al. A randomized clinical trial comparing ritonavir-boosted lopinavir versus raltegravir each with tenofovir plus emtricitabine for post-exposure prophylaxis for HIV infection. J Antimicrob Chemother 2016;71:1987-93.
170. Fatkenheuer G, Jessen H, Stoehr A, et al. PEPDar: A randomized prospective noninferiority study of ritonavir-boosted darunavir for HIV post-exposure prophylaxis. HIV Med 2016;17:453-9.
171. McAllister JW, Towns JM, McNulty A, et al. Dolutegravir with tenofovir disoproxil fumarate-emtricitabine as HIV postexposure prophylaxis in gay and bisexual men. AIDS 2017;31:1291-5. doi: 10.097/QAD.0000000000001447.
172. Molina JM, Cohen C, Katlama C, et al. Safety and efficacy of darunavir (TMC114) with low-dose ritonavir in treatment-experienced patients: 24-week results of POWER 3. Journal of acquired immune deficiency syndromes (1999) 2007;46:24-31.

173. Clotet B, Bellos N, Molina JM, et al. Efficacy and safety of darunavir-ritonavir at week 48 in treatment-experienced patients with HIV-1 infection in POWER 1 and 2: a pooled subgroup analysis of data from two randomised trials. Lancet 2007;369:1169-78.
174. Hammer SM, Squires KE, Hughes MD, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. AIDS Clinical Trials Group 320 Study Team. The New England journal of medicine 1997;337:725-33.
175. Montaner JS, Reiss P, Cooper D, et al. A randomized, double-blind trial comparing combinations of nevirapine, didanosine, and zidovudine for HIV-infected patients: the INCAS Trial. Italy, The Netherlands, Canada and Australia Study. Jama 1998;279:930-7.
176. Smith DK, Grohskopf LA, Black RJ, et al. Antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV in the United States: recommendations from the U.S. Department of Health and Human Services. MMWR Recomm Rep 2005;54:1-20.
177. Medicine. ASfH. National guidelines for post-exposure prophylaxis after non-occupational and occupational exposure to HIV. Available at: www.ashm.org.au/pep-guidelines. Accessed April 21, 2016. 2013.
178. Massud I, Mitchell J, Babusis D, al. E. Chemoprophylaxis With Oral FTC/TAF Protects Macaques From Rectal SHIV Infection. Conference on Retroviruses and Opportunistic Infections. Boston, MA. February 22 - 25, 2016. Abstract 107.
179. Rockstroh JK, DeJesus E, Henry K, et al. A randomized, double-blind comparison of coformulated elvitegravir/cobicistat/emtricitabine/tenofovir DF vs ritonavir-boosted atazanavir plus coformulated emtricitabine and tenofovir DF for initial treatment of HIV-1 infection: analysis of week 96 results. J Acquir Immune Defic Syndr 2013;62:483-6. doi: 10.1097/QAI.0b013e318286415c.
180. Wohl DA, Cohen C, Gallant JE, et al. A randomized, double-blind comparison of single-tablet regimen elvitegravir/cobicistat/emtricitabine/tenofovir DF versus single-tablet regimen efavirenz/emtricitabine/tenofovir DF for initial treatment of HIV-1 infection: analysis of week 144 results. J Acquir Immune Defic Syndr 2014;65:e118-20. doi: 10.1097/QAI.0000000000000057.
181. Patel DA, Snedecor SJ, Tang WY, et al. 48-week efficacy and safety of dolutegravir relative to commonly used third agents in treatment-naive HIV-1-infected patients: a systematic review and network meta-analysis. PLoS One 2014;9:e105653. doi: 10.1371/journal.pone.0105653. eCollection 2014.
182. Mayer KH, Jones D, Oldenburg C, et al. Optimal HIV Postexposure Prophylaxis Regimen Completion With Single Tablet Daily Elvitegravir/Cobicistat/Tenofovir Disoproxil Fumarate/Emtricitabine Compared With More Frequent Dosing Regimens. J Acquir Immune Defic Syndr 2017;75:535-9. doi: 10.1097/QAI.0000000000001440.
183. Valin N, Fonquernie L, Daguenel A, et al. Evaluation of tolerability with the co-formulation elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate for post-HIV exposure prophylaxis. BMC Infect Dis 2016;16:718.
184. Cahn P, Kaplan R, Sax PE, et al. Raltegravir 1200 mg once daily versus raltegravir 400 mg twice daily, with tenofovir disoproxil fumarate and emtricitabine, for previously untreated HIV-1 infection: a randomised, double-blind, parallel-group, phase 3, non-inferiority trial. Lancet HIV 2017;11:30128-5.
185. Tosini W, Muller P, Prazuck T, et al. Tolerability of HIV postexposure prophylaxis with tenofovir/emtricitabine and lopinavir/ritonavir tablet formulation. AIDS 2010;24:2375-80.
186. Diaz-Brito V, Leon A, Knobel H, et al. Post-exposure prophylaxis for HIV infection: a clinical trial comparing lopinavir/ritonavir versus atazanavir each with zidovudine/lamivudine. Antivir Ther 2012;17:337-46.

187. Kakuda TN, Opsomer M, Timmers M, et al. Pharmacokinetics of darunavir in fixed-dose combination with cobicistat compared with coadministration of darunavir and ritonavir as single agents in healthy volunteers. J Clin Pharmacol 2014;54:949-57. doi: 10.1002/jcph.290. Epub 2014 Mar 26.
188. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. The New England journal of medicine 2008;358:568-79.
189. Johnson S, Baraboutis JG. Adverse effects associated with use of nevirapine in HIV postexposure prophylaxis for 2 health care workers. JAMA 2000;284:2722-3.
190. Wiboonchutikul S, Thientong V, Sutha P, al. E. Significant Intolerability of Efavirenz in HIV Occupational Postexposure Prophylaxis. In Abstracts and Proceedings of the Conference on Opportunistic Infections and Retroviruses (CROI), February 23 - 25, 2015. Seattle, WA. Abstract 957 .
.
191. Foster R, McAllister J, Read TR, et al. Single-Tablet Emtricitabine-Rilpivirine-Tenofovir as HIV Postexposure Prophylaxis in Men Who Have Sex With Men. Clin Infect Dis 2015;61:1336-41.
192. Tsai CC, Emau P, Follis KE, et al. Effectiveness of postinoculation (R)-9-(2-phosphonylmethoxypropyl) adenine treatment for prevention of persistent simian immunodeficiency virus SIVmne infection depends critically on timing of initiation and duration of treatment. J Virol 1998;72:4265-73.
193. Ford N, Venter F, Irvine C, Beanland RL, Shubber Z. Starter packs versus full prescription of antiretroviral drugs for postexposure prophylaxis: a systematic review. Clin Infect Dis 2015;60 Suppl 3:S182-6.
194. Bogoch, II, Scully EP, Zachary KC, et al. Patient attrition between the emergency department and clinic among individuals presenting for HIV nonoccupational postexposure prophylaxis. Clin Infect Dis 2014;58:1618-24.
195. Wong K, Hughes CA, Plitt S, et al. HIV non-occupational postexposure prophylaxis in a Canadian province: treatment completion and follow-up testing. Int J STD AIDS 2010;21:617-21.
196. Armishaw J, Hoy JF, Watson KM, Wright EJ, Price BG, Pierce AB. Non-occupational post-exposure prophylaxis in Victoria, Australia: responding to high rates of re-presentation and low rates of follow-up. Int J STD AIDS 2011;22:714-8.
197. O'Byrne P, MacPherson P, Roy M, Orser L. Community-based, nurse-led post-exposure prophylaxis: results and implications. Int J STD AIDS 2016;12:0956462416658412.
198. de Vrieze NH, van Rooijen MS, van de Loeff MS, de Vries HJ. Additional gonorrhea and Chlamydia infections found with rapid follow-up screening in men who have sex with men with an indication for HIV postexposure prophylaxis. Sex Transm Dis 2014;41:515-7.
199. Sivachandran N, Siemieniuk RA, Murphy P, et al. Sexually transmitted infections and viral hepatitides in patients presenting for non-occupational HIV post-exposure prophylaxis: results of a prospective cohort study. Int J Infect Dis 2015;40:142-4.:10.1016/j.ijid.2015.10.001.
200. Chan A, Gough K, Yoong D, Dimeo M, Tan DHS. nPEP for HIV: A Retrospective Review of Patient Eligibility, Barriers to Uptake and Clinical Outcomes. Ontario HIV Treatment Network 14th Annual Research Conference; 2011; Toronto.
201. Leal L, Leon A, Torres B, et al. A randomized clinical trial comparing ritonavir-boosted lopinavir versus maraviroc each with tenofovir plus emtricitabine for post-exposure prophylaxis for HIV infection. J Antimicrob Chemother 2016;71:1982-6.
202. O'Keeffe C, Nwokolo N, McOwan A, Whitlock G. Does dropping day 5 PEP follow-up affect outcomes? An audit of HIV post-exposure prophylaxis at a central London sexual health clinic. Int J STD AIDS 2015;26:590-2. doi: 10.1177/0956462414547090. Epub 2014 Aug 12.

203. Bentz L, Enel P, Dunais B, et al. Evaluating counseling outcome on adherence to prophylaxis and follow-up after sexual HIV-risk exposure: a randomized controlled trial. AIDS Care 2010;22:1509-16. doi: 10.080/09540121.2010.484457.
204. Roland ME, Neilands TB, Krone MR, et al. A randomized noninferiority trial of standard versus enhanced risk reduction and adherence counseling for individuals receiving post-exposure prophylaxis following sexual exposures to HIV. Clin Infect Dis 2011;53:76-83. doi: 10.1093/cid/cir333.
205. Abrahams N, Jewkes R, Lombard C, Mathews S, Campbell J, Meel B. Impact of telephonic psycho-social support on adherence to post-exposure prophylaxis (PEP) after rape. AIDS Care 2010;22:1173-81. doi: 10.080/09540121003692185.
206. Landovitz RJ, Fletcher JB, Inzhakova G, Lake JE, Shoptaw S, Reback CJ. A novel combination HIV prevention strategy: post-exposure prophylaxis with contingency management for substance abuse treatment among methamphetamine-using men who have sex with men. AIDS Patient Care STDS 2012;26:320-8. doi: 10.1089/apc.2011.0432.
207. Landovitz RJ, Fletcher JB, Shoptaw S, Reback CJ. Contingency management facilitates the use of postexposure prophylaxis among stimulant-using men who have sex with men. Open Forum Infect Dis 2015;2:ofu114. doi: 10.1093/ofid/ofu114. eCollection 2015 Jan.
208. Taylor D, Durigon M, Davis H, et al. Probability of a false-negative HIV antibody test result during the window period: a tool for pre- and post-test counselling. Int J STD AIDS 2015;26:215-24.
209. Delaney KP, Hanson DL, Masciotra S, Ethridge SF, Wesolowski L, Owen SM. Time Until Emergence of HIV Test Reactivity Following Infection With HIV-1: Implications for Interpreting Test Results and Retesting After Exposure. Clin Infect Dis 2017;64:53-9. Epub 2016 Oct 12.
210. Terzi R, Niero F, Iemoli E, Capetti A, Coen M, Rizzardini G. Late HIV seroconversion after non-occupational postexposure prophylaxis against HIV with concomitant hepatitis C virus seroconversion. AIDS 2007;21:262-3.
211. Updated Guidelines for Antiretroviral Postexposure Prophylaxis After Sexual, Injection Drug Use, or Other Nonoccupational Exposure to HIV—United States, 2016. In: Centers for Disease Control and Prevention USDoHaHS, ed.2016.
212. de Souza MS, Pinyakorn S, Akapirat S, et al. Initiation of Antiretroviral Therapy During Acute HIV-1 Infection Leads to a High Rate of Nonreactive HIV Serology. Clin Infect Dis 2016;63:555-61.
213. Chan AC, Gough K, Yoong D, Dimeo M, Tan DH. Non-occupational post-exposure prophylaxis for HIV at St Michael's Hospital, Toronto: a retrospective review of patient eligibility and clinical outcomes. Int J STD AIDS 2013;24:393-7.
214. Conroy AA, Gamarel KE, Neilands TB, et al. Partner Reports of HIV Viral Suppression Predict Sexual Behavior in Serodiscordant Male Couples. J Acquir Immune Defic Syndr 2016;73:e31-3.
215. Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf. Accessed September 1, 2016. 2016.
216. Stek A, Best BM, Wang J, et al. Pharmacokinetics of Once Versus Twice Daily Darunavir in Pregnant HIV-Infected Women. J Acquir Immune Defic Syndr 2015;70:33-41.
217. Fowler MG, Qin M, Fiscus SA, et al. Benefits and Risks of Antiretroviral Therapy for Perinatal HIV Prevention. N Engl J Med 2016;375:1726-37.
218. Siemieniuk RAC, Lytvyn L, Mah Ming J, et al. Antiretroviral therapy in pregnant women living with HIV: a clinical practice guideline. BMJ 2017;358:j3961.:10.1136/bmj.j3961.
219. Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. Recommendations for Use of Antiretroviral Drugs in Pregnant Women with HIV Infection

and Interventions to Reduce Perinatal HIV Transmission in the United States. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf. Accessed October 24, 2017. 2017.
220. British HIV Association (BHIVA) response to BMJ article "Antiretroviral therapy in pregnant women living with HIV: a clinical practice guideline"1 published 11 September 2017. 2017.
221. Merck Canada Inc. Product Monograph: Isentress. 2015.
222. Janssen, Inc. Product Monograph: Prezista. 2014.
223. Remis RS, Swantee C, Liu J. HIV/AIDS in Ontario: Preliminary Report, 20102012.
224. Desai K, Sansom SL, Ackers ML, et al. Modeling the impact of HIV chemoprophylaxis strategies among men who have sex with men in the United States: HIV infections prevented and cost-effectiveness. AIDS 2008;22:1829-39. doi: 10.097/QAD.0b013e32830e00f5.
225. Juusola JL, Brandeau ML, Owens DK, Bendavid E. The cost-effectiveness of preexposure prophylaxis for HIV prevention in the United States in men who have sex with men. Ann Intern Med 2012;156:541-50.
226. Chen A, Dowdy DW. Clinical effectiveness and cost-effectiveness of HIV pre-exposure prophylaxis in men who have sex with men: risk calculators for real-world decision-making. PLoS One 2014;9:e108742.
227. Schneider K, Gray RT, Wilson DP. A cost-effectiveness analysis of HIV preexposure prophylaxis for men who have sex with men in Australia. Clin Infect Dis 2014;58:1027-34.
228. Ouellet E, Durand M, Guertin JR, LeLorier J, Tremblay CL. Cost effectiveness of 'on demand' HIV pre-exposure prophylaxis for non-injection drug-using men who have sex with men in Canada. Can J Infect Dis Med Microbiol 2015;26:23-9.
229. Ross EL, Cinti SK, Hutton DW. Implementation and Operational Research: A Cost-Effective, Clinically Actionable Strategy for Targeting HIV Preexposure Prophylaxis to High-Risk Men Who Have Sex With Men. J Acquir Immune Defic Syndr 2016;72:e61-7.
230. MacFadden DR, Tan DH, Mishra S. Optimizing HIV Pre-Exposure Prophylaxis Implementation Among Men Who Have Sex with Men in a Large Urban Center: A Dynamic Modeling Study. J Int AIDS Soc 2016;19: 20791.
231. Organization WH. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: what's new. Policy Brief. November 2015. Available at: http://www.who.int/hiv/pub/arv/policy-brief-arv-2015/en/. Accessed November 29, 2016.
232. Herida M, Larsen C, Lot F, Laporte A, Desenclos JC, Hamers FF. Cost-effectiveness of HIV post-exposure prophylaxis in France. AIDS 2006;20:1753-61.
233. Pinkerton SD, Martin JN, Roland ME, Katz MH, Coates TJ, Kahn JO. Cost-effectiveness of postexposure prophylaxis after sexual or injection-drug exposure to human immunodeficiency virus. Arch Intern Med 2004;164:46-54.
234. Pinkerton SD, Martin JN, Roland ME, Katz MH, Coates TJ, Kahn JO. Cost-effectiveness of HIV postexposure prophylaxis following sexual or injection drug exposure in 96 metropolitan areas in the United States. AIDS 2004;18:2065-73.
235. Guinot D, Ho MT, Poynten IM, et al. Cost-effectiveness of HIV nonoccupational post-exposure prophylaxis in Australia. HIV Med 2009;10:199-208.
236. Bryant J, Baxter L, Hird S. Non-occupational postexposure prophylaxis for HIV: a systematic review. Health Technol Assess 2009;13:iii, ix-x, 1-60.
237. Hornberger J, Holodniy M, Robertus K, Winnike M, Gibson E, Verhulst E. A systematic review of cost-utility analyses in HIV/AIDS: implications for public policy. Med Decis Making 2007;27:789-821.
238. Sharma M, Wilton J, Senn H, Fowler S, Tan DH. Preparing for PrEP: perceptions and readiness of canadian physicians for the implementation of HIV pre-exposure prophylaxis. PLoS One 2014;9:e105283. doi: 10.1371/journal.pone.0105283. eCollection 2014.

239. Karris MY, Beekmann SE, Mehta SR, Anderson CM, Polgreen PM. Are we prepped for preexposure prophylaxis (PrEP)? Provider opinions on the real-world use of PrEP in the United States and Canada. Clin Infect Dis 2014;58:704-12. doi: 10.1093/cid/cit796. Epub 2013 Dec 6.
240. Guideline on When to Start Antiretroviral Therapy and on Pre-Exposure Prophylaxis for HIV. World Health Organization, September, 2015. Available at: http://www.who.int/hiv/pub/guidelines/earlyrelease-arv/en/.
241. Brady M, Rodger A, Asboe D, et al. BHIVA/BASHH guidelines on the use of HIV pre-exposure prophylaxis (PrEP) - Consultation Draft. 2017.
242. Wright E, Grulich A, Roy K, et al. Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine HIV pre-exposure prophylaxis: clinical guidelines. J Virus Erad 2017;3:168-84.
243. Gunthard HF, Saag MS, Benson CA, et al. Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2016 Recommendations of the International Antiviral Society-USA Panel. JAMA 2016;316:191-210. doi: 10.1001/jama.2016.8900.
244. European AIDS Clinical Society Guidelines, version 8.2. 2017.
245. Buchbinder SP, Glidden DV, Liu AY, et al. HIV pre-exposure prophylaxis in men who have sex with men and transgender women: a secondary analysis of a phase 3 randomised controlled efficacy trial. Lancet Infect Dis 2014;14:468-75.
246. Cornett JK, Kirn TJ. Laboratory diagnosis of HIV in adults: a review of current methods. Clin Infect Dis 2013;57:712-8.
247. Pilcher CD, Fiscus SA, Nguyen TQ, et al. Detection of acute infections during HIV testing in North Carolina. The New England journal of medicine 2005;352:1873-83.

Acknowledgements

The panel thanks Mr. David Lightfoot for his assistance with designing and conducting the electronic literature search, Mr. Alex Schnubb for his assistance coordinating the Panel meetings, and Mr. Kevin Pendergraft for his assistance with coordinating community feedback. This guidelines process was supported by a grant from the Canadian Institutes of Health Research (Funding reference number PCS – 142089) and in-kind support from the CIHR Canadian HIV Trials Network. DHST is supported by a New Investigator Award from the CIHR and Ontario HIV Treatment Network.