Antiretroviral Medications for the Prevention of HIV Infection

A Clinical Approach to Preexposure Prophylaxis, Postexposure Prophylaxis, and Treatment as Prevention

Amila Heendeniya, MD[a], Isaac I. Bogoch, MD[a,b,c,*]

KEYWORDS

• HIV • Prevention • Preexposure prophylaxis • PrEP • Postexposure prophylaxis • PEP • Treatment as prevention

KEY POINTS

- Effective human immunodeficiency virus (HIV) prevention strategies include both behavioral and pharmacologic methods.
- Antiretroviral drugs to prevent HIV may be used proactively (preexposure prophylaxis), retroactively (postexposure prophylaxis), and at a population level (treatment as prevention).
- HIV prevention clinic appointments are opportune times to address other common comorbidities that may influence HIV acquisition risk, such as mental health issues and abuse (eg, sexual, drug, or alcohol).

INTRODUCTION

The past 30 years have seen tremendous progress in both the care of human immunodeficiency virus (HIV)-positive individuals and HIV prevention techniques, and currently the pendulum is swinging toward strategies and policies that will enable an HIV-free world. In 2014, The Joint United Nations Programme on HIV/AIDS

Disclosures: Both authors have no conflicts of interest to declare.
[a] Division of Infectious Diseases, Toronto General Hospital, Toronto General Hospital, 200 Elizabeth Street, Toronto, Ontario M5G 2C4, Canada; [b] Department of Medicine, University of Toronto, 190 Elizabeth Street, R. Fraser Elliott Building, 3-805, Toronto, Ontario M5G 2C4, Canada; [c] Division of General Internal Medicine, Toronto General Hospital, University Health Network, Toronto, Ontario, Canada
* Corresponding author. Toronto General Hospital, 200 Elizabeth Street – 14EN – 209, Toronto, Ontario M5G 2C4, Canada.
E-mail address: isaac.bogoch@uhn.ca

Infect Dis Clin N Am 33 (2019) 629–646
https://doi.org/10.1016/j.idc.2019.04.002
id.theclinics.com

(UNAIDS) unveiled their ambitious "90-90-90" plan, with the goal that 90% of HIV-infected individuals will have a diagnosis (from 79%), treatment rates will increase to 90% (from 59%), and the rates of individuals with a suppressed viral load will increase to 90% (from 47%).[1] These targets were established with the ambition to vastly curb the HIV epidemic by 2020 and eliminate the disease by 2030.[1] Recent global data have demonstrated increasing HIV treatment coverage and decreasing HIV-related deaths, culminating in the highest prevalence of people with HIV, at an estimated 36.9 million people in 2017.[2] Such metrics demonstrate the success of current programs and also highlight the need to continue advocating for policies that ensure people affected with HIV have access to necessary care.

Ending the global HIV epidemic will involve intersectoral cooperation and coordination with several partners, including the public sector, industry, academia, and civic representation.[3] Several active areas of research and quality improvement initiatives are focused on curbing the epidemic and include (1) the implementation of current knowledge to enable better access to HIV and HIV-prevention care, (2) vaccine development, and (3) cure research. Although HIV prevention strategies are one piece of a much larger puzzle pointing tward the global eliination of HIV, such prevention strategies are now viewed as integral aspects in routine clinical and public health care by frontline health care providers and policy makers. Successful HIV prevention care involves the use of both pharmacologic and nonpharmacologic tools (often referred to as "biological" and "nonbiological"), and although the focus here is on pharmacologic mechanisms of HIV prevention, the authors believe nonpharmacologic principles should be seamlessly integrated into routine clinical practice. Such nonpharmacologic principles may include safe sexual counseling, access to harm-reduction strategies (eg, safe injection sites), addressing psychosocial determinants of health, and circumcision, for example.[4–6]

Pharmacologic methods for HIV prevention generally focus on 3 main areas: postexposure prophylaxis (PEP), preexposure prophylaxis (PrEP), and treatment as prevention (TasP). Here, the authors discuss the evidence driving these HIV prevention modalities and provide practical clinical advice for frontline health care providers seeing patients at risk for HIV infection.

POSTEXPOSURE PROPHYLAXIS

Introduction

Exposures to HIV are generally classified as either occupational (requiring occupational PEP [oPEP]) or nonoccupational (requiring nonoccupational PEP [nPEP]).[7,8] This distinction is important, as there are occasionally unique challenges when managing nonoccupational compared with occupational HIV exposures. Although confirmed or potential HIV exposures may cause emotional distress in both occupational and nonoccupational settings, cases of oPEP are typically easier to manage for several reasons. First, there are usually more opportunities for source-patient HIV testing in occupational settings, whereas this is often very challenging to coordinate in nonoccupational settings. Secondly, antiretroviral therapy (ART) can be initiated rather quickly in most occupational settings and is often started within a few hours of the exposure, whereas there are frequently major delays in accessing PEP care in nonoccupational settings. Finally, occupational exposures typically have less physical or emotional trauma compared with nPEP cases, where, for example, sexual assault, intoxication, or physical violence are common themes and may affect access and adherence to care. Still, with all types of PEP, addressing the patient's pharmacologic and nonpharmacologic needs is paramount to ensure that patients adhere

to their 28-day ART regimen, return for follow-up testing, and access any additional support services that may be helpful.

PEP was first used following occupational exposures in the late 1980s,[9,10] and the US Center for Disease Control and Prevention (CDC) first introduced occupational guidelines for ART use in 1990.[11] An evaluation of risk factors for percutaneous HIV transmission and efficacy of PEP was first demonstrated in a large case-control study using zidovudine (AZT) monotherapy in health care workers with percutaneous exposures to HIV-positive patients. AZT monotherapy significantly reduced one's risk of HIV acquisition by about 80% in this landmark study.[12] Large cohort studies have also demonstrated PEP efficacy with 3 ART agents in nonoccupational settings; for example, one large cohort evaluating 702 individuals with nonoccupational HIV exposures demonstrated 7 seroconversions (1%) after PEP initiation and found that of these 7 seroconversions, several individuals may have not been adherent to their medications.[13] Currently 3-drug regimens are the norm for oPEP and nPEP, and most health care settings have protocolized the management of exposures, with evidence-based guidelines now widely available.[7,14–16]

PEP management involves addressing 5 key questions:

1. Did an HIV exposure occur?
2. If a confirmed or potential HIV exposure occurred, what is the risk of HIV transmission?
3. Should this patient initiate PEP and if so, with what drugs?
4. What other infectious and noninfectious disease issues should be addressed?
5. What is an appropriate follow-up strategy?

Did an exposure occur?

An exposure to HIV or bloodborne pathogens involves the source patient's blood, mucous membrane, or other potentially infectious bodily fluid coming into contact with a patient's blood or mucous membrane. Although this may seem obvious in the case of percutaneous injury (eg, needlestick injuries) or a history of condomless sexual activity, it is often challenging to confirm if an exposure occurred in nPEP cases involving intoxication or physical and psychological trauma. Many clinicians tend to treat "worst-case" scenarios and prescribe PEP in situations where there is uncertainty determining if an exposure occurred given the time-sensitive nature of initiating PEP (it must be initiated within 72 hours of the exposure), balanced with the relative tolerability of current PEP regimens.

What is the risk of human immunodeficiency virus transmission?

HIV exposures may be categorized by the type of exposure and the corresponding risk of HIV acquisition. Several factors should be considered when evaluating the risk of HIV transmission, including the following:

- The source patient:
  - Is the source patient known to be HIV-positive? If so,
    - Is the source patient currently on ART?
    - Does the source patient have a detectable viral load?
  - Does the source patient have an unknown HIV serostatus? If so,
    - Does the source patient belong to a cohort with a greater prevalence of HIV (eg, men who have sex with men [MSM], person who injects drugs [PWID], incarceration history, from a country with greater than 1% HIV seroprevalence, perpetrator of sexual assault or sexual partner of a member with one of the risk factors)[17]

- Is the source patient has very low risk for HIV? For example, does the source patient have a recent negative HIV test with no HIV risk factors? Is the source patient using and adherent to PrEP?
- Was this a mucosal or a percutaneous exposure?
- What was the type and volume of exposed body fluid?

The relative risks for HIV acquisition if exposed to a source patient with nonsuppressed HIV infection are outlined in **Table 1**.[17] Condomless sexual exposures with an HIV-positive individual who has a suppressed viral load (<200 copies/mL) for greater than 6 months have a zero-to-negligible risk for HIV transmission.[18] Although most PEP cases involve percutaneous or sexual exposures, occasionally there are exposures that fall outside of these traditional categories; however, such exposures are mostly very low-risk situations where PEP would have a negligible benefit.[19]

Should this patient initiate postexposure prophylaxis and if so, with what medications?

PEP should be initiated in a setting where there is greater than a negligible-to-low risk for HIV acquisition (see **Table 1**). PEP should be initiated as soon as possible and before 72 hours, following a potential or confirmed HIV exposure, and continued for 28 days.[7,14–16] Rarely, PEP can be initiated after the 72 hours window following an exposure; however, this is on a case-by-case basis and typically in cases of very high-risk exposures.

There are several options for PEP regimens, and **Fig. 1** highlights guideline-recommended approaches.[7,14–16] Dolutegravir was previously a common medication used in PEP regimens; however, it should be avoided in pregnant women and women of childbearing age, given the recent findings suggesting an increased risk of neural tube defects if a woman conceives while receiving this drug.[20,21] Although there are several drugs that may be used safely, certain drugs should be avoided, including abacavir, as there is the potential for hypersensitivity reactions and requires human leukocyte antigen testing before use, which may take several days to return.[22] In addition, efavirenz should be avoided due to short-term mental status changes and

Table 1
Human immunodeficiency virus transmission risks from exposure to an HIV-positive source with a nonsuppressive viral load

Risk Level	Exposure Category	HIV Transmission Risk from a Source with Nonsuppressed HIV Infection
High	Blood transfusion	92.5%
	Mother-to-child (vertical) transmission	22.6%
	Receptive anal intercourse	1.38%
	Needle sharing for injection drug use	0.63%
Moderate	Needlestick injury	0.23%
	Insertive anal intercourse	0.11%
	Vaginal intercourse (receptive)	0.08%
	Vaginal intercourse (insertive)	0.04%
Low	Insertive or receptive oral intercourse	No estimate
	Sharing sex toys	
	Blood on compromised skin	

Data from Tan DHS, Hull MW, Yoong D, et al. Canadian guideline on HIV pre-exposure prophylaxis and nonoccupational postexposure prophylaxis. *Can Med Assoc J*. 2017;189(47):E1448-E1458; and Patel P, Barkowf CB, Brooks JT, Lasry A, Lansky A, Mermin J. Estimating per-act HIV transmission risk: a systematic review. *AIDS*. 2014;28(10):1509-1519.

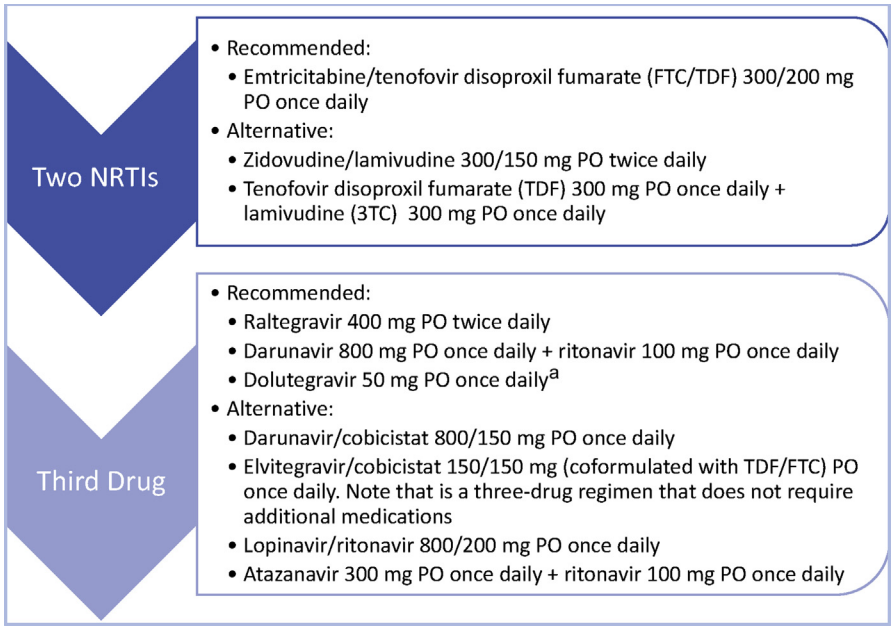

Fig. 1. Antiretroviral therapy options for PEP, favoring a 3-drug approach combining 2 NRTIs and an integrase inhibitor or a protease inhibitor. NRTIs, nucleoside reverse transcriptase inhibitors. [a] Dolutegravir should not be used in pregnant women and women of childbearing age, given the potential risk of neural tube defects.[20,21]. (*Data from* Refs. [7,14,16,24])

potential teratogenicity.[23,24] Older drugs that are no longer recommended for HIV treatment due to toxicity, such as indinavir, stavudine, and didanosine, should also not be used for PEP.[25,26]

What other infectious and noninfectious disease issues should be addressed?

The first point of health care contact following a potential HIV exposure is usually an emergency department or an outpatient clinical setting. Before initiating PEP, patients should have baseline investigations, including HIV testing (preferably with a fourth-generation assay that detects both HIV antibodies and p24 antigen), hepatitis B and C serology, in addition to a complete blood count, creatinine, electrolytes, liver enzyme testing, and a pregnancy test for female patients. Patients presenting after a sexual exposure should be screened for chlamydia and gonorrhea (with urine, pharyngeal, and rectal screening, using nucleic acid amplification tests, where available) and syphilis serology. Inquiry into concomitant medications (including nonprescribed "over-the-counter" medications) and allergies is important to limit the risk of potential drug interactions and adverse effects. If the patient is nonimmune to hepatitis B, consideration should be given to starting hepatitis B postexposure prophylaxis[27] as well as vaccination for hepatitis B and A where necessary.[28,29]

PEP visits are teachable moments and great opportunities for health promotion. Such clinic visits enable health care providers to explore concomitant syndemic health problems such as drug or alcohol abuse, other mental health issues, and physical and sexual abuse that may increase one's risk for HIV acquisition.[30–32] PEP visits are also an opportune time to liaise individuals with targeted resources to help mitigate these syndemic health issues.

During the consultation, patients should be counseled on the importance of PEP adherence and what an HIV seroconversion illness is, and that they should seek care should they have such symptoms. They should also be advised on taking necessary steps to prevent transmission to others until their follow-up HIV status is confirmed as negative, such as wearing barrier protection during intercourse and refraining from donating blood, plasma, semen, breast milk, or organs, in addition to refraining from sharing drug injection paraphernalia, razors, and tooth brushes.

What is an appropriate follow-up strategy?

Poor adherence to 28-day PEP regimens and to clinic appointments is a frequent issue.[33] PEP regimens containing integrase inhibitors are generally well tolerated, and PEP regimens may be changed to these if there are side effects with other ARV classes to help improve adherence.[34–37] Ensuring patients have a close friend, family member, or community support worker to help facilitate improved adherence to medications and clinic appointments is helpful.

A fourth-generation HIV assay and hepatitis C virus serology should be repeated at 3 to 4 months following the initial exposure. If hepatitis C was acquired from the exposure, HIV testing should be repeated at the 6-month mark as there may be delayed seroconversion in these instances.[7,16] Repeat testing for hepatitis B should be considered if the patient is hepatitis B nonimmune and did not receive HBV postexposure prophylaxis. Depending on the exposure, patients should be rescreened for other sexually transmitted infections (STIs) such as gonorrhea, chlamydia and syphilis. Female patients who require PEP for a sexual exposure should have a pregnancy test repeated at 6 to 12 weeks. Any baseline bloodwork that was noted to be abnormal will need ongoing monitoring while the patient is on PEP, typically at the 2-week mark, and this may include abnormal liver function tests, renal function tests, and glucose.[16] As with the initial PEP clinic appointment, follow-up appointments are also opportune times for health promotion and to screen for drug or alcohol abuse, conduct safe sexual counseling, and to connect patients with helpful resources. Many patients presenting for PEP may be good candidates for other HIV prevention modalities such as PrEP, and the final PEP appointment may be an appropriate time to transition from PEP to PrEP care in those with ongoing HIV risk factors.[38]

PREEXPOSURE PROPHYLAXIS

Introduction

Select populations remain at increased risk for HIV acquisition. For example, the risk of acquiring HIV is 27 times higher among MSM, 23 times higher among PWID, and 13 times higher among female commercial sex workers compared with the general public.[2] In 2016, MSM represented 64% of the population with HIV in the United States, and they accounted for 66% of new infections overall.[39,40] PWID accounted for an estimated 6% to 9% of new HIV diagnoses in the United States between 2010 and 2015.[39,40] Canadian statistics show similar estimates, with MSM and PWID accounting for 52.5% and 14.3% of HIV incidences, respectively.[41] Globally, Southern and Eastern Africa are home to more than half of the total number of people with HIV[42] and there continue to be several logistic, financial, cultural, and legal barriers that stand in the way of implementing widescale HIV prevention strategies in this region.[43,44] Harm-reduction counseling and education alone have not been able to reduce the rates of HIV in at-risk populations, and additional pharmacologic HIV prevention approaches are necessary to curb the epidemic.

PrEP is the proactive use of ART in HIV-negative individuals to mitigate the risk of HIV acquisition in those at greater risk for infection. This approach has gained ground

quickly in the past few years as part of an integrated strategy to reduce the global burden of HIV. PrEP was first introduced into routine clinical practice in 2012, with the US Food and Drug Administration (FDA) approving combined emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) for use in HIV-negative individuals[45] and then with the World Health Organization (WHO) releasing PrEP guidelines that same year.[46] To date, multiple public health organizations have released PrEP guidelines.[16,24,47–49] Although PrEP may reduce HIV acquisition at an individual level, it is also demonstrated to significantly reduce HIV transmission at a population level when implemented broadly,[50] and there are currently efforts to scale up PrEP use in both high- and low-resource settings outside of clinical trials and into routine clinical care.

Early Evidence for Preexposure Prophylaxis

The path toward the FDA and WHO's approval of PrEP involved decades of research beginning with nonhuman studies and culminating in large clinical trials. In 1995, Tsai and colleagues[51] were able to demonstrate reductions in Simian Immunodeficiency Virus transmission in macaques by using TDF before and shortly after inoculation. Multiple nonhuman primate studied followed, with sentinel human studies emerging in 2010 and outlined in **Table 2**.

The iPrEx study is an early landmark PrEP trial where 2499 HIV-negative MSM or transgender women received either FTC/TDF or placebo and were followed prospectively. This study demonstrated that those receiving FTC/TDF as PrEP had a 44% reduction in HIV incidence.[52] Several subsequent studies then evaluated the role of PrEP in heterosexual populations, notably women. The FEM-PrEP Study Group's trial in Kenya, South Africa, and Tanzania evaluated the effectiveness of PrEP for HIV-negative heterosexual women with HIV-positive partners but failed to show a reduction in HIV acquisition risk.[53] Similarly, the VOICE trial conducted in South Africa, Uganda, and Zimbabwe also failed to show a significant reduction in HIV acquisition with oral or vaginal PrEP in at-risk heterosexual women.[54] The lack of efficacy in these trials is attributed to the very low adherence to PrEP, measured at 12% in FEM-PrEP[53]

Table 2
Early landmark trials studying human immunodeficiency virus preexposure prophylaxis and their overall efficacies

Study Name (Year)	Population	PrEP Regimen	Overall HIV Reduction	HIV Reduction in Those Adhering to PrEP
iPrEx (2010)	MSM and transgender women	FTC/TDF daily	44%	92%
TDF2 (2012)	Heterosexual couples	TDF	62%	-
FEM-PrEP (2012)	Heterosexual women	FTC/TDF	0%[a]	-
Partners PrEP (2013)	Heterosexual serodiscordant couples	FTC/TDF TDF	75% 67%	86% 90%
Bangkok Tenofovir Study (2013)	People who use injection drugs	TDF	49%	70%
VOICE (2015)	Heterosexual women	FTC/TDF TDF	0%[a] 0%[a]	-
PROUD (2016)	MSM	FTC/TDF	86%	86%

[a] Low adherence was noted in these studies.

and between 25% and 30% of individuals in VOICE, despite a self-reported adherence rate of 90%.[54]

The Partners PrEP Study randomized serodiscordant heterosexual couples to once-daily TDF, FTC/TDF, or placebo in Kenya and Uganda. All participants were also educated on risk reduction and safe sexual practices. A reduction in HIV transmission was observed with the use of TDF or FTC/TDF, and although nonsignificant, FTC/TDF demonstrated a higher relative reduction in HIV incidence compared with TDF alone.[55] Unlike the FEM-PrEP and VOICE trials, the Partners PrEP Study reported better adherence (up to 92%) to prescribed medications.

The TDF2 trial attempted to demonstrate PrEP efficacy in heterosexual couples in Botswana with FTC/TDF; however, the study was not adequately powered for this purpose.[56] Although the trial was terminated early due to low retention rates, interim efficacy analyses demonstrated a 62.6% reduction in HIV infections, but these data must be interpreted in the appropriate context, given the early termination of the trial.

The PROUD study, published in 2016, was an open-label randomized trial conducted in England that looked to address the efficacy of PrEP in real-world settings.[57] Five hundred fourty-four individuals deemed to be at risk for HIV acquisition were randomized to receive FTC/TDF either immediately or a year later. The study reported an 86% relative reduction of HIV incidence in the early PrEP group compared with those in the delayed group.

Lastly, the Bangkok Tenofovir Study (BTS) evaluated PrEP with daily TDF (compared with placebo) in PWID in Bangkok, Thailand.[58] All participants received monthly HIV testing and individualized risk-reduction counseling and were offered condoms and methadone treatment. The study arm demonstrated a 48.9% reduction in HIV incidence without a significant difference in serious adverse outcomes. BTS highlights the efficacy of PrEP in PWID when used in combination with other harm-reduction strategies.

Outside of controlled trials, PrEP had demonstrated incredible efficacy in "real-world" situations with robust data emerging in Canada, United States, and Australia.[50,59–62]

Prescribing Preexposure Prophylaxis

The initial preexposure prophylaxis visit

Pragmatic, user-friendly PrEP Guidelines are now available from many public health bodies and outline routine PrEP care in clinical practice.[16,24,48,49] Patients presenting for PrEP may be referred to specialist clinics or present directly to primary care providers and occasionally nurse-led providers.[63] The initial visit should focus on evaluating a patient's current and near-future risk for HIV acquisition and other preventable infections, screening for syndemic health issues such as depression or drug and alcohol abuse, and reiterating education related to HIV risk reduction (**Table 3**).[64] The HIV Incidence Risk Index for Men who have Sex with Men is a tool to help identify MSM who may benefit from PrEP[16,65]; however, many clinicians do not use this in routine practice, as it may be time consuming in an otherwise busy clinic. Clinical appointments are an opportune time to link individuals with helpful resources, such as alcohol or drug abuse programs, or psychosocial support where necessary.

Baseline investigations should be obtained before PrEP initiation and include a complete blood count, liver enzyme tests, and creatinine. HIV screening should preferably use a fourth-generation assay. In the context of a potential acute HIV infection, testing for HIV RNA nucleic acid is preferable, and if it is not available, then repeat testing with another fourth-generation HIV screen 2 to 4 weeks later is

Table 3
Important aspects of the medical history specific to preexposure prophylaxis

Issues on Medical History	Relevance to PrEP
1. Past medical history including a focus on bone and renal health	Currently FTC/TDF is the only recommended PrEP medication, and this may reduce bone density and has the potential for nephrotoxicity[73,75]
2. Current medications	Prescribed and nonprescribed medication may interact with FTC/DTF
3. Allergies	Many STI treatments involve beta-lactam antibiotics (eg, ceftriaxone for gonorrhea treatment). Inquire about drug allergies, as many patients on PrEP are at increased risk for acquiring STIs.[89]
4. Risk of HIV acquisition	i. Sexual risk factors a. Frequency of sexual encounters b. Number of sexual partners c. Number of known HIV-positive partners d. Number of partners with known STI history e. Patterns of barrier protection usage f. Use of concomitant alcohol or drugs with sex or participation in chemsex[a] g. Current or past history of sexual abuse or challenges with condom negotiation
5. Injection drug use	i. Frequency of injection drug use ii. Sharing of drug paraphernalia iii. Safety of drug use (eg, inject with partner supervision, use of safe injection sites, naloxone kit availability)

[a] Intercourse under the influence of psychoactive substances to enhance sexual arousal; often associated with geolocating mobile applications.

recommended.[16,49] HIV testing should ideally be negative within a week before starting PrEP. Other blood work should include hepatitis A, B, and C serology and then ensuring individuals are immune to hepatitis A and B.[16,66,67] Patient should be screened for STIs, such as chlamydia, gonorrhea (urine nucleic acid amplification test, rectal and pharyngeal culture, or nucleic acid amplification tests, if indicated by exposure), and syphilis, and treated as per local guidelines.

What should you prescribe and how should you follow the patient?

FTC/TDF is currently the only medication approved for PrEP; however, the DISCOVER trial recently demonstrated the noninferiority of combined emtricitabine/tenofovir alafenamide (FTC/TAF) compared with FTC/TDF in PrEP care and will likely be used more regularly in this setting given the favorable renal and bone toxicity profiles.[68] Although once-daily FTC/TDF is the more widely used PrEP regimen, "on-demand" (also referred to as "event-driven") PrEP is an alternative method. The ANRS IPERGAY evaluated on-demand PrEP in 414 MSM participants who were randomized to either using FTC/TDF or placebo before and shortly after sex.[69] FTC/TDF was prescribed as a fixed-dose combination (200 mg of FTC and 300 mg of TDF per pill) and participants administered a loading dose of 2 pills 2 to 24 hours before sex, followed by a third pill 24 hours after the first pill, and finally a fourth pill 24 hours later. Although 14 HIV infections were seen in the placebo group, the on-demand PrEP group only saw 2

infections for a relative risk reduction of 86%.[69] We present both daily and on-demand PrEP options to most patients and find that most individuals prefer daily PrEP due to the high frequency of condomless sexual activity and ease of a once-daily medication.

Patients taking PrEP are to follow-up in clinic every 3 months to screen for HIV, STIs, medication toxicity, and medication adherence. These are also opportune times to discuss other health promotion strategies (eg, seasonal influenza vaccination) and continue to screen and offer support for additional issues such as alcohol and drug abuse or mental health issues. The authors prescribe PrEP in 4-month increments and ask patients to follow-up in 3- to 3.5-month increments, as some patients may miss a scheduled appointment and the longer prescription time allows for such scheduling issues while ensuring patients do not go without PrEP.

The authors also screen patients at each follow-up visit to determine if PrEP is still indicated. Many individuals have some fluidity in their sexual risk and may start and stop PrEP based on their most current risk. At follow-up visits, repeat HIV testing and STI screening should be performed as outlined in the initial visit, and safety laboratories include a complete blood count, creatinine, and a urine protein-to-creatinine ratio to screen for possible adverse effects of FTC/TDF.[16,48,49]

Additional Preexposure Prophylaxis Considerations

Other human immunodeficiency virus prevention modalities

Some patients may request a pharmacologic HIV prevention modality but have very few condomless sexual exposures to warrant daily PrEP. In such cases, it is challenging to balance using daily medications to prevent very rare HIV exposures with the costs of medication and potential side effects such as renal and bone toxicity. In addition, there is some uncertainty in the efficacy of on-demand PrEP in individuals with very infrequent potential HIV exposures. In these circumstances, one may consider "on-demand PEP," also termed "PEP-in-pocket," (or "PIP"), where patients who have up to 4 potential HIV exposures per year are given a prescription for a 28-day supply of PEP (see **Fig. 1**). Patients are counseled to fill the prescription and only take the medications should they have a potential HIV exposure. Patients are counseled to follow-up in clinic within a week of their exposure if they started PEP for baseline investigations. Such an approach may enable timely access to HIV prevention, promote autonomy over one's care, and avoid emergency department visits.[70]

Pregnancy and lactation

The effect of FTC/TDF on fetal and infant growth is not well understood but thought to be relatively safe.[71] FTC/TDF did not demonstrate any significant effect on pregnancy outcomes in the Partners PrEP trial,[55] and data from HIV-positive women exposed to TDF also corroborate the relative safety in pregnancy.[72] Given the limited evidence in peripartum use of PrEP, patients should be counseled on potential benefits versus risks of PrEP during pregnancy and lactation.[48]

Adverse effects

Serious adverse effects are very infrequent in those on PrEP. Mild gastrointestinal symptoms are reported to be the most common adverse symptoms and are generally limited to the first month of PrEP use.[52,55] PrEP has also been associated with a decline in renal function. For example, the Partners PrEP Study demonstrated a decrease in estimated glomerular filtration rate (eGFR) starting at 1 month of PrEP use; however, this decline in GFR did not progress and is not thought to be clinically relevant in those with normal baseline eGFRs.[73] Also reassuring is that renal function recovered with discontinuation of PrEP[74]; however, because of the potential for

nephrotoxicity, PrEP should only be used in those with a glomerular filtration rate of greater than or equal to 60 mL/min.[16,24,48,49] Several studies have demonstrated a mild but significant decrease in bone mineral density (BMD) on PrEP, even as early as 24 weeks after initiating FTC/TDF.[75] Although this is thought to be statistically significant, it has not demonstrated clinical significance in those with normal BMDs, and BMD returns to normal with discontinuation of PrEP. FTC/TAF has a favorable renal and bone toxicity profile compared with FTC/TDF.[68] With the recent noninferiority findings of this medication compared with FTC/TDF in PrEP care, we may see a reduced rate of adverse outcomes with scale-up of this drug; however, at the time of writing, this FTC/TAF has not been approved in HIV prevention guidelines.[68]

Change in sexual behavior and sexually transmitted infection risk while on preexposure prophylaxis

There are concerns for greater rates of condomless sexual activities and increasing rates of bacterial STIs with PrEP scale-up, especially in the context of emerging drug-resistant STIs.[76] Although behavioral data in real world settings are limited, several randomized controlled trials demonstrated decreasing rates of high-risk sexual behavior while on PrEP.[52,53,56,58] In contrast, the ANRS IPERGAY study demonstrated greater rates of condomless sex during the course of that study.[69] A recent systematic review looking at 16 studies demonstrated more condomless sexual acts and a significant increase in rectal chlamydia in those on PrEP,[77] but the utility of this review was limited by the heterogeneity of the included studies. Still this highlights the importance of safe sexual counseling and the need for frequent STI screening (and treatment if necessary) at 3-month intervals in those taking PrEP.

Antiviral resistance and human immunodeficiency virus acquisition

There is a risk of developing HIV resistant to FTC/TDF if HIV is acquired while on PrEP or if patients initiate PrEP with unrecognized HIV infection. For example, the FEM-PrEP trial reported antiretroviral resistance developing among 4 recently infected patients following PrEP initiation.[53] In addition, a man in Toronto acquired a multidrug-resistant HIV-1 strain despite using PrEP with biochemical data suggesting adequate drug adherence.[78] Hence, it is crucial to ensure patients are HIV-negative before initiating PrEP and to counsel those on PrEP to use barrier protection.

Treatment as Prevention

Treatment as Prevention (TasP) entails prescribing ART to everyone infected with HIV with the goal of reducing viral loads to non-detectable levels in individuals, and subsequently reducing HIV transmission in communities. Several studies over the past decade demonstrate that an individual's HIV transmission risk can theoretically be eliminated if their viral load is undetectable. Data published in 2011 demonstrated that the early initiation of ART significantly reduced transmission of HIV between serodiscordant couples.[79] In addition, a systematic review of HIV transmission in HIV-discordant heterosexual couples with viral load suppression less than 400 copies/mL showed a transmission rate of 1 per 79 person years.[80] Similarly, a prospective cohort analysis of HIV serodiscordant couples in 7 African nations demonstrated a 92% reduction in transmission in those on ART with suppressed viral loads.[81] A recent retrospective analysis of Taiwan's HIV surveillance data showed a 53% reduction in HIV transmission rates after providing free ART to all HIV-infected citizens,[82] and a similar population-based study in British Columbia demonstrated a 52% reduction in new HIV diagnoses with increasing financial coverage for ART.[83] Initiation of ART showed not only a significant impact on reduction of HIV

transmission but also a reduction in tuberculosis transmission in highly endemic regions.[84]

The PARTNER study from 2016 and the PARTNER 2 study from 2019 provided recent and robust data supporting TasP.[18,85] These studies evaluated condomless sexual activity among serodiscordant couples when the HIV-positive partner had an undetectable viral load (<200 copies/mL) that did not result in HIV transmission to the HIV-negative partner.[18] This prospective, observational, multicenter study included serodiscordant heterosexual couples and MSM and prompted the Undetectable = Untransmittable (U = U) movement.[86] U = U promotes the notion that those HIV-positive individuals on suppressive ART with undetectable viral loads (<200 copies/mL for >6 months) cannot sexually transmit the virus to their partners, and this is now being accepted by major public health bodies and integrated into guidelines.[8,49,87] Other recent studies that support U = U include the "Opposites Attract" study, where there were no phylogenetically linked cases of HIV transmission between 343 serodiscordant male couples (where one was virologically suppressed) and 232.2 couple years of follow-up in a prospective international study.[88]

Although TasP and U = U have widescale public health implications, these concepts are also applicable at the clinical level. These concepts (and the primary data that drives them) are frequently discussed in routine clinical settings while counseling patients at risk for HIV acquisition. TasP and U = U can help frame the discussion related to whether a patient is a candidate for PEP, PrEP, or other HIV prevention modalities and is helpful for patient-level education of HIV transmission risk, especially for serodiscordant couples.

SUMMARY

PEP, PrEP, and TasP are very effective HIV prevention modalities that have the potential to benefit individuals at risk for HIV acquisition and decrease HIV transmission in populations. Although these tools are now becoming more firmly entrenched into routine clinical practice, there is room for scale in many low-resource settings, especially those that are most affected by the HIV pandemic. Increasing global implementation of these HIV prevention modalities will be integral in halting the pandemic.

REFERENCES

1. UNAIDS. 90-90-90 an ambitious treatment target to help end the AIDS epidemic 2014. Available at: http://www.unaids.org/sites/default/files/media_asset/90-90-90_en.pdf. Accessed September 18, 2018.
2. Joint United Nations Programme on HIV/AIDS. UNAIDS Data 2018. Geneva (Switzerland): 2018. https://www.unaids.org/sites/default/files/media_asset/unaids-data-2018_en.pdf. Accessed May 20, 2019.
3. Commonwealth Secretariat. Guidelines for implementing a multi-sectoral approach to HIV and AIDS in Commonwealth countries. London: Commonwealth Secretariat Health Section; 2003.
4. Cook C, Phelan M, Sander G, et al. The case for a harm reduction decade: progress, potential and paradigm shifts. Harm reduction international 2016. Available at: https://www.hri.global/files/2016/03/10/Report_The_Case_for_a_Harm_Reduction_Decade.pdf. Accessed December 28, 2018.
5. Gray RH, Kigozi G, Serwadda D, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. Lancet 2007;369(9562):657–66.
6. Cepeda JA, Eritsyan K, Vickerman P, et al. Potential impact of implementing and scaling up harm reduction and antiretroviral therapy on HIV prevalence and

mortality and overdose deaths among people who inject drugs in two Russian cities: a modelling study. Lancet HIV 2018;5(10):e578–87.
7. US Centers for Disease Control and Prevention. Updated guidelines for antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV — United States, 2016. Morb Mortal Wkly Rep. https://doi.org/10.15585/mmwr.mm6517a5.
8. Kuhar DT, Henderson DK, Struble KA, et al. Updated US Public Health service guidelines for the management of occupational exposures to human immunodeficiency virus and recommendations for postexposure prophylaxis. Infect Control Hosp Epidemiol 2013;34(09):875–92.
9. Henderson DK, Gerberding JL. Prophylactic zidovudine after occupational exposure to the human immunodeficiency virus: an interim analysis. J Infect Dis 1989;160(2):321–7.
10. Tokars JI, Marcus R, Culver DH, et al. Surveillance of HIV infection and zidovudine use. Ann Intern Med 1993;118(12):913–9.
11. Polder J, Bell D, Barker E, et al. Public health service statement on management of occupational exposure to human immunodeficiency virus, including considerations regarding zidovudine postexposure use. vol. 39. 1990. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/00001556.htm. Accessed September 19, 2018.
12. Cardo DM, Culver DH, Ciesielski CA, et al. A case-control study of HIV seroconversion in health care workers after percutaneous exposure. N Engl J Med 1997;337(21):1485–90.
13. Roland ME, Neilands TB, Krone MR, et al. Seroconversion following nonoccupational postexposure prophylaxis against HIV. Clin Infect Dis 2005;41(10):1507–13.
14. Cresswell F, Waters L, Briggs E, et al. UK Guideline for the use of HIV Post-Exposure Prophylaxis Following Sexual Exposure, 2015. Int J STD AIDS 2016;27(9):713–38.
15. World Health Organization. Guidelines on post-exposure prophylaxis for HIV and the use of Co-Trimoxazole prophylaxis for HIV-related infections among adults, adolescents and Children: recommendations for a public health approach 2014. Available at: https://www.who.int/hiv/pub/guidelines/arv2013/arvs2013upplement_dec2014/en/. Accessed December 10, 2018.
16. Tan DHS, Hull MW, Yoong D, et al. Canadian guideline on HIV pre-exposure prophylaxis and nonoccupational postexposure prophylaxis. Can Med Assoc J 2017;189(47):E1448–58.
17. Patel P, Barkowf craig b, Brooks john t, et al. Estimating per-act HIV transmission risk: a systematic review. AIDS 2014;28(10):1509–19.
18. 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. J Am Med Assoc 2016. https://doi.org/10.1001/jama.2016.5148.
19. Rawal S, Bogoch II. Evaluation of non-sexual, non-needlestick, non-occupational HIV post-exposure prophylaxis cases. AIDS 2017;31(10):1500–2.
20. Zash R, Makhema J, Shapiro RL. Neural-tube defects with dolutegravir treatment from the time of conception. N Engl J Med 2018;379(10):979–81.
21. Zash R, Jacobson DL, Diseko M, et al. Comparative safety of dolutegravir-based or efavirenz-based antiretroviral treatment started during pregnancy in Botswana: an observational study. Lancet Glob Health 2018;6(7):e804–10.

22. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med 2008;358:568–79.
23. Ford N, Calmy A, Mofenson L. Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis. AIDS 2011;25(18):2301–4.
24. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva (Switzerland): World Health Organization; 2013.
25. Food and Drug Administration. CRIXIVAN® (Indinavir Sulfate) Capsules 2015. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020685s077lbl.pdf. Accessed December 13, 2018.
26. Timmermans S, Tempelman C, Godfried MH, et al. Nelfinavir and nevirapine side effects during pregnancy. AIDS 2005;19(8):795–9.
27. Schillie S, Murphy TV, Sawyer M. CDC guidance for evaluating health-care personnel for hepatitis B virus protection and for administering postexposure management. MMWR Recomm Rep 2013;62(RR-10):1–19, rr6210a1 [pii].
28. Freidl GS, Sonder GJ, Bovée LP, et al. Hepatitis A outbreak among men who have sex with men (MSM) predominantly linked with the EuroPride, the Netherlands, July 2016 to February 2017. Euro Surveill 2017. https://doi.org/10.2807/1560-7917.ES.2017.22.8.30468.
29. Friesema IHM, Sonder GJB, Petrignani MWF, et al. Spillover of a hepatitis A outbreak among men who have sex with men (MSM) to the general population, the Netherlands, 2017. Euro Surveill 2018;23(23) [pii:1800265].
30. 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(6):939–42.
31. Parsons JT, Millar BM, Moody RL, et al. Syndemic conditions and HIV transmission risk behavior among HIV-negative gay and bisexual men in a U.S. national sample. Health Psychol 2016;36(7):695–703.
32. Morrison SA, Yoong D, Hart TA, et al. High prevalence of syndemic health problems in patients seeking post-exposure prophylaxis for sexual exposures to HIV. PLoS One 2018;13(5):1–16.
33. 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(11):1618–24.
34. Bogoch II, Siemieniuk RAC, Andrews JR, et al. Changes to initial postexposure prophylaxis regimens between the emergency department and clinic. J Acquir Immune Defic Syndr 2015;69(5):e182–4.
35. Mayer KH, Mimiaga MJ, Gelman M, et al. 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(4):354–9.
36. Mulka L, Annandale D, Richardson C, et al. 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(2):107.
37. Thomas R, Galanakis C, Vézina S, et al. Adherence to post-exposure prophylaxis (PEP) and incidence of HIV seroconversion in a major North American cohort. PLoS One 2015;10(11):1–10.
38. Siemieniuk RAC, Sivachandran N, Murphy P, et al. Transitioning to HIV pre-exposure prophylaxis (PrEP) from non-occupational post-exposure prophylaxis

(nPEP) in a comprehensive HIV prevention clinic: a prospective cohort study. AIDS Patient Care STDS 2015;29(8):431–6.
39. CDC. Diagnoses of HIV infection among adults aged 50 Years and older in the United States and dependent areas, 2011–2016, vol. 23, 2018. Available at: http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html. Accessed October 5, 2018.
40. CDC. Estimated HIV incidence and prevalence in the United States, 2010–2015, vol. 23, 2018. Available at: http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html. Accessed October 5, 2018.
41. Public Health Agency of Canada. Summary: estimates of HIV incidence, prevalence and Canada's progress on Meeting the 90-90-90 HIV targets, 2016 2018. Available at: https://www.canada.ca/content/dam/phac-aspc/documents/services/publications/diseases-conditions/summary-estimates-hiv-incidence-prevalence-canadas-progress-90-90-90/pub-eng.pdf. Accessed October 5, 2018.
42. Joint United Nations Programme on HIV/AIDS. UNAIDS Data 2018. Geneva, Switzerland, 2018. Available at: https://www.unaids.org/sites/default/files/media_asset/unaids-data-2018_en.pdf. Accessed May 20, 2019.
43. Mbonu NC, van den Borne B, De Vries NK. Stigma of people with HIV/AIDS in Sub-Saharan Africa: a literature review. J Trop Med 2009;1–14. https://doi.org/10.1155/2009/145891.
44. HIV, TB and human rights in Southern and East Africa: report 2016. Available at: http://www.arasa.info/files/3314/8119/1044/ARASA_2016_Human_Rights_report.pdf. Accessed December 29, 2018.
45. Truvada for PrEP fact Sheet: ensuring safe and proper use. U.S. Food and Drug Administration. Available at: https://www.fda.gov/downloads/Drugs/DrugSafety/.../UCM312290.pdf. Accessed October 10, 2018.
46. New South Wales Ministry of Health. Pre-exposure prophylaxis of HIV with antiretroviral medications - NSW guideline summary. Sydney (Australia); 2016. Available at: https://www1.health.nsw.gov.au/pds/ActivePDSDocuments/GL2016_011.pdf. Accessed October 5, 2018.
47. NSW M of H. Pre-exposure prophylaxis of HIV with antiretroviral medications - NSW guideline summary. Sydney (Australia): NSW Government; 2016. Available at: https://www1.health.nsw.gov.au/pds/ActivePDSDocuments/GL2016_011.pdf. Accessed October 5, 2018.
48. CDC. Preexposure prophylaxis for the prevention of HIV infection in the United States—2017 update: a clinical practice guideline 2018. Available at: https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf. Accessed October 10, 2018.
49. Asboe D, Cambiano V, Clutterbuck D, et al. BHIVA/BASHH guidelines on the use of HIV pre-exposure prophylaxis (PrEP) 2018. London: BHIVA; 2018. Available at: http://www.bhiva.org/documents/Publications/PrEP_BHIVA_BASHH_Update-2-FINAL_19-Apr-16.pdf. Accessed October 10, 2018.
50. Grulich AE, Guy R, Amin J, et al. Population-level effectiveness of rapid, targeted, high-coverage roll-out of HIV pre-exposure prophylaxis in men who have sex with men: the EPIC-NSW prospective cohort study. Lancet HIV 2018;3018(18):30215–7.
51. Tsai C, Follis KE, Sabo A, et al. Prevention of SIV infection in macaques by (R)-9-(2-Phosphonylmethoxypropyl)adenine. Science 1995;270(5239):1197–9.
52. 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(27):2587–99.

53. Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African Women. N Engl J Med 2012;367(5):411–22.
54. Marrazzo JM, Ramjee G, Richardson BA, et al. Tenofovir-based preexposure prophylaxis for HIV Infection among African Women. N Engl J Med 2015;372(6):509–18.
55. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV-1 prevention among heterosexual men and women. N Engl J Med 2013;367(5):399–410.
56. Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. N Engl J Med 2012;367(5):423–34.
57. 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(10013):53–60.
58. 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(9883):2083–90.
59. 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(1):75–84.
60. Marcus JL, Hurley LB, Hare CB, et al. Preexposure prophylaxis for HIV prevention in a large integrated health care system : adherence , renal safety , and discontinuation. J Acquir Immune Defic Syndr 2016;73(5):540–6.
61. Rajchgot J, Siemieniuk RAC, Sivachandran N, et al. Feasibility of HIV preexposure prophylaxis as part of routine care in Toronto, Canada. J Acquir Immune Defic Syndr 2016;72(3):80–1.
62. 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(10):1601–3.
63. Schmidt HA, Mciver R, Houghton R, et al. Nurse-led pre-exposure prophylaxis : a non-traditional model to provide HIV prevention in a resource-constrained , pragmatic clinical trial. Sex Health 2018;15(6):595–7.
64. Wilton J, Noor SW, Schnubb A, et al. High HIV risk and syndemic burden regardless of referral source among MSM screening for a PrEP demonstration project in Toronto, Canada. BMC Public Health 2018;18(1):1–11.
65. Wilton J, Mishra S, Tan DHS. Considerations for using the HIRI-MSM screening tool to identify MSM who would benefit most from PrEP. J Acquir Immune Defic Syndr 2017;76(2):e58–61.
66. Charre C, Ramiere C, Roque-Afonso AM, et al. Hepatitis A outbreak in HIV-infected MSM and in PrEP-using MSM despite a high level of immunity, Lyon, France, January to June 2017. Euro Surveill 2017;22(48):1–4.
67. Ismail MF, Wong DK, Bogoch II. The role for hepatitis A vaccination in HIV preexposure prophylaxis. AIDS 2018;32(5):675–6.
68. Hare C, Coll J, Ruane P, et al. The phase 3 discover study: daily F/TAF or F/TDF For HIV preexposure prophylaxis, Abstract 104. In: Conference on Retroviruses and Opportunistic Infections. Seattle, WA; 2019. Available at: http://www.croiconference.org/sessions/phase-3-discover-study-daily-ftaf-or-ftdf-hiv-preexposure-prophylaxis. Accessed March 25, 2019.
69. Molina J-M, Capitant C, Spire B, et al. On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. N Engl J Med 2015;373(23):2237–46.

70. Tumarkin E, Heendeniya A, Murphy P, et al. HIV post-exposure prophylaxis-in-pocket ("PIP") for individuals with low frequency, high risk, HIV exposures. J Acquir Immune Defic Syndr 2018;1. https://doi.org/10.1097/QAI.0000000000001639.
71. Mugo NR, Hong T, Celum C, et al. Pregnancy incidence and outcomes among women receiving preexposure prophylaxis for HIV prevention a randomized clinical trial. J Am Med Assoc 2014;312(4):362–71.
72. Gibb DM, Kizito H, Russell EC, et al. Pregnancy and infant outcomes among HIV-infected women taking long-term ART with and without Tenofovir in the DART trial. PLoS Med 2012;9(5):1–16.
73. 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(2):246–54.
74. 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(4):374–80.
75. 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(4):572–80.
76. Weston E, T Wi JP. Surveillance for antimicrobial drug-resistant Neisseria gonorrhoeae through the enhanced gonococcal antimicrobial surveillance program. Emerg Infect Dis 2017;23:47–52.
77. Traeger MW, Schroeder SE, Wright EJ, et al. Effects of pre-exposure prophylaxis for the prevention of HIV infection on sexual risk behavior in men who have sex with men: a systematic review and meta-analysis. Clin Infect Dis 2018;67(5). https://doi.org/10.1093/cid/ciy182.
78. Knox DC, Anderson PL, Harrigan PR, et al. Multidrug-resistant HIV-1 infection despite preexposure prophylaxis. N Engl J Med 2017;376(5):501–2.
79. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med 2011;365(6):493–505.
80. Attia S, Egger M, Müller M, et al. Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. AIDS 2009. https://doi.org/10.1097/QAD.0b013e32832b7dca.
81. Donnell D, Baeten JM, Kiarie J, et al. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. Lancet 2010. https://doi.org/10.1016/S0140-6736(10)60705-2.
82. Fang C, Hsu H, Twu S-H, et al. JID - 2004 - HAART in HIV transmission. J Infect Dis 2004;190:879–85.
83. Lima VD, Lepik KJ, Zhang W, et al. Regional and temporal changes in HIV-related mortality in British Columbia, 1987-2006. Can J Public Health 2010;101(5):415–9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21214059.
84. Lawn SD, Kranzer K, Wood R. Antiretroviral therapy for control of the HIV-associated tuberculosis epidemic in resource-limited settings. Clin Chest Med 2009. https://doi.org/10.1016/j.ccm.2009.08.010.
85. Rodger AJ, Cambiano V, Bruun T, et al, Risk of HIV transmission through condomless sex in serodifferent gay couples with the HIV-positive partner taking suppressive antiretroviral therapy (PARTNER): final results of a multicentre, prospective, observational study. Lancet 2019. [Epub ahead of print].
86. The Lancet HIV. U=U taking off in 2017. Lancet 2017;4(11):e475.

87. UNAIDS. Undetectable = untransmittable: public health and HIV viral load suppression. Geneva (Switzerland): UNAIDS; 2018. Available at: http://www.unaids.org/sites/default/files/media_asset/undetectable-untransmittable_en.pdf. Accessed December 10, 2018.
88. Bavinton BR, Pinto AN, Phanuphak N, et al. Viral suppression and HIV transmission in serodiscordant male couples: an international, prospective, observational, cohort study. Lancet HIV 2018;5:e438–47.
89. Kojima N, Davey DJ, Jeffrey D. Pre-exposure prophylaxis for HIV infection and new sexually transmitted infections among men who have sex with men. AIDS 2016;30:2251–2.