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The Initiation, Discontinuation and Re-Starting of HIV Pre-exposure Prophylaxis (PrEP): An Ongoing Evolution of Implementation Strategies

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Summary

When used appropriately, PrEP dramatically reduces the risk of HIV acquisition. Early implementation outcomes often suggest poor PrEP adherence and "persistence"; however, PrEP is a time-limited intervention, the need for which fluctuates as risk behaviors change. In this Viewpoint article we examine the current guidelines and early programmatic outcomes around starting, stopping, and restarting PrEP, as well as review the implications of starting and stopping PrEP as it relates to HIV testing algorithms. Guidelines suggest discontinuation of PrEP when persons are no longer at risk for HIV, but effectively implementing this strategy requires decision support tools around stopping and restarting PrEP that capture the complex relationship between risk perceptions and risk behaviors. Safely discontinuing PrEP also requires greater understanding around the duration of daily dosing needed for protection after last HIV exposure, and clear strategies to re-engage persons as their HIV exposure risk changes overtime.

Introduction

When taken consistently, daily oral preexposure prophylaxis (PrEP) with tenofovir disoproxil fumarate (TDF) (or for men who have sex with men (MSM), tenofovir

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alafenamide (TAF) plus emtricitabine (FTC)[1]), alone[2] or in combination with FTC or lamivudine (3TC), significantly reduces risk of HIV acquisition for MSM,[3, 4] heterosexual men and women,[5] and people who inject drugs (PWID).[6] The enthusiasm for PrEP's anticipated HIV prevention potential is underscored by UNAIDS' ambitious target of having 3 million persons at high risk for HIV on PrEP by 2020.[7] PrEP is also a key component of the United States' (US) "Ending the HIV Epidemic" initiative[8]. Modeling exercises suggest that progress towards "the end of HIV" will require a strong commitment to PrEP,[9] including widespread uptake of PrEP for persons at risk of HIV and drug continuation while these persons remain at risk.

Early experience from PrEP implementation studies offer insight into the challenges with PrEP uptake and effectiveness.[10] Inadequate adherence[11, 12] and poor PrEP persistence[13–19] may help explain as-yet somewhat disappointing real-world HIV prevention effectiveness of PrEP. Alternatives to oral PrEP that may mitigate problems with adherence include long acting injectables[20] or implantable devices,[21] but deployment of these agents will have their own challenges. Accordingly, investigators are exploring innovative approaches to improve PrEP uptake and persistence – studying motivations, obstacles, preferences, perceptions, and patient, provider, and system-level interventions.[10] More attention is needed to examine the opportunities to support PrEP users and providers in making the decision to stop PrEP and strategies to re-engage persons when PrEP should be restarted.

In this article we examine example national and international guidelines regarding PrEP initiation, discontinuation, and re-initiation identifying critical knowledge gaps – specifically those from the WHO, Europe, South Africa, and the United States. We explore the complex relationship between risk perceptions, fluctuating risk behaviors, and PrEP persistence. We also review the implications of starting, stopping, and restarting PrEP in relation to HIV testing algorithms. Finally, we summarize the key literature surrounding the ability of patients or providers to accurately assess HIV risk so as to improve PrEP utilization during periods of elevated HIV risk.

Search strategy and selection criteria

This Viewpoint Article attempts to summarize the state of the literature regarding PrEP implementation using PubMed searches, cross-referencing, and review of representative society and international guidelines. English-language articles published through January 2020 were included. Given the paucity of data on some of the topics explored herein, we also include abstracts from recent peer-reviewed conference proceedings.

PrEP implementation: current recommendations on initiation and discontinuation

Major national and international PrEP guidelines largely agree on eligibility criteria for initiation of PrEP (Table 1). Common features for PrEP initiation criteria include persons at "substantial" risk of HIV acquisition, as assessed by estimated annual local incidence (World Health Organization (WHO) recommends prioritizing persons with ≥3% annual incidence), or behavioral risk factors (i.e., known HIV-infected partners not on treatment,

high numbers of sexual or injecting partners, recent STI, etc.). For the most part guidelines specify similar pre-start screening processes for initiating and re-initiating PrEP.

Guidelines to support patient and provider decision-making regarding appropriate PrEP discontinuation or suspension (i.e., intentional periods off PrEP but remaining engaged in care and potentially restarting PrEP) are critical. Some PrEP users may reach a stage in which risk behaviors no longer necessitate PrEP (e.g., a stable monogamous partner who is HIV-negative or HIV-positive but virally suppressed on ART, able to consistently use condoms, etc.), and further research is needed to help identify the patterns and frequency of fluctuating risk. Current guidelines offer risk-based factors for considerations on when to initiate and to discontinue PrEP (Table 1).

De facto, the indications under which the person was initially eligible for PrEP must no longer be present to support PrEP discontinuation. Accordingly, the 2016 WHO ART guidelines specify: “PrEP can be discontinued if a person taking PrEP is no longer at risk and when this situation is likely to be sustained”[22]. The WHO PrEP Implementation Tool Clinical module goes further to state: “Ways to lower risk include: adopting safer sexual practices, such as not having vaginal or anal intercourse, or using condoms for all vaginal and anal intercourse; changing circumstances such as leaving sex work or stopping injecting drug use; or, moving to a place that has a low prevalence of HIV infection. For people in a serodiscordant relationship, HIV transmission risk is very low when the HIV-positive partner is virally suppressed on ART.”[23]

The 2017 Centers for Disease Control and Prevention and US Public Health Service (CDC/USPHS) PrEP Guideline identifies multiple patient-driven reasons for potential discontinuation, including personal choice, life situation change with lower risk of acquisition, or provider-driven discontinuation based on toxicity or chronic nonadherence[24]. The CDC guidelines also suggest that the need to continue PrEP as part of HIV prevention should be evaluated at least every 12 months. The Australasian Society of HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) also suggests that PrEP duration should depend on persistence of HIV risk, though does not suggest a frequency for risk assessment[25]. The EACS (2018)[26] PrEP guidelines do not explicitly mention PrEP discontinuation.

How long should PrEP be continued once the decision has been made to stop? The WHO PrEP guidelines indicate: “As with PEP, PrEP may be discontinued 28 days after the last potential exposure to HIV-infected fluids if people do not have continuing substantial risk for acquiring HIV infection”. The rationale for the 28-day course is based on earlier WHO post-exposure prophylaxis (PEP) recommendations, which in turn reflect earlier studies with rhesus macaques.[27] MSM with episodic risk who are using WHO’s event-driven PrEP protocol are expected to take two pills before and two pills 24 hours apart after a potential HIV exposure[28]. The South African HIV Clinicians Society[29] and ASHM also recommend 28 days after last exposure for persons taking daily PrEP, but ASHM also specify that MSM with event-driven usage could stop taking PrEP after completing the post-coital two doses, 24-hours apart.

Given that early HIV replication is presumably blocked by PrEP, a shorter period after last potential exposure might be adequate[30, 31]. Contrasting the WHO 28-day period, the CDC, British HIV Association (BHIVA) [32], and IAS-USA (2018)[33] suggest that PrEP protection from HIV acquisition will wane over 7–10 days, and CDC specifically advises providers discuss the need for alternative risk reduction techniques after PrEP discontinuation.

Overall, premature PrEP discontinuation remains a major barrier to its effectiveness[30, 31]. Incident HIV infections after PrEP discontinuation [34, 35] confirm that PrEP is sometimes being stopped prematurely without using other effective prevention strategies, emphasizing not just the need for additional research regarding the appropriate "wash-out" period, but also highlighting the challenge in accurately recognizing potential HIV exposure events or risk[13, 36].

Patient-driven PrEP discontinuation and the role of perceived risk

PrEP discontinuation often occurs within months of starting (Table 2). With the exception of the rare provider-initiated discontinuation for non-adherence or adverse drug effects, the vast majority of PrEP discontinuations are patient-driven, often related to persons no longer perceiving themselves to be at risk of HIV acquisition[13, 37, 38] or losing one's ability to pay for PrEP[18], and generally executed without physician consultation[14].

MSM are currently half of the world's PrEP users, and US MSM account for the majority of data regarding real-world PrEP experience[39]. MSM in the US frequently discontinue PrEP; younger age, cannabis use, having sexually transmitted infections (STI), and having fewer partners are all associated with PrEP discontinuation[19, 40]. In San Francisco Primary Care Clinics, 16% of patients discontinued PrEP before 90 days, 46% discontinued after 90 days and only 38% were retained in care over ~12 months of follow-up[41]. More than 60% of young MSM in Georgia discontinued PrEP after a median of ~6 months[19]; most restarted but more than half discontinued a second time during study follow-up. Internet-based surveys of MSM in Washington state suggest much more conservative estimates – with only 20% discontinuing within 12 months – though this was likely an overestimation of PrEP persistence given self-report and cross-sectional study design[42].

Pharmacy refill data from a national survey of US PrEP prescription records suggest that only two of every five users persisted on PrEP over a two-year period[43]. Early drop out was common in Boston-[13] and New York City-based cohorts of MSM; in New York, only 35% of MSM were retained until their third follow-up visit (between ~5 and ~10 months), however, 38% of patients re-started PrEP within that same period[44]. Discontinuation was primarily driven by decreased HIV risk perception[45], and, less commonly, concern regarding long-term side effects of use[46].

Among adolescent girls and young women (AGYW) in sub-Saharan Africa (SSA), qualitative studies suggest PrEP discontinuation is frequently related to low perceived risk of HIV, stigma, age, drug costs, drug side effects, or pill burden[47, 48]. Implementation trials among AGYW in SSA indicate high rates of PrEP discontinuation – nearly 50% of AGYW discontinued PrEP within 6 months in the open-label POWER study (NCT03490058)[49].

Interestingly, nearly 20% of women subsequently restarted PrEP and research is ongoing to determine what motivated early stopping and who chooses to restart PrEP, and over what time interval. Preliminary data from the PrEP implementation for Young Women and Adolescents (PrIYA) project in Kenya, in which PrEP was offered during the antenatal and breastfeeding period, suggest even higher rates of PrEP discontinuation: at 1, 3, and 6 months, the percentage of women who had discontinued PrEP was 61%, 78%, and 88%, respectively. Low perceived risk of HIV (20.6%), side effects (25%), pill burden (17%), and known HIV-negative partner (18%) were reported by patients as reasons for discontinuation; in multi-variable analyses, having a partner living with HIV was the only predictor of PrEP continuation at one month.[48]

Forthcoming data on PrEP discontinuation patterns from POWER, as well as other implementation projects in the region (Community PrEP (NCT03977181), PlusPills (NCT03142256), EMPOWER (South African National Clinical Trials 4353), 3P (Partners, Perception, Pills) (NCT03142256), the Kingdom of Eswatini, and HPTN 082 (NCT02732730)) will provide additional insight into PrEP utilization behaviors. In the studies of PrEP use among AGYW in East and southern Africa, community knowledge and understanding about PrEP was and remains low. This contrasts with knowledge about and interest in PrEP among MSM in high income countries. This may help account for the current lower continuation on PrEP among AGYW in SSA. Although more data is emerging from implementation and demonstration projects worldwide through Global PrEPWatch, publicly available data does not currently include PrEP persistence outcomes, and is limited to the number of persons who have taken PrEP [39]. Even less is known regarding PrEP discontinuation in certain high-risk sub populations such as transgender women (TGW) and sex workers.

There is no doubt that among other barriers to PrEP persistence, perceived limited or reduced HIV risk contributes to the decision to discontinue PrEP altogether[38]. In SSA, the majority of the published PrEP data comes from randomized controlled trials, where both poor adherence and early discontinuation compromised PrEP outcomes in some studies[11, 12]. Inadequate risk insight among participants in VOICE and Fem-PrEP likely contributed to poor adherence; women reported low perceived risk for HIV despite high STI incidence[12] and 52% of women who seroconverted said they had “no chance of acquiring HIV”[37].

Preliminary results from the PrEP evaluation study HPTN 082 suggests that nearly half (47%) of enrollees reported “no risk at all” of getting HIV in the next year while another 31% reported perceiving themselves at a “small chance” of getting HIV in the next year. These perceptions fall in stark contrast to the >30% STI incidence rate in this cohort [50]. Early data out of the Kingdom of Eswatini also suggests frequent deferral of PrEP based on low perceived risk of infection, despite objective markers of the AGYW being at substantial risk of HIV infection[51]. Other studies suggest reported HIV-risk perceptions do not align with actual risk among young South African women with identical HIV-incidence rates regardless of self-reported risk categories[52]. Perceived risk as endorsed by study participants may be under-reported; women may not accurately disclose perceived risk due to social norms, stigma, or discrepancies between intended and interpreted survey questions[53].

Nonetheless, the disconnect between perceived risk and true risk remains an important target and better aligning the two may improve PrEP persistence, and ultimately support providers and patients in making informed decisions about PrEP.

Suspending or Stopping PrEP: aligning risk with PrEP use

Appropriate education and messaging about the time-limited nature of PrEP might improve PrEP uptake and persistence. Conceptualizing PrEP as an intervention that can be paused and later restarted as needed based on HIV risk may help ease the emotional burden many African AGYW associate with PrEP, help to tangibly distinguish PrEP from ART, and, if incorporated into PrEP counseling, may increase PrEP adherence and persistence during higher risk periods.

The dynamic nature of HIV-acquisition risk behaviors is reflected in more flexible PrEP utilization in the "prevention-effective adherence" strategy[54]. Among sero-discordant couples in the Partners Demonstration Project in Kenya and Uganda, HIV-negative partners adjusted PrEP use based on risk, with increased PrEP utilization temporally related to sexual encounters with their HIV-infected partners [55]. This approach has not yet been validated in the general population. When questioned regarding hypothetical PrEP utilization over the prior 6 months, half of the Kenyan and South African women interviewed indicated that they would have suspended PrEP use[38]. Reasons for PrEP interruption were related to perceived low risk in a stable partnership or other life events (holidays or travel), highlighting the relevance of so-called *seasons of risk*[56] with true or perceived risk variation influencing PrEP utilization.

Another example of aligning HIV risk and PrEP use is the "event-driven" (ED)-PrEP (also called "2–1-1" regimen), which offers flexibility for oral PrEP utilization for MSM. Initially there was concern that the efficacy in the event-driven strategy of the landmark IPERGAY study was only generalizable to MSM with very frequent high risk behaviors, in whom "event-driven" closely approximated daily PrEP dosing [4]. Encouragingly, subsequent sub-group follow-up suggests HIV protection even among men reporting less frequent sex[57]. More recent findings from the European open-label extension of on-demand dosing suggests a 97% reduction in HIV incidence, compared to placebo group from the randomized phase of investigation[58]. Although not included in the 2017 CDC recommendations, based on data from randomized controlled trials, open-label studies, and implementation evaluations, ED-PrEP as an alternative to daily PrEP has been endorsed by some national and international guidelines for MSM (Table 1).

ED-PrEP is not appropriate or desired by all MSM as its effectiveness relies on the user appropriately recognizing potential risky encounters and taking PrEP immediately before and after exposure. In the ADAPT (HPTN 067) feasibility study, MSM and transgender women (TGW) in Harlem (US) achieved significantly higher protective drug concentrations with daily PrEP compared to time- (twice weekly plus post-coital), or event-driven (1 tablet pre- and post-coital) dosing, whereas MSM and TGW in Bangkok achieved similar coverage of sex events comparing daily and time-driven dosing strategies, with a trend towards less coverage in the event-driven arm[59].

In one of the few studies investigating feasibility of ED-PrEP for women, heterosexual cisgender South African women in the ADAPT study were more likely to have sex events covered by PrEP if assigned to daily dosing compared to time- or event-driven dosing[60]. Daily PrEP remains the recommendation for heterosexual women and men, transgender populations, and PWID.

Risk assessments and PrEP persistence

Risk assessments are key for both patients and providers to more consistently evaluate risk for HIV acquisition and thus weigh the merits of starting, stopping, or restarting PrEP. Some programs are using risk scores to help identify appropriate candidates for PrEP with the goal of improving uptake amongst the highest HIV-risk sub-populations. However, it is unclear how or if providers incorporate risk assessments into their PrEP counseling for established users to determine future intention to need or discontinue PrEP. Furthermore, while risk tools have been developed for a number of populations (i.e., pregnant women, serodiscordant heterosexual couples, MSM)[61–63] these tools may not be appropriate or validated for all PrEP users[64]; WHO cautions the reliance on risk scores if they have not been validated in the intended population or if using them to exclude people from being able to access PrEP, as this may discourage people who do not want to reveal or discuss certain risks.

In 2012, the CDC published the HIV Incidence Risk Index for MSM (HIRI-MSM) risk screening tool, which includes age, self-reported number of partners in the last 6 months, number of encounters with insertive or receptive anal intercourse, HIV-status of partners, and use of drugs with sex[65]. In addition to helping to identify persons at greatest risk of HIV, these tools again expose the disconnect between perceived and actual risk even among some of the riskiest sub-populations: nearly 70% of Canadian MSM visiting a sexual health clinic who scored in the top quartile of HIRI-MSM (≥26), did not consider themselves to be at moderate or high risk of HIV[66].

The VOICE risk score may help identify AGYW at risk of infection who meet WHO PrEP eligibility (≥3% annual risk of HIV acquisition)[67], consolidating easily-attainable clinical and behavioral factors. Although developed and validated in SSA to facilitate PrEP initiation, recent data suggests poor performance of the VOICE risk score among HIV-negative AGYW in South Africa, failing to predict HIV incidence after one year of follow-up among a cohort of more than 2100 young women[64]. Even for AGYW for whom risk is accurately captured with a risk score, many currently refuse PrEP[51]

To-date, risk scores have been used to identify persons who are at “substantial risk” for HIV infection for the purposes of PrEP initiation, not as a tool to gauge risk-based necessity of continuing PrEP, nor evaluated in the context of restarting PrEP as prior PrEP use may be relevant to the user risk profile/risk assessment. Incorporating self-reported and objective clinical markers (i.e., pregnancy or incident STI) to develop risk profiles that are then relayed to patients during PrEP follow-up visits may help align predicted and perceived risk and improve PrEP persistence. Modifications to existing risk scores could provide an evidence-based platform to inform patient and provider decisions regarding discontinuation

of PrEP when HIV acquisition risk is no longer elevated, or inform how or if risk assessment should differ for someone restarting PrEP.

Interpreting incident STIs for PrEP initiation and continuation

Detection of one or more STIs is an indication to consider initiation of PrEP (Table 1), and for most PrEP users, an incident STI diagnosis is a good indication that PrEP use should continue. For example, detection of syphilis among MSM in New York City suggested 5% risk of HIV acquisition in the next 12 months.[68] High rates of curable, often asymptomatic STIs are detected in African AGYW in PrEP studies [69].

However, STIs do not automatically infer HIV risk. STIs can be detected at high levels in communities with low prevalence of incident HIV[70]. STIs transmitted within an HIV sero - different couple in whom the HIV infected person is virally suppressed will not lead to HIV transmission.

PrEP use may have an important effect on the risk of STI acquisition. STI incidence rates may be increasing among PrEP users[10, 69–73], though not all studies support this trajectory[74]. Increased sexual activity and/or reduced condom usage observed in some studies of PrEP user suggests “risk compensation” as a possible explanation for increased STIs, while other studies suggest the trend can be explained by increased frequency of STI testing. In a recent Australian study of MSM, where 48% of all participants had an incident STI and 76% of the nearly 3000 incident STIs were diagnosed among only 25% of participants. In this cohort, increasing STI incidence after PrEP was initiated was not entirely explained by more frequent testing.[72] Importantly, the inflammation associated with STIs does not appear to overwhelm the preventive benefits of PrEP with TDF-FTC.[70, 72]

Special HIV testing considerations in PrEP and PrEP-eligible patients

All guidelines require that potential PrEP users have a documented negative HIV antibody test result prior to initiating or reinitiating PrEP, and then every 3 months while PrEP is being used. HIV testing algorithms are the same for persons just starting PrEP, persons restarting PrEP, and persons retained on PrEP and attending quarterly PrEP visits. These recommendations are critical to avoid inadvertently starting inadequate antiretroviral therapy, which might promote HIV resistance and compromise future treatment options[12, 75, 76]. PrEP -eligible patients with a new STI may be at increased risk of acute HIV infection[77].

A more nuanced appreciation for how intermittent PrEP use may influence HIV testing results is critical to maximize PrEP implementation outcomes. Most guidelines specify that the preferred test is the combined antigen/antibody test and advocates that clinicians inquire regarding signs or symptoms of acute retroviral syndrome for persons with a known recent exposure. When acute HIV is suspected a test for HIV RNA can be used. If there is concern for acute HIV infection, PrEP provision can be deferred for one month with repeat testing, or the provider could offer triple-drug PEP if high risk exposure was in the preceding 72 hours delaying standard PrEP until HIV status is confirmed[24, 33]. EACS also advocates for antigen/antibody testing, but does not mention acute infection in the pre-PrEP evaluation[26].

The WHO testing algorithms include serial testing prior to PrEP initiation, but in most settings available assays are limited to HIV antibody tests. WHO PrEP implementation guidelines specify that PrEP can be initiated with a negative serology test and in the absence of clinical concern for acute infection, otherwise the recommendation is to delay PrEP and repeat testing or offer PEP with plans to transition to PrEP after repeat testing ("PEP-to-PrEP")[78].

Currently available HIV tests may perform less well in persons on PrEP who have acquired HIV infection during lapses in protective drug levels compared to persons who acquire HIV infection without any PrEP use, resulting in false negative antibody or antigen tests[79]. PrEP use after infection may delay or reduce antibody response resulting in atypical HIV-antibody test results [80, 81] and delayed time to seroconversion[82]. PrEP use during (unrecognized) acute HIV infection also suppresses viral replication, affecting antigen detection. The suppressed viral replication was demonstrated with the atypical progression and diagnosis for new infections identified among participants in the ADAPT (HPTN 067) trial[83]. Among the 12 persons who seroconverted while taking PrEP (out of 622 participants), antibody point-of-care tests expectedly missed all eight of the persons with acute infection, but more surprising were the five cases with a negative antigen/antibody test and four with viral loads ≤400 copies/mL found to be positive on sensitive HIV RNA assays. In Partners PrEP, 11% of persons who seroconverted on PrEP had undetectable HIV RNA versus only three percent of persons in the placebo (non-PrEP) arm[82], emphasizing the complexity of diagnosis and monitoring HIV status even when RNA testing is available or indicated. The potential impact of false negative HIV testing in the context of PrEP fundamentally depends on PrEP adherence as it is in the setting of inadequate drug levels that most HIV infections occur. Nonetheless, testing strategies may need to account for the viral suppressive effects of PrEP if infection has occurred during gaps in PrEP use, including possibly measuring viral load or antigen to avoid inadvertently undertreating persons with HIV infection

Next steps: support PrEP persistence and appropriate discontinuation

An enormous effort went into development of TDF-FTC and TAF FTC as PrEP and "next generation PrEP" development continues. Promising signals of population-wide effects have been seen in Australia[84], the UK[85], and the US[86]. Guidelines largely agree on PrEP indications and monitoring; however, gaps in knowledge regarding strategies for stopping and restarting PrEP compromise maximal benefit of this intervention. Although it should not come at the price of a patient's autonomy in making decisions regarding their risk and need for PrEP, provider-driven strategies to identify barriers to PrEP utilization, target retention resources to persons at greatest risk of early PrEP discontinuation despite ongoing risk, and to re-engage persons entering periods of elevated risk are need to maximize the benefits of PrEP.

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Table 1:

PrEP Initiation, monitoring, and discontinuation according to guidelines

Society/ organization	Eligibility criteria	Preferred regimen	Event-driven[1] option?	Monitoring recommendations	Discontinuation
WHO[22, 28]	All HIV-negative persons at substantial risk of HIV acquisition, prioritizing sub-populations or persons with ≥3% annual HIV incidence in the absence of PrEP	Oral, containing TDF	Yes, for MSM	- Renal function testing every 3 months for first 12 months, then annually - HBV surface antigen - HIV testing every 3 months	-If person is no longer at risk and when this is likely to be sustained -28 days after last potential exposure to HIV-infected fluids if no continuing substantial infection acquisition risk
CDC/ USPHS[24]	Adult (≥18) MSM, heterosexually active men and women, or PWID at substantial risk defined as: MSM/heterosexual: HIV+ partner Recent STI High number of partners Inconsistent/no condoms Commercial sex work PWID: HIV+ injecting partner Sharing injection equipment	Daily oral fixed-dose combination TDF/FTC (300/200)	No	-HIV testing every 3 months -Renal function every 6 months -Adherence counseling -Behavioral risk reduction -STI testing (every 3–6 months)	-Discuss alternative risk reduction strategies -Document HIV status, reason for discontinuation, and recent medication adherence/sexual risks - Continue medication for 7–10 days after last exposure
IAS-USA[33]	All populations with annual HIV incidence at least ≥2%	Oral fixed-dose combination TDF/FTC (300/200)	Yes for MSM with infrequent sexual exposures, without HBV	-HIV and STI testing every 3 months -Renal function testing every 6 months	-Continue medication for 1 week after last sexual exposure
EACS[26]	Adults at high-risk of acquiring HIV infection, specifically: Recommended for HIV-negative MSM/ transgender: Condoms not used consistently with casual partners HIV+ partners not on treatment Recent STI, use of PEP, or chemsex may mark increased risk Considered for HIV-negative heterosexual men/women: With inconsistent condom use and multiple partners where some are likely to be HIV+ and not on treatment	Oral fixed-dose combination TDF/FTC (300/200)	Yes for MSM	-HIV testing every 3 months -HBV surface antigen -STI screen at start and “regularly” -Renal function and bone mineral density according to TDF guidelines	No mention
BHIVA[32]	MSM and trans women at elevated risk of HIV w condomless anal sex; Heterosexual men and women with	Oral fixed-dose combination TDF/FTC (300/200) TDF alone can be	Yes for MSM	- HIV and STI testing every 3 months - HCV screening in MSM, trans women and others at risk of HCV every 3 months	-Continue 48 hours after last sexual risk if HIV risk is through anal sex -Continue for 7 days after last sexual risk if HIV risk is through vaginal sex

Society/ organization	Eligibility criteria	Preferred regimen	Event-driven[1] option?	Monitoring recommendations	Discontinuation
	condomless sex with known HIV-positive partners (not virally suppressed)	offered to heterosexual men/women with FTC contraindication		- Renal function and bone mineral density according to TDF guidelines	
ASHM[25]	All people at risk for HIV infection	Oral fixed-dose combination TDF/FTC (300/200)	Yes for MSM	- HIV and STI testing every 3 months - Renal function and bone mineral density according to TDF guidelines	-Duration to depend on persistence of HIV risk -on-demand PrEP stopped with single tablet for 2 days after last exposure -daily PrEP should be continued for 28 days after last exposure
SAHCS[29]	Any sexually active MSM or transgender person Heterosexual men and women targeting: HIV-positive partners not confirmed virologically suppressed, or partner(s) status unknown Recent STI Multiple sexual partners Commercial sex work History of inconsistent or no condom use	Oral fixed-dose combination TDF/FTC (300/200)		- HIV testing every 3 months - renal function testing (month 1, month 4, then every 12 months) - STI screen (syndromic or testing, depending on resources) every 6 months	-28 days after last potential exposure to HIV-infected fluids if no continuing substantial infection acquisition risk

ASHM – Australasian Society of HIV, Viral Hepatitis and Sexual Health Medicine; BHIVA – British HIV Association; CDC – Centers for Disease Control and Prevention; FTC – emtricitabine; HBV – hepatitis B virus; MSM – men who have sex with men; PrEP – pre-exposure prophylaxis; PWID – persons who inject drugs; SAHCS – South African HIV Clinicians Society; TDF – tenofovir disoproxil fumarate;

[1] also termed “2-1-1” by IAS USA

Table 2:

PrEP discontinuation in implementation and observational studies

Authors (year)	Study design (study period)	Population	Location(s)	N	Follow-up	PrEP discontinuation rates	PrEP discontinuation associations & HIV seroconversions[1]
Chan et al (2016)[15]	Retrospective chart review (2014)	Predominantly MSM	Rhode Island, Mississippi, Missouri, U.S.	267	6-months	-81% filled prescriptions -Among 171 with PrEP in last 6 months, 28% discontinued by 3 months and 43% discontinued by 6 months	-3 HIV seroconversions in 6 months following PrEP prescriptions
Costagliola et al (2019)[87]	Prospective cohort (2017–2019)	Predominantly MSM	Paris, France	2699	1–2 years	-16% at 12 months - 32% at 30 months	-younger age associated with increased likelihood of stopping
Coy at al (2019)[43]	Pharmacy fill records (2015)	All comers (97% male)	U.S.	7148	24 months	-44% discontinued in year 1 -63% discontinued in year 2 -59% discontinued between 0–2 years	-Younger age, female sex, non-commercial insurance all associated with worse PrEP persistence
Hevey et al (2018)[88]	Retrospective chart review (2010–2016)	Predominantly MSM	Milwaukee, Wisconsin, U.S.	116	0–6 years	-19% discontinued (average time on PrEP for persons who had not discontinued 11 months) -6% temporarily stopped PrEP	-6% moved out of study city, 14% reported monogamous relationship, 14% drug-related side effects.
Hojilla et al (2018)[16]	Retrospective chart review (2014–2015)	MSM	San Francisco, California, U.S.	344	13 months	-78% started PrEP -21% discontinued by 7 months -38% discontinued by 13 months	-Persons with STI at initiation 44% less likely to be retained on PrEP
Kinuthia et al., (2019)[48]	Prospective cohort	AGYW	Kisumu, Kenya	2030	6 months	-61% discontinued by 1 month -78% discontinued by 3 months -88% discontinued by 6 months	- Having an HIV+ partners was associated with continuation at 1 month -Reasons for discontinuation include low perceived risk (21%), side effects (25%), pill burden (17%) and partner known to be HIV negative (18%)
Krakower et al (2019)[13]	Retrospective chart review (2011–2015)	Predominantly MSM	Community health centers Boston, Massachusetts, U.S.	663	1–4 years	- 36% 1 or more discontinuation (defined as PrEP interruption >7 days) - Time to discontinuation: median 4.1 months (IQR 2.0, 8.5)	-7 HIV seroconversions, 4 after discontinuation -Factors associated with discontinuation: age<30, transgender women, mental health disorder
Liu et al (2016)[71]	Cohort study (2012–2015)	MSM, TGW	San Francisco, California, Miami, Florida, Washington D.C., U.S.	557	48 weeks	-21.5% discontinued by 48 weeks	-2 HIV seroconversions -African American less likely to have protected drug levels Stable housing and at least 2 condomless anal sex partners in last 3 months were more likely to have protective drug levels.
Marcus et al (2016)[18]	Cohort study (2012–2015)	Predominantly male	Members of Kaiser Permanente North California, U.S.	972	ongoing	-22.5% discontinued PrEP	-No HIV seroconversions in 850 person-years of follow-up on PrEP - 2 HIV seroconversions after discontinuation -Female sex, drug/alcohol abuse associated with discontinuation

Authors (year)	Study design (study period)	Population	Location(s)	N	Follow-up	PrEP discontinuation rates	PrEP discontinuation associations & HIV seroconversions[1]
							- 17.4% (38/219) restarted PrEP after discontinuing
Morgan et al (2018)[14]	Cohort study (2015–2017)	MSM	Chicago, Illinois, U.S.	197	ongoing	- 33% discontinued at time of interview	-Reasons for discontinuation: difficulty getting to appointment (21.5%), insurance (20%). -21% of persons who discontinued discussed with PrEP provider first
Ornelas Pereira et al (2019)[89]	Retrospective chart review (2018)	All comers	Brazil	8097	One year	-10% did not attend first follow-up visit	-younger age and sex workers more likely to discontinue -cis and transwomen more likely to discontinue compared to MSM
Rao et al (2019)[42]	Online survey (2017)	MSM	Washington State, U.S.	1080	n/a	-19% surveyed reported current PrEP use - 20% of PrEP users discontinued within 12 months	-Lower educational attainment more likely to discontinue PrEP
Ryan et al., (2019)[90]	Prospective Cohort (PrEPX) (2016–2018)	All persons at high risk of HIV acquisition	Victoria, Australia	2541	n/a	-21% discontinued within 12-months	-age <30, PrEP naivete, consistent condom use with casual partners all associated with study (PrEP) discontinuation. -25% (130/515) accessed post-study testing, 3.3% (4/130) HIV-seroconverted
Scott et al (2019)[40]	Prospective cohort (2012–2017)	Mixed (66% MSM, 13% TGWSM, 16% sero-discordant relationship, 4.9% heterosexual)	San Francisco, California, U.S.	348	18 months	- 24% with PrEP use gap (defined as documentation by provider or PrEP prescription gap >90 days) - Time to discontinuation: median 8.3 months	-Factors associated with gap in PrEP use included black (vs white) race and younger age
Serota et al (2019)[19]	Prospective cohort (2015–2017)	MSM	Atlanta, Georgia, U.S.	298	24 months	-69% with at least one PrEP discontinuation - Time to first discontinuation: median 159 days (IQR 97, 237) -64% restarted PrEP at least once	-Reasons for discontinuation: 34% low perceived risk, 13% difficulty making appointment, 10% side effects -Younger age, cannabis use, STI diagnosis, and fewer sex partners associated with earlier PrEP discontinuation -23 incident HIV infections (5.23/100 person years); 3.15/100 person-years among persons started on PrEP
Shover et al (2019) [35]	Retrospective chart review (2014–2017)	Federally funded Lesbian Gay Bisexual Transgender Health Center	Los Angeles, California, U.S.	3121	1–4 years	-46% had one or more gaps (>20 days) between PrEP prescriptions -Average time to first PrEP discontinuation 6 months	-Younger age, private (or no) insurance, homelessness or unstable housing were all associated with increased rates of PrEP discontinuation -13 incident HIV infections. HIV incidence 2.1/100 person-years (discontinued) vs 0.1/100 person years (active PrEP use)
van Epps et al (2018)[17]	Retrospective chart review (2012–2016)	Veterans Health Administration clinics	U.S.	1086	One year	-44% discontinued within 12 months (defined as PrEP medication possession gap >120 days)	-PrEP adherence associated with older age, white (vs black) race, and male sex

Authors (year)	Study design (study period)	Population	Location(s)	N	Follow-up	PrEP discontinuation rates	PrEP discontinuation associations & HIV seroconversions[1]
Zucker et al (2019)[44]	Retrospective chart review (2015–2017)	All comers (93% male)	New York City, New York, U.S.	696	3+ years	-32% discontinued by first follow-up visit (1 month) -52% discontinued by second follow-up visit (4 months) -65% discontinued by third follow-up visit (7 months)	-Younger age, PrEP same-day start, and PrEP start in sexual health clinic associated with decreased retention at third follow-up visit

[1] HIV seroconversions presented, if reported

AGYW – adolescent girls and young women; MSM – men who have sex with men; PrEP – pre-exposure prophylaxis; STI – sexually transmitted infection; TGW – transgender women; TGWSM – transgender women who sex men; U.S. – United States;