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Antiretrovirals for Primary HIV Prevention: the Current Status of Pre- and Post-exposure Prophylaxis

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Abstract In light of the 2 million HIV infections that occur globally each year, there is a need to optimize strategies that integrate biomedical and behavioral approaches to HIV prevention. Post-exposure prophylaxis (PEP) immediately after acute high-risk exposures and pre-exposure prophylaxis (PrEP) for those who engage in recurrent high-risk behaviors are promising bio-behavioral approaches to decreasing HIV transmission. Guidelines have recommended PEP for occupational and non-occupational exposures for over 15 years, but uptake of PEP has been limited, partly as a result of insufficient awareness of this intervention among persons at highest risk for acquiring HIV. However, since the publication of large randomized clinical trials demonstrating the efficacy of PrEP, and the dissemination of guidelines endorsing its use, there is a renewed focus on bio-behavioral prevention. Numerous studies have recently assessed the acceptability of bio-behavioral prevention programs among diverse populations or described experiences implementing these programs in "real-world" settings. As research and clinical data informing optimal utilization of PEP and PrEP are rapidly accumulating, this review provides a timely summary of recent progress in bio-behavioral prevention. By contextualizing the most noteworthy recent findings regarding PEP and PrEP, this review seeks to inform the successful implementation of these promising prevention approaches.

Keywords HIV · Bio-behavioral · Prevention · Post-exposure prophylaxis · Pre-exposure prophylaxis

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Introduction

Despite major advances in antiretroviral treatment and chemoprophylaxis, 50,000 infections occur in the USA [1] and 2 million new HIV infections occur globally each year [2]. The suboptimal control of the epidemic is partially a result of the insufficient use of post-exposure prophylaxis (PEP) and pre-exposure prophylaxis (PrEP) for primary HIV prevention when indicated, even though the US Centers for Disease Control and Prevention (CDC) have issued guidelines for the use of PEP for more than 15 years [3, 4] and for the use of PrEP for nearly 4 years [5–7]. This is partially because awareness of PEP and PrEP has generally been low among men who have sex with men (MSM) [8–11], who represent the majority of prevalent and new infections in the USA [1] and because of limited implementation by medical providers [12•, 13].

PEP uptake may also be low because of the lack of certainty about efficacy. The clinical use of PEP is based on a case-control study that demonstrated an 81 % reduction of HIV transmission among health care workers that were given prophylactic zidovudine [14], as well as multiple animal model studies, which used zidovudine and tenofovir [15–18].

Randomized, controlled clinical trials of PEP regimens have not been feasible because of ethical and logistical constraints, including the relative inefficiency of HIV transmission after a single exposure, which would necessitate inordinately large studies. However, animal model and observational human studies have established the biological plausibility of preventing HIV acquisition by prior use of nucleotide and nucleoside reverse transcriptase inhibitors [14–17, 19], as well as protease inhibitors [18] and integrase strand transfer inhibitors [20•]. Occupational guidelines were updated by the US Public Health Service (USPHS) in 2013 [21], and newer drugs enable providers to prescribe better tolerated regimens. However, cases of possible PEP failures have been reported, pointing to the need to carefully review regimens, timing of medication initiation, duration of treatment, and PEP behavioral counseling [22–25].

In contrast to PEP, for which there are limited efficacy data in humans, several large prospective studies have established the efficacy of PrEP in preventing HIV acquisition in diverse at-risk populations [26–29]. However, experience with PrEP in care settings is more limited than for PEP, as the first study to demonstrate the efficacy of PrEP was completed in 2010 [28], and the uptake of PrEP has been gradual [11, 30]. For both PEP and PrEP, important considerations for successful implementation include identifying those persons who are most likely to benefit from these interventions, selecting medication regimens that are optimally safe and well tolerated, and assessing and supporting adherence. For PrEP, new data are also rapidly accumulating on innovative approaches to delivering chemoprophylaxis, such as episodic dosing of oral PrEP [31, 32], long-acting injectable formulations [33••], topical gels [34], and drug-eluting intravaginal rings [35]. These new approaches to delivering chemoprophylaxis could enhance the attractiveness of PrEP to individuals with diverse product preferences. Given the evolving science regarding optimal approaches to implementing PEP and PrEP, this review is designed to summarize and contextualize the latest clinical trends and research findings for these promising biobehavioral strategies.

Post-exposure Prophylaxis

When to Utilize PEP

Historically, normative guidelines for PEP separated risks that occurred in the context of occupational [21] and non-occupational [4] exposures. However, most recently, the WHO consolidated its guidance [21], arguing that the same principles apply to PEP, whether the exposure was occupational or not. The USPHS defines an occupational exposure of healthcare personnel that would require PEP as a percutaneous injury from a needlestick, or a cut with a sharp object from an HIV-infected or high-risk source, or contact of potentially infectious body fluids (i.e., blood, anogenital secretions) with mucous membranes or non-intact skin [21]. The CDC also recommends non-occupational PEP (NPEP) for HIV-uninfected patients after having possible exposures to HIV-infected blood, genital secretions, and rectal secretions [4]. Such exposures in adults typically occur in the setting of condomless sex, protected sex with condom failure, or shared paraphernalia when intravenous drugs are used, and in children and older populations may occur in the context of sexual assault. The exposures associated with the highest per-act risk of HIV transmission include needle sharing when injecting drugs and condomless receptive anal intercourse, so PEP is clearly indicated after these types of exposures. Insertive anal intercourse and penile-vaginal intercourse pose lesser risks, but would still warrant PEP in the appropriate clinical setting. Insertive or receptive oral sex and human bites pose minimal risk of HIV transmission, though PEP may be considered in special circumstances [4, 21, 36•].

Since exposures can occur at any time of day, and immediate treatment is necessary for PEP to be optimally effective, providers should be prepared to promptly administer PEP in diverse clinical settings, including emergency rooms and primary care practices. Once a decision has been made that PEP is warranted, PEP is most effective when started as soon as possible after high-risk exposures, ideally within 72 h per 2005 CDC NPEP guidelines [4] and 2013 USPHS occupational PEP guidelines [21]. This recommendation is based upon studies with macaques demonstrating that the prevention of viral acquisition was greater when (R)-9-(2-phosphonylmethoxypropyl)adenine (PMPA), a derivative of tenofovir, was administered sooner and given for 28 days after subcutaneous injection with simian immunodeficiency virus (SIV), as compared to later initiation and shorter treatment courses [15]. Similar results were demonstrated in macaques after intravaginal exposure to SIV, which showed a greater benefit of PMPA administration within 36 h as compared to 72 h post-exposure [17]. Thus, PEP should be initiated within 72 h but ideally as soon as possible after the exposure.

HIV Testing of Source and Exposed Patients When PEP Is Used

One of the most important principles of PEP provision is for providers to make every effort to determine the source patient's HIV status either by testing the source and/or obtaining medical record information. Unfortunately, the HIV status of the source is often unknown in the setting of NPEP when partners are anonymous, or if the source partner is unwilling to undergo HIV testing. Providers should consider HIV RNA testing only if acute antiretroviral syndrome is suspected in either the source or exposed patient, particularly if fourth generation HIV antigen-antibody assays are not readily available.

Since PEP is more likely to be effective when given sooner rather than later, PEP should be initiated while awaiting test results. Exposures from HIV-infected source patients with undetectable HIV RNA on antiretroviral therapy may be deemed lower risk based on the results of studies with HIV serodiscordant couples [37], but this assessment should be based on having access to the source's recent laboratory results, as opposed to relying on source self-report. PEP is warranted if the adherence patterns of an HIV-infected source are unknown. If the HIV status unknown source of the exposure that warranted PEP subsequently tests negative for HIV, PEP can be discontinued.

Follow-up HIV testing for the exposed person should occur at 4–6 weeks, 3 months, and 6 months after the exposure, if HIV rapid tests or other third generation antibody tests are used [21]. If a fourth generation HIV antigen-antibody assay is used and the result is negative, then no further testing is required after 4 months post-exposure per the 2013 USPHS guidelines [21] or after 3 months per the 2013 New York State AIDS Institute guidelines [38].

Selecting a PEP Regimen

The CDC's 2005 guidelines recommended several two-drug or three-drug NPEP regimens based on information regarding the HIV treatment history of a known HIV-infected source and the exposed person's experience with prior NPEP, for those not presenting for the first time. If the source is HIV-infected, documentation of prior resistance mutations and treatment history may guide PEP regimen choice when available. Many of the antiretroviral combinations in the CDC's 2005 NPEP guidelines are no longer as widely used for HIV treatment, particularly those that are zidovudine based and/or those that use some of the older protease inhibitors, and hence are not preferred for NPEP. The USPHS and the New York State AIDS Institute issued new occupational PEP guidelines in 2013 that advocate for using a three-drug regimen for 28 days regardless of the severity of exposure [21, 38], preferring tenofovir-emtricitabine with raltegravir based on improved tolerability of these newer antiretrovirals [39••, 40]. When raltegravir cannot be used, the USPHS recommends darunavir, atazanavir, or fosamprenavir boosted with ritonavir as "preferred alternative" occupational PEP agents.

On December 1, 2014, the World Health Organization released its revised PEP guidelines which recommended similar protocols whether exposures were occupational or non-occupational. They recommended that a three-drug low pill burden regimen was preferable, favoring tenofovir-emtricitabine plus raltegravir or ritonavir-boosted darunavir, or where these newer agents may not be available, ritonavir-boosted lopinavir or atazanavir [41••]. The guidelines also recommended that patients should receive the full 28-day regimen at the initial visit in order to optimize regimen completion [41••].

For pregnant patients, data are limited. Normative bodies allow for use of raltegravir for PEP in pregnancy, and there is longstanding experience with the use of lopinavir for HIV treatment in pregnancy. A recent review provides more detailed discussion of NPEP trial data and management, and suggests that several newer agents, such as the integrase strand inhibitors elvitegravir and dolutegravir, may be useful agents for PEP when combined with tenofovir and emtricitabine but require further study [42].

Adherence Challenges with PEP

While excellent, well-tolerated treatment regimens are available, adherence to PEP medications and attendance at clinical visits may be suboptimal in certain groups of individuals. With respect to MSM, low rates of PEP follow-up have been observed in some studies. In a large (N=1864) Australian cohort of mainly MSM, only 34 % had follow-up testing at 12 weeks after the initiation of PEP [43]. An analysis of 53 MSM in Los Angeles who used methamphetamine and who were enrolled in a contingency management program found that PEP non-adherence was associated with both lifetime and recent high-risk sexual behavior [44]. A randomized trial comparing standard to an enhanced adherence counseling intervention demonstrated a statistically non-significant trend toward improved PEP adherence in the intervention group (P= 0.078) [45], so providing enhanced counseling may be beneficial if resources are available to support this practice.

Recent sexual assault data have demonstrated variable follow-up [46, 47] and generally poor completion rates for PEP [47–49]. Morgan et al. reviewed the patient charts of 275 victims of either single or multiple perpetrator sexual assault and observed a 53.5 % rate of clinic follow-up and only 33.3 % PEP regimen completion [47]. A retrospective study of sexual assault survivors at a US-based emergency department noted that 87 % of 143 women initiated PEP, but only 27 % of the 124 women that initiated PEP over a 4-year period had documented completion of their regimen [48]. The underlying reasons for low observed rates of clinic follow-up and completion rates after sexual assault have not yet been fully examined, but it is thought that post-traumatic stress responses among survivors could make it difficult for them to use a daily pill reminding them of the event. Further investigation of behavioral interventions to improve PEP adherence is warranted.

Pre-exposure Prophylaxis (PrEP)

Evidence That PrEP Is Efficacious

Although PEP has been prescribed in care settings for over a decade, PrEP provision in clinical practice is a very recent

phenomenon. The approval of tenofovir-emtricitabine for use as daily oral PrEP by the US Food and Drug Administration only occurred in 2012 [50], based on the preponderant data from four of six randomized, controlled trials that demonstrated efficacy in at-risk men who have sex with men, heterosexual discordant couples, young African heterosexuals, and injection drug users [26–29, 51, 52]. The intent-to-treat efficacy of oral tenofovir-emtricitabine as PrEP ranged from 44 to 75 % among the four studies that demonstrated reductions in HIV incidence, and levels of protection correlated with medication adherence across studies [26–29]. In two studies of African women where PrEP efficacy was not demonstrated, drug levels were far lower than levels observed in the other four studies [53]. These low drug levels, which suggest medication non-adherence, are the primary explanation for why these two studies were unable to demonstrate protection with the same regimen [51, 52]. Low adherence to study medications was likely due to the ambivalence of some participants regarding participating in a research study, misgivings about using medication for an unproven benefit, and motivations to participate for non-altruistic reasons (i.e., access to medical care and modest study incentives).

Given the relationship between adherence and efficacy observed in PrEP studies, novel approaches to assessing and supporting adherence to PrEP in care settings are being developed, such as "neutral" adherence assessment, in which providers attempt to make patients feel comfortable reporting non-adherence when it occurs [54], SMS text-based adherence assessments [55], and measurement of drug levels in hair samples [56].

Potential Unintended Consequences with PrEP Use: Medication Toxicities, Drug Resistance, and Risk Compensation

Few adverse effects from using tenofovir-based PrEP have been observed in clinical studies. In most studies, less than 10 % of trial participants reported self-limited gastrointestinal symptoms, anorexia, or malaise [26–28]. The use of tenofovir-emtricitabine in iPrEx associated a mild, nonprogressive decrease in renal function in a minority of patients that was reversible upon discontinuing the medication [57]. This regimen was also associated with a statistically significant but small decrease in bone mineral density that is of uncertain significance and not associated with clinical symptoms after more than 18 months of follow-up [58, 59]. However, longer term safety data from PrEP utilization in care settings are needed, as participants in PrEP efficacy studies were required to be healthy (i.e., have normal renal function) to enroll.

Studies also examined whether HIV acquisition while utilizing tenofovir-emtricitabine as PrEP would select for drug-resistant viral strains. The detection of drug-resistant viral strains was uncommon among study participants who became infected with HIV during the studies, and nearly all drug-resistant strains were detected among persons who inadvertently initiated PrEP during undiagnosed acute HIV infection [26–29, 60]. However, among non-adherent participants who became infected, the levels of tenofovir-emtricitabine may have been too low to select for resistant viruses, so surveillance for drug resistance with PrEP use in clinical settings will be important.

In addition to biomedical safety data, efficacy studies also collected data on whether PrEP use was associated with increased sexual risk (i.e., risk compensation). It is important to note that engaging in condomless sex and/or sharing needles (in the Thai IDU study) were among the entry criteria for study participation. None of the placebo-controlled PrEP efficacy studies or an open-label study of tenofovir-emtricitabine as daily PrEP among MSM and transgender women found evidence of risk compensation based on participant self-report [26, 28, 29, 61••]. However, some participants maintained pre-trial levels of risk, and all participants in these studies were routinely provided with intensive risk reduction counseling and condoms, so studies to assess for risk compensation with PrEP use in routine care settings are needed.

PrEP Uptake in Care Settings

Studies suggest that initial uptake of PrEP by persons who are most likely to benefit has been gradual. Surveys of MSM who were members of a large online partner-seeking website in the USA found that only 1 % of respondents had taken PrEP as of early 2011, a few months after the iPrEx study demonstrated the efficacy of daily oral PrEP among MSM [28], and only 3 % had used PrEP as of early 2014 [10]. Analyses of nationally representative US retail pharmacy data suggested a slow but upward trend in PrEP prescribing in the first years after FDA approval, with an estimated 150 unique individuals starting PrEP nationwide in their system in 2011, 1316 in 2012, 1057 in the first three quarters of 2013, and 880 in the last quarter of 2013 and the first quarter of 2014 [30, 62]. Given that there are 50,000 new HIV infections in the USA each year [1], these trends suggest that the great majority of individuals who are likely to benefit from PrEP have not yet availed themselves of this intervention. The slow increase in PrEP utilization is consistent with theories suggesting that the gradual diffusion of medical innovations into clinical practice takes time, and initially, use is limited to early adopters [63]. The ongoing assessments of secular trends in PrEP utilization will be important given the evolving rates of uptake reported in these early studies.

Accessing PrEP: Cost and Insurance Considerations

The expense of PrEP, with medication costs of over $10,000 annually [64], and uncertainty about insurance coverage for

PrEP have been cited by some healthcare practitioners as perceived barriers to prescribing in care settings [12•, 13, 65]. However, several state Medicaid programs have agreed to cover the cost of PrEP [66, 67], and many private insurers also cover these costs given FDA approval, so expenses may not be prohibitive for patients with insurance. For patients who do not have insurance or who cannot afford prescription co-pays, a drug assistance program administered by the manufacturer of tenofovir-emtricitabine (Gilead Sciences; http://www.truvada.com/truvada-patient-assistance) is a potential option for accessing PrEP. Systematic studies of formulary coverage among public and private insurers, and studies to ascertain how much individuals are actually paying in out-of-pocket costs for using PrEP, have not yet been conducted but will help clarify the impact of financial barriers on PrEP uptake. Under the Affordable Care Act, insurance plans must cover preventive services with an A or B rating by the US Preventive Services Task Force (USPSTF) [68], so coverage for PrEP could be greatly facilitated if the USPSTF considers the evidence base for PrEP to merit a high rating.

Experiences with "Real-World" PrEP Provision in the USA

A US PrEP Demonstration project ("The Demo Project") conducted in public health STD clinics in San Francisco and Miami, and an LGBT community health center in Washington, D.C., provided PrEP to participants at no cost for 1 year and established that many MSM in these cities who engaged in high-risk sexual behaviors were interested in using PrEP. Of 959 potentially eligible clients approached by study staff for participation, 557 (58.1 %) elected to enroll and use PrEP; the majority of participants reported condomless anal sex behaviors that would suggest a benefit from using PrEP [69]. About one third of participants in the Demo Project self-referred to the study (versus clinic-based referrals), and self-referral was correlated with higher risk sexual behaviors, greater self-perceived risk of acquiring HIV, older age, being White, and higher educational attainment [70]. These findings suggest that some individuals who are likely to benefit from PrEP are informed and actively seek to utilize PrEP but that greater attention toward educating disenfranchised populations about PrEP is needed. Efforts to engage younger MSM of color will be particularly important, given the increasing burden of HIV in this population [71]. Adherence rates as measured by levels of tenofovir detected in dried blood spots were high among Demo Project participants, with 77 % of participants having levels consistent with taking at least four doses per week, though participants in Miami were less likely than those in San Francisco to be highly adherent (57 versus 92 %) [70], underscoring the need for locally and culturally tailored adherence interventions.

In a large health care maintenance organization in California, among 123 clients assessed for PrEP eligibility during a yearlong period between 2012 and 2013, over half initiated PrEP, demonstrating that PrEP implementation is feasible in a truly real-world care setting. However, 25 % of those who initiated PrEP during this period discontinued its use due to various reasons, including decreased risk perception, side effects or toxicities, or difficulty with medication adherence or monitoring requirements [72••], so further studies to understand why PrEP is discontinued in primary care settings outside of clinical trials will be important.

PrEP Implementation Outside of the USA

Few studies have reported on the experience of PrEP use in care settings outside the USA, given the limited availability of PrEP in resource-constrained settings and the lack of normative body approval to prescribe tenofovir-emtricitabine as PrEP outside of the USA. The PROUD study conducted at genitourinary medicine clinics across the UK randomized MSM to receive daily PrEP at the time of study enrollment or to a waiting list delay for 12 months to examine whether PrEP use would alter sexual risk behaviors. An interim analysis in October 2014 found that prompt PrEP initiation was protective against HIV acquisition [73]. The study investigators therefore began to offer PrEP to all study participants, and the study's final results, expected in 2015, could motivate the National Health Service to approve the use of tenofovir-emtricitabine for PrEP [73]. Other demonstration projects that provide open-label tenofovir-emtricitabine are getting underway in Brazil, Australia, Kenya, India, South Africa, and other countries [74].

Pharmacology Studies to Inform Clinical Care

Data from a 72-week open-label study of daily PrEP among MSM and transgender women (iPrEx OLE) suggest that less-than-perfect adherence to daily PrEP may still provide high levels of protection. In this study, incident HIV infections were not detected among participants with dried blood spot medication levels that correlated with taking four or more tablets per week [61••]. With these results, clinicians can reassure patients who use daily PrEP that an occasional missed dose is not likely to decrease its protective benefits substantially, though studies to understand how persons using PrEP will interpret and potentially adapt pill-taking behaviors in response to this nuanced information about adherence will be important. It is not known whether patients who are recommended to take daily doses are more likely to take most of their medication, than those who are told that they can miss occasional doses, or whether the information about forgiveness could enhance engagement and long-term PrEP adherence.

Recent insights in the pharmacology of PrEP have also shed light on the time to onset of protection after PrEP initiation and the duration of protection after discontinuation. An intensive pharmacokinetic study demonstrated that after eight daily doses of tenofovir-emtricitabine, 93 % of 21 adults achieved drug levels of tenofovir-diphosphate equivalent to levels associated with a 90 % relative risk reduction in anogenital HIV acquisition in the iPrEx study (known as the EC90) [75•]. Participants were given daily tenofovir-emtricitabine for 30 days, and 2 days after discontinuation, 86 % of participants still had drug levels that remained above the EC90 [75•]. Based on these data, clinicians can advise patients who are MSM that PrEP is most likely to offer maximal protection 1 week after the initiation of daily tenofovir-emtricitabine dosing. Providers should also counsel patients that PrEP should not be relied upon as the sole method of preventing infection before that time period has elapsed, which is important counseling for persons who have episodic periods of risk (e.g., when vacationing) and might prefer to initiate daily PrEP only in advance of these periods. The optimal tail end for PrEP dosing after periods of risk is not fully understood, but animal data suggest that post-event dosing is important [76].

Pharmacological data suggest that tenofovir levels in cervicovaginal secretions and tissues are less than those in rectal secretions and mucosa after a comparable dose [77, 78], which might mean that average adherence for women may need to be higher than for MSM and heterosexual men in order to optimize PrEP efficacy. Other local genital milieu factors, such as concomitant sexually transmitted diseases and inflammation, may influence PrEP efficacy [79].

Non-daily Dosing of PrEP

For patients who have episodic HIV risks and do not wish to take daily medications, studies are underway to determine whether event-driven or fixed interval dosing of PrEP is efficacious. The Ipergay study randomized MSM at several sites in France, Berlin, and Montreal to take two tablets of tenofovir-emtricitabine or placebo on the day of sexual intercourse and one pill daily for 2 days thereafter, with the final pill taken 2 days after the last sexual contact. The study team offered tenofovir-emtricitabine to all participants after an interim analysis in October 2014 found that this PrEP regimen reduced HIV incidence to a degree that was "much higher" than the 44 % efficacy observed in the iPrEx study. However, the exact degree of efficacy observed in Ipergay will not be available until 2015. When the study results are reported in greater detail at that time, the patterns of sexual behavior and medication adherence among participants will need to be reviewed to determine if the regimen was effective when contacts were less frequent [32]. The ongoing ADAPT (Alternative Dosing to Augment PrEP Tablet use) study is testing whether less than daily dosing, either as fixed doses twice weekly with a post-exposure boost or as event-driven use of a pill before and after sex, is acceptable and associated with fewer side effects and lower numbers of pills used as compared to daily dosing [31], so more information about the potential benefits of fixed interval and event-driven PrEP will be forthcoming.

Episodic PrEP may be beneficial during the periconception period for female-infected (F+M−) HIV serodiscordant couples who prefer to conceive children through natural conception instead of insemination without intercourse and for male-infected (M+F−) HIV serodiscordant couples who cannot access sperm processing. For these couples, a comprehensive safer conception strategy involving ART for HIV-infected members of couples, limiting condomless intercourse to peak fertility, voluntary medical male circumcision (for F+M− couples), treatment of STIs, and periconception PrEP has been recommended [80]. During a PrEP efficacy study (Partners PrEP), differences in pregnancy incidence and birth outcomes were not statistically different for women receiving PrEP compared with placebo at conception [81], and women who experienced pregnancy had high medication adherence near the time of conception [82], providing evidence that periconception PrEP may be a safe and acceptable option for some women.

Novel PrEP Agents and Methods of Drug Delivery

There are several reasons why developing chemoprophylaxis agents besides oral tenofovir-emtricitabine may be beneficial. Other agents might be preferable if some PrEP users experience bone and renal toxicities or do not otherwise tolerate tenofovir. Additional agents could potentially improve adherence (e.g., if they can be given intermittently), create competition to reduce costs, or provide options for persons in HIV discordant relationships if the HIV-infected partner has developed resistance to tenofovir-emtricitabine.

The topical administration of PrEP could potentially reduce the risk of toxicities by decreasing systemic drug exposure. The safety and efficacy of using a pericoital intravaginal gel containing tenofovir was demonstrated in the CAPRISA-004 study [34], though a study of daily use of this gel by women in Africa did not show efficacy [52]. The ongoing FACTS-001 study is replicating the pericoital dosing schedule from CAPRISA-004 [83], and if this study also demonstrates efficacy of the gel, this could accelerate the path toward licensure and production for clinical use.

Maraviroc is an orally administered entry inhibitor with an excellent safety profile when used for HIV treatment. NEXT-PrEP (HPTN 069) is an ongoing study testing the safety and tolerability of maraviroc alone or in combination with tenofovir or emtricitabine [84].

Long-acting injectable agents are being developed and tested, as it is hypothesized that some persons may have greater adherence to intermittent injections than a daily pill. Long-acting rilpivirine is a nanosuspension formulation of a non-nucleoside reverse transcriptase inhibitor (NNRTI). In a pre-clinical study, it was shown to be safe and achieves high genital tract and rectal compartment concentrations within days after injection, and drug levels remained measurable 84 days post-dose [85]. The detection of a rilpivirine-resistant viral strain after HIV acquisition in one participant receiving the lowest dose of rilpivirine tested in this study suggests that monitoring for drug resistance among any persons who become infected while using rilpivirine will be important. These results also suggest that higher doses of this agent may be necessary to prevent HIV acquisition [86]. Another agent, cabotegravir, is a long-acting injectable integrase strand transfer inhibitor that protected macaques against rectal challenge with simian/human immunodeficiency virus at plasma concentrations achievable with quarterly injections in humans [33••]. Phase 2 studies of injectable rilpivirine and cabotegravir are underway [87].

Drug-eluting rings that deliver antiretroviral medications directly to mucosal sites are being tested, as this approach could limit systemic exposure to medications and could improve adherence if rings can remain in situ for extended periods of time. Intravaginal rings containing dapivirine (another NNRTI) with or without maraviroc were used by healthy women for 28 days and were found to be safe and well tolerated. The use of the rings was associated with high tissue concentrations of dapivirine but very low concentrations of maraviroc. Dapivirine was also found to inhibit HIV replication in an ex vivo cervical tissue model [35]. The results of this study support further testing of NNRTI-based vaginal rings, and two large efficacy trials of the dapivirine ring are underway in African women [88]. The delivery of dapivirine through intravaginal films has also been shown to achieve drug concentrations comparable to those achieved with the use of vaginal rings [89].

To meet multiple reproductive health needs for women, including the prevention of HIV acquisition and unintended pregnancy, multipurpose prevention technologies that deliver antiretroviral and contraceptive agents are also being developed. Interviews with African women participating in HIV prevention trials demonstrated substantial interest in using multipurpose products [90]. Ideally, multiple approaches to delivering PrEP will be efficacious and manufactured for public use, including topical, oral, and injectable formulations, so that prevention options may be individualized based on each person's sexual behaviors, patterns of exposure, and personal preferences.

Practitioner Identification of Persons Most Likely to Benefit from PrEP

Although some persons who engage in HIV risk behaviors will accurately gauge their risk and seek PrEP from providers, as with persons who self-referred to the US PrEP Demonstration Project [69, 70], others may not be aware that they are at substantial risk for HIV acquisition [91], so providers need to be skilled in risk assessments. Patient-provider discussions about sexual orientation and HIV risk behaviors are infrequent in primary care settings due in part to patient and provider discomfort with discussing sensitive topics and lack of provider training [92–94], so novel approaches to facilitating these discussions are needed. In-person or webinar trainings to enhance providers' interviewing skills, structured questionnaires that practitioners can utilize to elicit comprehensive sexual histories [95], routine collection of sexual orientation and gender identity ("SOGI") data by clinics [96], and algorithms that incorporate patient-reported data to generate personal estimates of risk [97, 98] have been explored to enhance risk assessments, though the effectiveness of these interventions requires further evaluation.

Cost-Effectiveness of PrEP

The provision of PrEP to those individuals at highest risk for HIV acquisition is necessary for PrEP to be cost-effective and sustainably implemented. A modeling study of the South African HIV epidemic concluded that providing PrEP to the general population would be costly, whereas the focused provision of PrEP to those at greatest risk of HIV acquisition would be highly cost-effective or cost saving. The study concluded that universal HIV treatment and focused PrEP provision would be the most cost-effective way to utilize antiretroviral medications for prevention [99]. A systematic review of studies modeling the cost-effectiveness of PrEP in diverse populations came to a similar conclusion that delivering PrEP to populations with the highest HIV incidence is likely to be the most cost-effective strategy [100]. In the USA, a 20-year program that would provide daily PrEP with 44 % efficacy to MSM in the top quintile of HIV risk would result in incremental costs of approximately $50,000 per quality-adjusted life-year (QALY). This cost would meet standard willingness-to-pay thresholds to be considered cost-effective [101]. However, other cost-effectiveness models for MSM in the USA have produced estimates ranging from $32,000 to $300,000 per QALY [102, 103]. A model applied to Australian MSM found that PrEP was only cost-effective when utilized by MSM in HIV serodiscordant regular partnerships (approximately $10,000 per QALY) versus high-risk MSM more generally (>$110,000 per QALY) [104].

From a cost-effectiveness perspective, if adherence to PrEP and efficacy are high, then daily tenofovir-emtricitabine may

compare favorably to some other primary prevention interventions. For example, statin use for the primary prevention of cardiovascular disease among moderate risk men in the USA has been estimated to cost $42,000 per QALY (estimate range among studies $3 to $594,830 per QALY [105]). However, until the price of PrEP decreases substantially (i.e., when its US patent expires), PrEP is likely to be less cost-effective than most colorectal cancer screening interventions among average-risk persons, which may be cost saving [106]. As the time horizon to realize economic benefits from implementing and expanding programs that provide antiretroviral medications for treatment and prevention may be decades in the future, support for scaling up these programs will depend on forethought and sustained commitment by multiple stakeholders, including economic policy makers, national governments, non-governmental aid organizations, drug manufacturers, and patient advocates.

Conclusions

The expansion of PEP and PrEP provision could help to stem the number of new HIV infections globally. Studies are underway to optimize their tolerability with novel regimens and methods of delivery in the hope that persons with diverse patterns of sexual risk and personal preferences will find chemoprophylaxis to be acceptable and beneficial. However, in addition to antiretroviral regimen tolerability and efficacy, there are clearly social and behavioral factors that impact adherence to medications and associated clinical monitoring, which remain suboptimal in some populations; developing interventions to support adherence to chemoprophylaxis will be essential. It will also be important to identify ways to facilitate successful and sustainable implementation of PEP and PrEP programs, including methods to help providers identify persons who are most likely to benefit from PEP and/or PrEP.

As we learn lessons from real-world experiences about how best to implement PEP and PrEP, the transition from PEP to PrEP will also require active investigation, since some patients who receive PEP may engage in recurrent high-risk behaviors [107, 108] and may therefore benefit from ongoing chemoprophylaxis to prevent HIV acquisition. Unfortunately, the awareness of NPEP has been limited even among high-risk MSM, as demonstrated by several studies [109–111]. The expansion of PrEP programs will likely stimulate the awareness and utilization of PEP as a complementary method of biomedical prevention for patients that have episodic behavioral HIV risk or who may have suboptimal PrEP adherence. Additional implementation research is necessary to learn how to best integrate PEP and PrEP provision for patients with a spectrum of risk for HIV acquisition over time.

Compliance with Ethics Guidelines

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- • Of importance
- •• Of major importance

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