HHS Public Access

Author manuscript

Curr HIV/AIDS Rep. Author manuscript; available in PMC 2016 March 01.

Published in final edited form as:

Curr HIV/AIDS Rep. 2015 March ; 12(1): 127–138. doi:10.1007/s11904-014-0253-5.

Antiretrovirals for Primary HIV Prevention: The Current Status of Pre- and Post-Exposure Prophylaxis

Douglas S. Krakower[1,2], **Sachin Jain**[3], and **Kenneth H. Mayer**[1,2]

Douglas S. Krakower: dkrakowe@bidmc.harvard.edu; Sachin Jain: SAJAIN@montefiore.org; Kenneth H. Mayer: kmayer@fenwayhealth.org

[1]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA

[2]The Fenway Institute, Fenway Health, Boston, MA

[3]Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY

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 successful implementation of these promising prevention approaches.

Keywords

HIV; bio-behavioral; prevention; post-exposure prophylaxis; pre-exposure prophylaxis

Corresponding Author: Douglas S. Krakower, MD, Beth Israel Deaconess Medical Center, Division of Infectious Diseases, 110 Francis Street, Suite GB, Boston, MA 02215-5501, Phone: 617-632-0760, Fax: 617-632-7626.

Compliance with Ethics Guidelines

Conflict of Interest

Sachin Jain declares no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

INTRODUCTION

Despite major advances in antiretroviral treatment and chemoprophylaxis, 50,000 infections occur in the United States [1] and 2 million new HIV infections occur globally each year [2]. Suboptimal control of the epidemic is partially a result of insufficient use of post-exposure prophylaxis (PEP) and pre-exposure prophylaxis (PrEP) for primary HIV prevention when indicated, even though the U.S. 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 U.S [1] and because of limited implementation by medical providers [12, 13].

PEP uptake may also be low because of lack of certainty about efficacy. 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 U.S. 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 post-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 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 bio-behavioral 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 U.S. Public Health Service (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 hours per 2005 CDC NPEP guidelines [4] and 2013 USPHS occupational PEP guidelines [21]. This recommendation is based upon studies with macaques demonstrating that 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 hours as compared to 72 hours post-exposure [17]. Thus, PEP should be initiated within 72 hours 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 4th 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 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 4th 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 2-drug or 3-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 3-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 3 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 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 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 demonstrated variable follow-up [46, 47] and generally poor completion rates [47–49]. Morgan et al reviewed 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 U.S.-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 4 of 6 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 4 studies that demonstrated reductions in HIV incidence, and levels of protection correlated with medication adherence across studies [26–29]. In 2 studies of African women where PrEP efficacy was not demonstrated, drug levels were far lower than levels observed in the other 4 studies [53]. These low drug levels, which suggest medication non-adherence, are the primary explanation for why these 2 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 attempts 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 was 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. 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, 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 U.S. 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 U.S. 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 3 quarters of 2013, and 880 in the last quarter of 2013 and the first quarter of 2014 [30, 62]. Given 50,000 new HIV infections in the U.S. 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]. 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 U.S. 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 U.S

A U.S. 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 towards 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 4 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 U.S.

Few studies have reported on the experience of PrEP use in care settings outside the US, given limited availability of PrEP in resource-constrained settings and lack of normative body approval to prescribe tenofovir-emtricitabine as PrEP outside of the U.S.. The PROUD study conducted at Genitourinary Medicine clinics across the United Kingdom 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 4 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 8 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 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 2 tablets of tenofovir-emtricitabine or placebo on the day of sexual intercourse and 1 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.

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 towards 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. In a pre-clinical study, it was shown to be safe and achieve 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 1 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. 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]. Delivery of dapivirine through intravaginal films has also been shown to achieve drug concentrations comparable to those achieved with use of vaginal rings [89].

To meet multiple reproductive health needs for women, including 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 U.S. 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

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 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 U.S., 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 U.S. 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 primary prevention of cardiovascular disease among moderate risk men in the U.S. 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 U.S. 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 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.

Acknowledgments

Douglas Krakower reports grants from National Institutes of Health (K23 MH098795), Gilead Sciences, Bristol Myers Squibb, and personal fees from Medscape.

Kenneth Mayer reports unrestricted research grants from Merck, Gilead and Bristol Myers Squibb, funding from the Harvard University Center for AIDS Research (CFAR), and an NIH funded program (P30 AI060354; PI: Walker).

REFERENCES

Papers of particular interest, published recently, have been highlighted as:

• Of importance •• Of major importance

1. Prejean J, Song R, Hernandez A, Ziebell R, Green T, Walker F, et al. Estimated HIV Incidence in the United States, 2006–2009. PLoS One. 2011; 6:e17502. [PubMed: 21826193]
2. UNAIDS Report on the Global AIDS Epidemic 2013. Joint United Nations Programme on HIV/AIDS (UNAIDS). Accessed at http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2013/gr2013/UNAIDS_Global_Report_2013_en.pdf on 2 November 2014.
3. Public Health Service guidelines for the management of health-care worker exposures to HIV and recommendations for postexposure prophylaxis. Centers for Disease Control and Prevention. MMWR Recomm Rep. 1998; 47:1–33.
4. Smith DK, Grohskopf LA, Black RJ, Auerbach JD, Veronese F, Struble KA, et al. Antiretroviral postexposure prophylaxis after sexual, injection-drug use or other nonoccupational exposure to HIV in the United States: recommendations from the U.S Department of Health and Human Services. MMWR Recomm Rep. 2005; 54:1–20. [PubMed: 15660015]
5. Interim guidance: preexposure prophylaxis for the prevention of HIV infection in men who have sex with men. MMWR Morb Mortal Wkly Rep. 2011; 60:65–68. [PubMed: 21270743]
6. Interim guidance for clinicians considering the use of preexposure prophylaxis for the prevention of HIV infection in heterosexually active adults. MMWR Morb Mortal Wkly Rep. 2012; 61:586–589. [PubMed: 22874836]
7. Update to Interim Guidance for Preexposure Prophylaxis (PrEP) for the Prevention of HIV Infection: PrEP for injecting drug users. MMWR Morb Mortal Wkly Rep. 2013; 62:463–465. [PubMed: 23760186]
8. Mimiaga MJ, Case P, Johnson CV, Safren SA, Mayer KH. Preexposure antiretroviral prophylaxis attitudes in high-risk Boston area men who report having sex with men: limited knowledge and experience but potential for increased utilization after education. J Acquir Immune Defic Syndr. 2009; 50:77–83. [PubMed: 19295337]
9. Joshi M, Basra A, McCormick C, Webb H, Pakianathan M. Post-exposure prophylaxis after sexual exposure (PEPSE) awareness in an HIV-positive cohort. Int J STD AIDS. 2014; 25:67–69. [PubMed: 23970629]
10. Mayer, KH.; Oldenburg, CE.; Novak, DS.; Krakower, DS.; Mimiaga, MJ. Differences in PrEP Knowledge and Use in U.S. MSM Users of a Popular Sexual Networking Site Surveyed in August 2013 and January 2014. R4P conference; 28–31 October 2014; Cape Town.
11. Krakower D, Mimiaga M, Rosenberger J, Novak B, Mitty JA, White J, et al. Limited Awareness and Low Immediate Uptake of Pre-Exposure Prophylaxis among Men who have Sex with Men Using an Internet Social Networking Site. Submitted to PLoS One. 2011 Sep.
12. Karris MY, Beekmann SE, Mehta SR, Anderson CM, Polgreen PM. Are we prepped for preexposure prophylaxis (PrEP)? Provider opinions on the real-world use of PrEP in the United States and Canada. Clin Infect Dis. 2014; 58:704–712. [PubMed: 24319083] . This study assessed attitudes and intentions regarding PrEP provision among a national sample of infectious diseases specialists in the United States.

13. Krakower D, Ware N, Mitty JA, Maloney K, Mayer KH. HIV providers' perceived barriers and facilitators to implementing pre-exposure prophylaxis in care settings: a qualitative study. AIDS Behav. 2014; 18:1712–1721. [PubMed: 24965676]
14. Cardo DM, Culver DH, Ciesielski CA, Srivastava PU, Marcus R, Abiteboul D, et al. A Case–Control Study of HIV Seroconversion in Health Care Workers after Percutaneous Exposure. New England Journal of Medicine. 1997; 337:1485–1490. [PubMed: 9366579]
15. Tsai CC, Follis KE, Sabo A, Beck TW, Grant RF, Bischofberger N, et al. Prevention of SIV infection in macaques by (R)-9-(2-phosphonylmethoxypropyl)adenine. Science. 1995; 270:1197–1199. [PubMed: 7502044]
16. Subbarao S, Otten RA, Ramos A, Kim C, Jackson E, Monsour M, et al. Chemoprophylaxis with tenofovir disoproxil fumarate provided partial protection against infection with simian human immunodeficiency virus in macaques given multiple virus challenges. J Infect Dis. 2006; 194:904–911. [PubMed: 16960777]
17. Otten RA, Smith DK, Adams DR, Pullium JK, Jackson E, Kim CN, et al. Efficacy of postexposure prophylaxis after intravaginal exposure of pig-tailed macaques to a human-derived retrovirus (human immunodeficiency virus type 2). J Virol. 2000; 74:9771–9775. [PubMed: 11000253]
18. Bourry O, Brochard P, Souquiere S, Makuwa M, Calvo J, Dereudre-Bosquet N, et al. Prevention of vaginal simian immunodeficiency virus transmission in macaques by postexposure prophylaxis with zidovudine, lamivudine and indinavir. AIDS. 2009; 23:447–454. [PubMed: 19240457]
19. Van Rompay KK, McChesney MB, Aguirre NL, Schmidt KA, Bischofberger N, Marthas ML. Two low doses of tenofovir protect newborn macaques against oral simian immunodeficiency virus infection. J Infect Dis. 2001; 184:429–438. [PubMed: 11471100]
20. Dobard C, Sharma S, Parikh UM, West R, Taylor A, Martin A, et al. Postexposure protection of macaques from Vaginal SHIV infection by topical integrase inhibitors. Sci Transl Med. 2014; 6:227ra235.. This study is the first to offer animal data supporting the use of integrase inhibitors for NPEP.
21. Kuhar DT, Henderson DK, Struble KA, Heneine W, Thomas V, Cheever LW, 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; 34:875–892. [PubMed: 23917901]
22. Li H, Blair L, Chen Y, Learn G, Pfafferott K, John M, et al. Molecular mechanisms of HIV type 1 prophylaxis failure revealed by single-genome sequencing. J Infect Dis. 2013; 208:1598–1603. [PubMed: 24023257]
23. Roland ME, Neilands TB, Krone MR, Katz MH, Franses K, Grant RM, et al. Seroconversion following nonoccupational postexposure prophylaxis against HIV. Clin Infect Dis. 2005; 41:1507–1513. [PubMed: 16231265]
24. Hawkins DA, Asboe D, Barlow K, Evans B. Seroconversion to HIV-1 following a needlestick injury despite combination post-exposure prophylaxis. J Infect. 2001; 43:12–15. [PubMed: 11597149]
25. Beltrami EM, Luo CC, de la Torre N, Cardo DM. Transmission of drug-resistant HIV after an occupational exposure despite postexposure prophylaxis with a combination drug regimen. Infect Control Hosp Epidemiol. 2002; 23:345–348. [PubMed: 12083242]
26. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med. 2012; 367:399–410. [PubMed: 22784037]
27. Choopanya K, Martin M, Suntharasamai P, Sangkum U, Mock PA, Leethochawalit M, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2013; 381:2083–2090. [PubMed: 23769234]
28. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med. 2010; 363:2587–2599. [PubMed: 21091279]

29. Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. N Engl J Med. 2012; 367:423–434. [PubMed: 22784038]

30. Flash C, Landovitz R, Mera Giler R, Ng L, Magnuson D, Bush Wooley S, et al. Two years of Truvada for pre-exposure prophylaxis utilization in the US. J Int AIDS Soc. 2014; 17:19730. [PubMed: 25397476]

31. HPTN 067: The ADAPT Study: A Phase II, Randomized, Open-Label, Pharmacokinetic and Behavioral Study of the Use of Intermittent Oral Emtricitabine/Tenofovir Disoproxil Fumarate Pre-Exposure Prophylaxis (PrEP). HIV Prevention Trials Network; Accessed at: http://www.hptn.org/research_studies/hptn067.asp on 30 October 2014. In.

32. A significant breakthrough in the fight against hiv/aids - A drug taken at the time of sexual intercourse effectively reduces the risk of infection. Press release from the ANRS IPERGAY trial. 2014 Oct 29. Accessed at http://www.avac.org/sites/default/files/u44/ipergayPR.pdf on 30 October, 2014.

33. Andrews CD, Spreen WR, Mohri H, Moss L, Ford S, Gettie A, et al. Long-Acting Integrase Inhibitor Protects Macaques from Intrarectal Simian/Human Immunodeficiency Virus. Science. 2014; 343:1151–1154. [PubMed: 24594934] . This study demonstrated that a long-acting injectable agent sucessfully protected macaques from viral acquisition, which paves the way for studies of long-acting injectable agents for use as PrEP in humans.

34. Abdool Karim Q, Abdool Karim SS, Frohlich JA, Grobler AC, Baxter C, Mansoor LE, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. Science. 2010; 329:1168–1174. [PubMed: 20643915]

35. Chen, B.; Panther, L.; Hoesley, C.; Hendrix, C.; Van der Straten, A.; Husnik, M., et al. Safety and Pharmacokinetics/Pharmacodynamics of Dapivirine and Maraviroc Vaginal Rings [abstract 41]. Presented at the 2014 Conference on Retroviruses and Oppportunistic Infections; March 3–6, 2014; Boston.

36. Patel P, Borkowf CB, Brooks JT, Lasry A, Lansky A, Mermin J. Estimating per-act HIV transmission risk: a systematic review. AIDS. 2014; 28:1509–1519. [PubMed: 24809629] . This paper enumerates the risk of HIV transmission for different types of exposures, which is important for risk assessment when evaluating patients for PEP and risk-reduction counseling.

37. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med. 2011; 365:493–505. [PubMed: 21767103]

38. New York State Department of Health AIDS Institute. UPDATE: HIV Prophylaxis Following Non-Occupational Exposure. 2013 Jul. Accessed at: http://www.hivguidelines.org/clinical-guidelines/post-exposure-prophylaxis/hiv-prophylaxis-following-non-occupational-exposure/ on 2 November 2014.

39. Mayer KH, Mimiaga MJ, Gelman M, Grasso C. Raltegravir, tenofovir DF, and emtricitabine for postexposure prophylaxis to prevent the sexual transmission of HIV: safety, tolerability, and adherence. J Acquir Immune Defic Syndr. 2012; 59:354–359. [PubMed: 22267017] . This trial has been pivotal in informing several guidelines for a preferred NPEP regimen that consists of tenofovir-emtricitabine and raltegravir.

40. Mayer KH, Mimiaga MJ, Cohen D, Grasso C, Bill R, Van Derwarker R, et al. Tenofovir DF plus lamivudine or emtricitabine for nonoccupational postexposure prophylaxis (NPEP) in a Boston Community Health Center. J Acquir Immune Defic Syndr. 2008; 47:494–499. [PubMed: 18176318]

41. 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. December 2014 supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. . This document summarizes the World Health Organization's most recent clinical guidelines for post-exposure prophylaxis.

42. Jain S, Mayer KH. Practical guidance for nonoccupational postexposure prophylaxis to prevent HIV infection: an editorial review. AIDS. 2014; 28:1545–1554. [PubMed: 24785956]

43. Armishaw J, Hoy JF, Watson KM, Wright EJ, Price BG, Pierce AB. Non-occupational post-exposure prophylaxis in Victoria, Australia: responding to high rates of representation and low rates of follow-up. Int J STD AIDS. 2011; 22:714–718. [PubMed: 22174051]
44. Fletcher JB, Rusow JA, Le H, Landovitz RJ, Reback CJ. High-risk Sexual Behavior is Associated with Post-Exposure Prophylaxis Non-adherence among Men who have Sex with Men Enrolled in a Combination Prevention Intervention. J Sex Transm Dis. 2013; 2013:210403. [PubMed: 24527254]
45. Roland ME, Neilands TB, Krone MR, Coates TJ, Franses K, Chesney MA, et al. A randomized noninferiority trial of standard versus enhanced risk reduction and adherence counseling for individuals receiving post-exposure prophylaxis following sexual exposures to HIV. Clin Infect Dis. 2011; 53:76–83. [PubMed: 21653307]
46. Oldenburg CE, Barnighausen T, Harling G, Mimiaga MJ, Mayer KH. Adherence to post-exposure prophylaxis for non-forcible sexual exposure to HIV: a systematic review and meta-analysis. AIDS Behav. 2014; 18:217–225. [PubMed: 23877791]
47. Morgan L, Brittain B, Welch J. Medical care following multiple perpetrator sexual assault: A retrospective review. Int J STD AIDS. 2014
48. Krause KH, Lewis-O'Connor A, Berger A, Votto T, Yawetz S, Pallin DJ, et al. Current practice of HIV postexposure prophylaxis treatment for sexual assault patients in an emergency department. Womens Health Issues. 2014; 24:e407–e412. [PubMed: 24981399]
49. Ford, N.; Irvine, C.; Doherty, M.; Vitoria, M.; Baggaley, R.; Shuuber, Z. Variation in adherence to post-exposure prophylaxis by exposure type: a meta-analysis [abstract TUPE154]. Presented at the 2014 International AIDS Conference; July 20–25, 2014.; Melbourne.
50. FDA approves first drug for reducing the risk of sexually acquired HIV infection. 2012 Jul 16. Accessed at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm312210.htm on 3 April 2014.
51. Van Damme L, Corneli A, Ahmed K, Agot K, Lombaard J, Kapiga S, et al. Preexposure prophylaxis for HIV infection among African women. N Engl J Med. 2012; 367:411–422. [PubMed: 22784040]
52. Marrazzo, JM.; Ramjee, G.; Nair, GB.; Palanee, T.; Mkhiza, B.; Nakabiito, C., et al. Pre-exposure Prophylaxis for HIV in Women: Daily Oral Tenofovir, Oral Tenofovir/Emtricitabine, or Vaginal Tenofovir Gel in the VOICE Study (MTN 003). Conference on Retroviruses and Opportunistic Infections; 3–6 March 2013; Atlanta. Accessed at http://www.retroconference.org/2013b/Abstracts/47951.htm on 12 April 2013.
53. van der Straten A, Stadler J, Montgomery E, Hartmann M, Magazi B, Mathebula F, et al. Women's Experiences with Oral and Vaginal Pre-Exposure Prophylaxis: The VOICE-C Qualitative Study in Johannesburg, South Africa. PLoS One. 2014; 9:e89118. [PubMed: 24586534]
54. Amico KR, McMahan V, Goicochea P, Vargas L, Marcus JL, Grant RM, et al. Supporting study product use and accuracy in self-report in the iPrEx study: next step counseling and neutral assessment. AIDS Behav. 2012; 16:1243–1259. [PubMed: 22460228]
55. Mayer K, Safren S, Haberer J, Elsesser S, Clarke W, Hendrix C, et al. Project PrEPARE: High Levels of Medication Adherence with Continued Condomless Sex in U.S. Men who Have Sex with Men in an Oral PrEP Adherence Trial. HIV Research for Prevention 2014. Abstract OA07.06 LB.
56. Liu AY, Yang Q, Huang Y, Bacchetti P, Anderson PL, Jin C, et al. Strong relationship between oral dose and tenofovir hair levels in a randomized trial: hair as a potential adherence measure for pre-exposure prophylaxis (PrEP). PLoS One. 2014; 9:e83736. [PubMed: 24421901]
57. Solomon MM, Lama JR, Glidden DV, Mulligan K, McMahan V, Liu AY, et al. Changes in renal function associated with oral emtricitabine/tenofovir disoproxil fumarate use for HIV pre-exposure prophylaxis. AIDS. 2014; 28:851–859. [PubMed: 24499951]
58. Mulligan, K.; Glidden, DV.; Gonzales, P.; Ramirez-Cardich, ME.; Liu, A.; Namwongprom, S., et al. Effects of FTC/TDF on Bone Mineral Density in Seronegative Men from 4 Continents: DEXA Results of the Global iPrEx Study [Abstract #94LB]. 18th Conference on Retroviruses and Opportunistic Infections; 27 February–2 March 2011; Boston. Accessed at http://www.retroconference.org/2011/Abstracts/42550.htm on 1 June 2012.

59. Liu AY, Vittinghoff E, Sellmeyer DE, Irvin R, Mulligan K, Mayer K, et al. Bone Mineral Density in HIV-Negative Men Participating in a Tenofovir Pre-Exposure Prophylaxis Randomized Clinical Trial in San Francisco. PLoS One. 2011; 6:e23688. [PubMed: 21897852]
60. Liegler T, Abdel-Mohsen M, Bentley LG, Atchison R, Schmidt T, Javier J, et al. HIV-1 Drug Resistance in the iPrEx Preexposure Prophylaxis Trial. J Infect Dis. 2014; 210:1217–1227. [PubMed: 24740633]
61. Grant RM, Anderson PL, McMahan V, Liu A, Amico KR, Mehrotra M, et al. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. Lancet Infect Dis. 2014; 14:820–829. [PubMed: 25065857] . This study involved open label PrEP provision to a large sample of men and transgender women who have sex with men. An important finding is that none of the participants who used 4 doses of PrEP weekly acquired HIV, so this level of adherence is likely to provide high levels of protection.
62. Rawlings, K.; Mera, R.; Pechonika, A.; Rooney, JF.; Peschel, T.; Cheng, A. Status of Truvada (TVD) for HIV Pre-Exposure Prophylaxis (PrEP) in the United States: An Early Drug Utilization Analysis [abstract H-663a]. Presented at the 2013 Interscience Conference on Antimicrobial Agents and Chemotherapy; September 9–September 13, 2013; Denver.
63. Berwick DM. Disseminating innovations in health care. JAMA. 2003; 289:1969–1975. [PubMed: 12697800]
64. Tenofovoir and emtricitabine: Drug information. Lexicomp.
65. Sharma M, Wilton J, Senn H, Fowler S, Tan DH. Preparing for PrEP: perceptions and readiness of canadian physicians for the implementation of HIV pre-exposure prophylaxis. PLoS One. 2014; 9:e105283. [PubMed: 25133648]
66. Washinton State Department of Public Health. [Last accessed December 19, 2014] Pre-Exposure Prophyalxis Drug Assistance Program (PrEP DAP). Available at http://www.doh.wa.gov/YouandYourFamily/IllnessandDisease/HIVAIDS/HIVCareClientServices/PrEPDAP
67. [Last accessed December 19, 2014] New York State Medicaid Pharmacy and Therapeutics Committee Meeting Summary. 2012 Nov 15. Available at http://www.health.ny.gov/health_care/medicaid/program/ptcommittee/meetings/2012/11/ptsummary11-15-12_with_comm_final_determi.pdf
68. Crowley, JS.; Kates, J. Kaiser Family Foundation Report - The Affordable Care Act, the Supreme Court, and HIV: What are the Implications?. 2012 Sep. Accessed at http://www.americanbar.org/content/dam/aba/administrative/human_rights/acc_crowley_hiv_aca.authcheckdam.pdf on 12 December, 2014.
69. Elion, R.; Doblecki-Lewis, S.; Cohen, S.; Castro, J.; Buchbinder, S.; Estrada, Y., et al. High levels of interest in PrEP and baseline risk behaviors among MSM enrolled in the US PrEP Demonstration (Demo) project [abstract THPE187]. Presented at the 20th International AIDS Conference; July 20–25, 2014; Melbourne.
70. Cohen, SE.; Vittinghoff, E.; Anderson, PL.; Doblecki-Lewis, S.; Bacon, O.; Chege, W., et al. Implementation of PrEP in STD Clinics: High Uptake and Drug Detection Among MSM in the Demonstration Project [abstract 954]. Presented at the 21st Conference on Retroviruses and Opportunistic Infections; March 3–6, 2014; Boston.
71. Koblin BA, Mayer KH, Eshleman SH, Wang L, Mannheimer S, del Rio C, et al. Correlates of HIV acquisition in a cohort of Black men who have sex with men in the United States: HIV prevention trials network (HPTN) 061. PLoS One. 2013; 8:e70413. [PubMed: 23922989]
72. Liu A, Cohen S, Follansbee S, Cohan D, Weber S, Sachdev D, et al. Early Experiences Implementing Pre-exposure Prophylaxis (PrEP) for HIV Prevention in San Francisco. PLoS Med. 2014; 11:e1001613. [PubMed: 24595035] . The authors summarize early "real-world" experiences with PrEP provision from 3 programs: a demonstration project, a health maintenance organization, and a reproductive services clinic/
73. PROUD study interim analysis finds pre-exposure prophylaxis (PrEP) is highly protective against HIV for gay men and other men who have sex with men in the UK. 2014 Oct 16. Accessed at http://www.proud.mrc.ac.uk/PDF/PROUD%20Statement%20161014.pdf on 30 October, 2014.
74. AIDS Vaccine Advocacy Coalition - Ongoing and Planned PrEP Evaluation Studies. Accessed at http://www.avac.org/resource/ongoing-and-planned-prep-evaluation-studies on 9 November 2014.

75. Seifert S, Glidden DV, Meditz AL, Castillo-Mancilla JR, Klein B, Kerr BJ, et al. Estimated onset and duration of PrEP activity for daily TDF/FTC using the EC90 from iPrEx. Presented at the15th International Workshop on Clinical Pharmacology of HIV and Hepatitis TherapyMay 19–21, 2014Washington, DC. This pharmacology study demonstrated that daily use of tenofovir-emtricitabine is likely to result in highly protective drug levels for men who have sex with men after approximately 1 week of use, which has important implications for counseling of persons who initiate daily PrEP.
76. Garcia-Lerma JG, Cong ME, Mitchell J, Youngpairoj AS, Zheng Q, Masciotra S, et al. Intermittent prophylaxis with oral truvada protects macaques from rectal SHIV infection. Sci Transl Med. 2010; 2:14ra14.
77. Patterson KB, Prince HA, Kraft E, Jenkins AJ, Shaheen NJ, Rooney JF, et al. Penetration of tenofovir and emtricitabine in mucosal tissues: implications for prevention of HIV-1 transmission. Sci Transl Med. 2011; 3:112re114.
78. Louissaint NA, Cao YJ, Skipper PL, Liberman RG, Tannenbaum SR, Nimmagadda S, et al. Single dose pharmacokinetics of oral tenofovir in plasma, peripheral blood mononuclear cells, colonic tissue, and vaginal tissue. AIDS Res Hum Retroviruses. 2013; 29:1443–1450. [PubMed: 23600365]
79. Naranbhai V, Abdool Karim SS, Altfeld M, Samsunder N, Durgiah R, Sibeko S, et al. Innate immune activation enhances hiv acquisition in women, diminishing the effectiveness of tenofovir microbicide gel. J Infect Dis. 2012; 206:993–1001. [PubMed: 22829639]
80. Matthews LT, Smit JA, Cu-Uvin S, Cohan D. Antiretrovirals and safer conception for HIV-serodiscordant couples. Curr Opin HIV AIDS. 2012; 7:569–578. [PubMed: 23032734]
81. Mugo NR, Hong T, Celum C, Donnell D, Bukusi EA, John-Stewart G, et al. Pregnancy incidence and outcomes among women receiving preexposure prophylaxis for HIV prevention: a randomized clinical trial. JAMA. 2014; 312:362–371. [PubMed: 25038355]
82. Matthews LT, Heffron R, Mugo NR, Cohen CR, Hendrix CW, Celum C, et al. High medication adherence during periconception periods among HIV-1-uninfected women participating in a clinical trial of antiretroviral pre-exposure prophylaxis. J Acquir Immune Defic Syndr. 2014; 67:91–97. [PubMed: 25118795]
83. Follow-on African Consortium for Tenofovir Studies (FACTS) [website]. Accessed at http://www.facts-consortium.co.za/?page_id=83 on 31 October 2014.
84. HPTN 069: NEXT-PREP: A Phase II Randomized, Double-Blind, Study of the Safety and Tolerability of Maraviroc (MVC), Maraviroc + Emtricitabine (MVC+FTC), Maraviroc + Tenofovir disoproxil fumarate (MVC+TDF), or Tenofovir disoproxil fumarate + Emtricitabine (TDF+FTC) for Pre-Exposure Prophylaxis (PrEP) to Prevent HIV Transmission in At-Risk Men Who Have Sex with Men and in At-Risk Women. HIV Prevention Trials Network; Accessed at: http://www.hptn.org/research_studies/hptn069.asp on 16 October 2014.
85. Jackson AG, Else LJ, Mesquita PM, Egan D, Back DJ, Karolia Z, et al. A compartmental pharmacokinetic evaluation of long-acting rilpivirine in HIV-negative volunteers for pre-exposure prophylaxis. Clin Pharmacol Ther. 2014; 96:314–323. [PubMed: 24862215]
86. Penrose, KJ.; Parikh, UM.; Hamanishi, KA.; Panousis, C.; Else, L.; Back, D., et al. Selection of Rilpiverine Resistant HIV-1 in a Seroconverter on Long-acting Rilpiverine (TMC278LA) from the Lowest Dose Arm of the SSAT 040 Trial [abstract OA27.01]. Presented at the 2014 Research for Prevention Conference; October 28à31, 2014; Cape Town.
87. Dolgin E. Long-acting HIV drugs advanced to overcome adherence challenge. Nat Med. 2014; 20:323–324. [PubMed: 24710366]
88. MTN (Microbicide Trials Network) - Studies. Accessed at: http://www.mtnstopshiv.org/studies on 11 November 2014.
89. Bunge, KE.; Dezzutti, CS.; Macio, I.; Hendrix, C.; Rohan, LC.; Marzinke, MA., et al. FAME-02: A Phase I Trial to Assess Safety, PK and PD of Gel and Film Formulations of Dapivirine [abstract 42LB]. Presented at the 2014 Conference on Retroviruses and Oppportunistic Infections; March 3–6, 2014; Boston.
90. Woodsong C, Musara P, Chandipwisa A, Montgomery E, Alleman P, Chirenje M, et al. Interest in multipurpose prevention of HIV and pregnancy: perspectives of women, men, health professionals

and community stakeholders in two vaginal gel studies in southern Africa. BJOG: An International Journal of Obstetrics & Gynaecology. 2014; 121:45–52. [PubMed: 25335840]

91. Golub SA. Tensions between the epidemiology and psychology of HIV risk: implications for pre-exposure prophylaxis. AIDS Behav. 2014; 18:1686–1693. [PubMed: 24719201]
92. Stott DB. The training needs of general practitioners in the exploration of sexual health matters and providing sexual healthcare to lesbian, gay and bisexual patients. Med Teach. 2013; 35:752–759. [PubMed: 23808564]
93. Sherman MD, Kauth MR, Shipherd JC, Street RL Jr. Communication between VA providers and sexual and gender minority veterans: a pilot study. Psychol Serv. 2014; 11:235–242. [PubMed: 24588107]
94. Sherman MD, Kauth MR, Shipherd JC, Street RL. Provider Beliefs and Practices About Assessing Sexual Orientation in Two Veterans Health Affairs Hospitals. LGBT Health. 2014; 1:185–191.
95. Lanier Y, Castellanos T, Barrow RY, Jordan WC, Caine V, Sutton MY. Brief sexual histories and routine HIV/STD testing by medical providers. AIDS Patient Care STDS. 2014; 28:113–120. [PubMed: 24564387]
96. Cahill S, Singal R, Grasso C, King D, Mayer K, Baker K, et al. Do ask, do tell: high levels of acceptability by patients of routine collection of sexual orientation and gender identity data in four diverse american community health centers. PLoS One. 2014; 9:e107104. [PubMed: 25198577]
97. Smith DK, Pals SL, Herbst JH, Shinde S, Carey JW. Development of a Clinical Screening Index Predictive of Incident HIV Infection Among Men Who Have Sex With Men in the United States. J Acquir Immune Defic Syndr. 2012; 60:421–427. [PubMed: 22487585]
98. Menza TW, Hughes JP, Celum CL, Golden MR. Prediction of HIV acquisition among men who have sex with men. Sex Transm Dis. 2009; 36:547–555. [PubMed: 19707108]
99. Alistar S, Grant P, Bendavid E. Comparative effectiveness and cost-effectiveness of antiretroviral therapy and pre-exposure prophylaxis for HIV prevention in South Africa. BMC Medicine. 2014; 12:46. [PubMed: 24629217]
100. Gomez G, Borquez A, Case K, Wheelock A, Vassall A, Hankins C. The cost and impact of scaling up pre-exposure prophylaxis for HIV prevention: a systematic review of cost-effectiveness modelling studies. PLoS Med. 2013; 10:e1001401. [PubMed: 23554579]
101. Juusola JL, Brandeau ML, Owens DK, Bendavid E. The cost-effectiveness of preexposure prophylaxis for HIV prevention in the United States in men who have sex with men. Ann Intern Med. 2012; 156:541–550. [PubMed: 22508731]
102. Desai K, Sansom SL, Ackers ML, Stewart SR, Hall HI, Hu DJ, et al. Modeling the impact of HIV chemoprophylaxis strategies among men who have sex with men in the United States: HIV infections prevented and cost-effectiveness. AIDS. 2008; 22:1829–1839. [PubMed: 18753932]
103. Paltiel AD, Freedberg KA, Scott CA, Schackman BR, Losina E, Wang B, et al. HIV preexposure prophylaxis in the United States: impact on lifetime infection risk, clinical outcomes, and cost-effectiveness. Clin Infect Dis. 2009; 48:806–815. [PubMed: 19193111]
104. Schneider K, Gray RT, Wilson DP. A cost-effectiveness analysis of HIV preexposure prophylaxis for men who have sex with men in Australia. Clin Infect Dis. 2014; 58:1027–1034. [PubMed: 24385445]
105. Mitchell AP, Simpson RJ. Statin cost effectiveness in primary prevention: a systematic review of the recent cost-effectiveness literature in the United States. BMC Res Notes. 2012; 5:373. [PubMed: 22828389]
106. Sharaf RN, Ladabaum U. Comparative Effectiveness Cost-Effectiveness of Screening Colonoscopy vs Sigmoidoscopy and Alternative Strategies. Am J Gastroenterol. 2013; 108:120–132. [PubMed: 23247579]
107. Jain S, Oldenburg CE, Mimiaga MJ, Mayer KH. Subsequent HIV Infection Among Men Who Have Sex with Men Who Used Non-Occupational Post-Exposure Prophylaxis at a Boston Community Health Center: 1997–2013. AIDS Patient Care STDS. 2014
108. Jain S, Oldenburg CE, Mimiaga MJ, Mayer KH. Longitudinal Trends in HIV Nonoccupational Postexposure Prophylaxis Use at a Boston Community Health Center Between 1997 and 2013. J Acquir Immune Defic Syndr. 2015; 68:97–101. [PubMed: 25321180]

109. Poynten IM, Jin F, Mao L, Prestage GP, Kippax SC, Kaldor JM, et al. Nonoccupational postexposure prophylaxis, subsequent risk behaviour and HIV incidence in a cohort of Australian homosexual men. AIDS. 2009; 23:1119–1126. [PubMed: 19417578]

110. Mehta SA, Silvera R, Bernstein K, Holzman RS, Aberg JA, Daskalakis DC. Awareness of post-exposure HIV prophylaxis in high-risk men who have sex with men in New York City. Sex Transm Infect. 2011; 87:344–348. [PubMed: 21357600]

111. Fernandez-Balbuena S, Belza MJ, Castilla J, Hoyos J, Rosales-Statkus ME, Sanchez R, et al. Awareness and use of nonoccupational HIV post-exposure prophylaxis among people receiving rapid HIV testing in Spain. HIV Med. 2013; 14:252–257. [PubMed: 23088284]