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CURRENT OPINION

Pre-Exposure Prophylaxis to Prevent HIV Infection: Current Status, Future Opportunities and Challenges

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Abstract As the global incidence of HIV exceeds 2 million new infections annually, effective interventions to decrease HIV transmission are needed. Randomized, placebo-controlled studies have demonstrated that daily oral antiretroviral pre-exposure prophylaxis (PrEP) with a fixed-dose combination tablet containing tenofovir disoproxil fumarate and emtricitabine can significantly reduce HIV incidence among diverse at-risk populations. In these studies, the efficacy of PrEP was correlated with levels of adherence. Official guidelines recommend provision of PrEP to people at greatest risk of HIV acquisition, and demonstration projects suggest that high levels of uptake and adherence are possible outside of controlled studies. However, several potential barriers to implementing PrEP remain. These challenges include low awareness and utilization of PrEP by at-risk individuals, uncertainty about adherence in 'real-world' settings, the majority of healthcare providers being untrained in PrEP provision, limited data about potential adverse effects from long-term use of tenofovir–emtricitabine, high costs of PrEP medications, and stigma associated with PrEP use and the behaviors that would warrant PrEP. Innovative pharmacologic chemoprophylactic approaches could provide solutions to some of these challenges. Less-than-daily oral dosing regimens and long-acting injectable medications could reduce pill burdens and facilitate adherence, and local delivery of PrEP medications to genital compartments via gels, rings and films may limit systemic drug exposure and potential toxicities. As the portfolio of chemoprophylactic agents and delivery systems expands to meet the diverse sexual health needs and product preferences of individuals who may benefit from PrEP, it is hoped that antiretroviral chemoprophylaxis could become an acceptable, feasible, and highly effective addition to existing HIV prevention strategies.

Key Points

The efficacy of daily oral pre-exposure prophylaxis (PrEP) with tenofovir–emtricitabine (TDF–FTC) has been demonstrated in several randomized studies, and normative guidance supports provision of this regimen to individuals at risk for becoming infected with HIV who can adhere to PrEP.

Demonstration projects that have provided TDF–FTC to at-risk individuals suggest that high levels of uptake and adherence are achievable in clinical settings, although low awareness of PrEP among people who could benefit, suboptimal HIV risk assessment skills and comfort with PrEP prescribing among healthcare practitioners, as well as cost and stigma are challenges that need to be addressed to successfully implement PrEP.

Novel pharmacologic strategies, including non-tenofovir antiretroviral agents and innovative routes of delivery, could offer numerous chemoprophylaxis options to engage potential PrEP consumers with diverse sexual health needs and personal preferences.

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1 Introduction

As there are 50,000 new HIV infections in the US [1] and approximately 2 million new infections worldwide each year [2], effective strategies to prevent HIV transmission are needed. Over the past few years, studies have demonstrated that the use of oral antiretroviral medications by HIV-infected individuals before immunologic decline, known as 'Treatment as Prevention' [3], and by HIV-uninfected individuals who are at risk for becoming infected, referred to as pre-exposure prophylaxis (PrEP) [4–7], can substantially decrease HIV transmission. These studies have generated optimism that bio-behavioral approaches to HIV prevention, which combine innovative pharmacologic approaches with complementary behavioral strategies, have the potential to alter the trajectory of the HIV epidemic.

In 2012, the US FDA approved a fixed-dose co-formulated tablet containing tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) [TDF–FTC] for use as a once-daily PrEP regimen among individuals at risk for becoming infected with HIV through sexual transmission [8]. The FDA approval was based on evidence from several placebo-controlled, phase III studies demonstrating the efficacy of this regimen [4, 6, 7]. In early 2014, the US Public Health Services (USPHS) issued guidelines for healthcare practitioners regarding provision of TDF–FTC to people at greatest risk of HIV acquisition [9]. With FDA approval and USPHS guidelines in support of prescribing TDF–FTC as PrEP to appropriate individuals, the stage has been set for implementing PrEP in care settings in the US.

However, challenges to successfully implementing PrEP exist. Awareness of PrEP among people who may benefit from this intervention has been low [10, 11], and many of these people may not be engaged in ongoing healthcare if they have no chronic medical condition. This lack of engagement in care could limit access to PrEP as TDF–FTC is only available by prescription and requires longitudinal clinical monitoring by providers. TDF–FTC is costly [12], therefore people without insurance, or those who have insurance but cannot afford monthly co-pays, may face financial barriers to accessing PrEP. The company that manufactures TDF–FTC, Gilead Sciences, maintains a patient assistance program, which can be helpful but requires knowledgeable consumers and providers to access it. The efficacy of PrEP is dependent on adherence [4–7, 13–15], and adherence to PrEP medications in efficacy studies has been variable [4–7, 13, 14], raising questions about whether people who are prescribed PrEP in clinical settings will be adherent enough to derive protection. Although TDF–FTC was found to be safe and generally well-tolerated over the 1- to 3-year time frame of completed efficacy and safety studies [4–7, 13, 14, 16], the safety of long-term use of TDF–FTC as PrEP has not yet been established, which some healthcare providers have viewed as a reason to be cautious about prescribing PrEP to otherwise healthy people [17–20].

To address concerns about cost, adherence, and safety with use of daily oral TDF–FTC, several novel approaches to administering antiretroviral drugs as PrEP are being explored. These solutions include (a) topical administration of antiretroviral medications to limit any systemic toxicities that may arise with oral tablets; (b) less-than-daily use of PrEP medications to reduce costs and overall drug exposure while potentially enhancing adherence; and (c) utilizing other classes of antiretroviral medications to decrease the risk of developing drug resistance among people who become infected with HIV while using PrEP, given the role of TDF–FTC as a first-line part of combination treatment of HIV infection [21] (Table 1).

The development of chemoprophylactic agents with desirable properties and novel methods of delivery could broaden the appeal of PrEP to those individuals who prefer alternatives to using daily oral TDF–FTC. However, even if new agents are developed for public use, the potential benefits of PrEP will only be realized if barriers to implementing PrEP in care settings are addressed, including stigma, low consumer awareness, provider-related barriers to identifying individuals at risk for HIV acquisition, adherence, and potential increases in sexual risk behaviors with PrEP use. If pharmacologic advances occur and innovative strategies to overcome social and behavioral barriers to implementation are developed, PrEP has the potential to impact HIV incidence as part of combination bio-behavioral approaches to HIV prevention.

2 Current status of Pre-Exposure Prophylaxis (PrEP)

TDF is a nucleotide reverse transcriptase inhibitor that has been studied as a potential PrEP medication because it was found to be generally safe when used for HIV treatment [22, 23], achieve high concentrations in genital compartments [24, 25], and have a high genetic barrier to resistance [26, 27]. Studies with macaques have shown that it can protect against retroviral challenge when administered as PrEP [28]. Concentrations of tenofovir are particularly high in rectal mucosa [29], which may provide protection to individuals who have exposure to HIV through receptive anal intercourse, including men who have sex with men (MSM), as well as heterosexual women. FTC is a nucleoside reverse transcriptase inhibitor (NRTI) that also has an excellent safety profile and achieves high concentrations in the female genital tract [24, 25], which could enhance its protective effects for women. Given numerous properties

Table 1 Pharmacologic agents undergoing evaluation for use as HIV antiretroviral pre-exposure prophylaxis

Drug name	Mechanism of action	Formulation(s) being evaluated	Status of trials[a]
TDF	NRTI	Oral, topical gel, drug-eluting ring	Daily oral TDF–FTC: FDA-approved based on preponderant evidence from efficacy studies
			iPrEx OLE: open-label use of daily oral TDF–FTC, completed
			Multiple demonstration projects with daily oral TDF–FTC, underway
			Ipergay: episodic dosing oral TDF–FTC, phase III efficacy study, underway
			ADAPT: fixed-interval plus post-exposure dosing oral TDF–FTC, phase II safety and acceptability study, underway
			CAPRISA-004: pericoital intravaginal gel, completed; demonstrated efficacy
			VOICE: daily intravaginal gel, completed; did not demonstrate efficacy
			FACTS-001: pericoital intravaginal gel, phase III efficacy study, underway
			Intravaginal rings: phase I studies, ongoing
FTC	NRTI	Oral	See above for trials with TDF–FTC
Dapivirine	NNRTI	Drug-eluting ring, rapidly dissolving film, gel	ASPIRE: intravaginal ring, phase III efficacy study, ongoing
			The Ring Study: intravaginal ring, phase III efficacy study, ongoing
			Intravaginal ring, films, gel: phase I–II studies, completed or ongoing
Rilpivirine	NNRTI	Long-acting injection	Phase I–II, completed and ongoing
Cabotegravir	Integrase strand transfer inhibitor	Long-acting injection	Phase I–II, completed and ongoing
Maraviroc	CC chemokine receptor inhibitor	Oral, drug-eluting ring	NEXT-PrEP: phase II safety and acceptability study, oral (with or without TDF or FTC), underway
			Intravaginal ring: phase I completed
Darunavir	Protease inhibitor	Drug-eluting ring	Intravaginal ring (with or without dapivirine): preclinical, completed

FTC emtricitabine, *NRTI* nucleotide reverse transcriptase inhibitor, *NNRTI* non-nucleoside reverse transcriptase inhibitor, *OLE* open-label extension, *TDF* tenofovir disoproxil fumarate

[a] Trial stage information adapted from the AIDS Vaccine Advocacy Coalition [75]

that would be favorable for PrEP agents, TDF–FTC and TDF alone were the first agents to be tested in large-scale human studies.

Several large, randomized, placebo-controlled studies have demonstrated that daily oral PrEP with TDF–FTC is safe, well-tolerated, and efficacious among populations at increased risk of becoming infected with HIV, including men and transgender women who have sex with men [6], members of HIV-serodiscordant couples [4], heterosexual men and women living in areas with generalized HIV epidemics [7], and people who inject drugs [5]. These studies demonstrated decreases in the relative risk of acquiring HIV infection among groups randomized to use TDF–FTC that ranged from 44 to 75 % [4–7]. High adherence to study medications, based on having detectable levels of TDF or FTC at study visits, was correlated with 92 % efficacy in one study [6]. Two additional studies of daily TDF–FTC or TDF alone among young African women at risk of HIV acquisition were discontinued early after interim analyses suggested that efficacy could not be demonstrated over the planned timeline of the studies [13, 14]. However, as blood tests to detect study drug in these trials suggested that few women were taking study tablets as instructed [13, 14], levels of adherence were probably too low to demonstrate efficacy.

TDF–FTC has been associated with nephrotoxicity [30, 31] and loss of bone mineral density [32, 33] in a minority of patients when used as treatment for HIV infection. Studies of PrEP demonstrated no differences in rates of serious renal or bone-related adverse outcomes between participants assigned to use PrEP or placebo [4–7, 14]. However, more participants assigned to use TDF–FTC had decreases in renal function that resolved with discontinuation of drug [34, 35], and were more likely to experience a small ($\sim$1 %) decline in bone mineral density. The decline in bone mineral density is of uncertain clinical significance since it was not associated with clinical findings, and when tenofovir is used for HIV treatment, any bone changes tend to plateau after 12–18 months on medication [36, 37]. As participants in PrEP studies were generally healthy and needed to have normal renal function to enroll, monitoring for kidney and bone toxicities with

PrEP use in care settings and accrual of long-term safety data will be important. Tolerability of TDF–FTC as PrEP in efficacy studies was generally excellent; approximately 10 % of participants experienced gastrointestinal symptoms such as nausea or diarrhea over the first 4 weeks of use, but these symptoms tended to resolve without additional interventions and were not associated with study product discontinuation [4–7, 14].

Based on the evidence of efficacy, safety, and tolerability of TDF–FTC from these controlled studies involving thousands of participants in several continents, several demonstration projects are being conducted to assess the acceptability and feasibility of PrEP in care settings. A demonstration project known as the Demo Project provided daily TDF–FTC at no cost to men and transgender women who have sex with men at risk for HIV acquisition for a 1-year period in San Francisco, Miami, and Washington, DC. In the Demo Project, interest in using PrEP was high; in San Francisco, 58 % of nearly 1,000 MSM who were screened and eligible for enrollment elected to use PrEP [38]. Although approximately one-third of participants self-referred to the study, the remaining two-thirds enrolled after referral by clinicians, suggesting that interest in using PrEP may be high among MSM who are actively seeking PrEP and among those whose healthcare providers recommend this intervention [39]. Nearly all (98 %) Demo Project participants had detectable levels of TDF–FTC on analyses of dried blood spots, and three-quarters had drug levels consistent with taking four or more doses per week [39]. Overall, the Demo Project findings suggest that translating PrEP utilization from controlled studies to selected real-world settings is feasible among urban MSM in the US.

3 Remaining Challenges

Although findings from demonstration projects in the US are encouraging regarding potential uptake and adherence to PrEP, few people have been prescribed PrEP in clinical settings, which is probably a result of low awareness of PrEP among people in the community and a need for greater practitioner training in identifying people most likely to benefit from PrEP and subsequently prescribing PrEP [40]. A national study of US retail pharmacy data estimated that fewer than 2,000 people in the US had been prescribed TDF–FTC for use as PrEP, as of early 2013 [41], which was 2 years after this regimen was demonstrated to be efficacious (the iPrEx study [6]) and interim guidance from the US Centers for Disease Control and Prevention (CDC) to healthcare practitioners regarding PrEP provision had been released [42]. Studies of MSM also suggest gradual uptake of PrEP in the community; surveys of several thousand members of a large online network for MSM in the US found that only 1 % of participants had used PrEP as of early 2011, and only 3 % had used PrEP as of early 2014 [10, 11]. One explanation for low utilization of PrEP is limited community awareness as these surveys found that only one-quarter of the MSM surveyed had heard of PrEP, even though a majority of respondents would be interested in using daily PrEP [10, 11]. Creative ways to disseminate messages about PrEP directly to potential consumers, including using online media and educational materials in healthcare settings, may be helpful in disseminating knowledge about PrEP and facilitate uptake. The study also found that MSM who were less comfortable disclosing their sexuality to their providers were less likely to have used PrEP, an additional challenge to uptake [43].

Healthcare practitioners are generally aware of PrEP [17, 40], although some have indicated that additional training would be important to help them feel comfortable prescribing PrEP [40]. Providers may also benefit from training to enhance skills with HIV risk assessments as comprehensive discussions about sexual behaviors and sexual orientation, which are important for identifying people who may benefit from PrEP, are infrequent in clinical settings [44–46]. Debate exists about which providers are best positioned to prescribe PrEP. Some HIV specialists have postulated that generalists, with whom most HIV-uninfected individuals would engage in care, would be optimal for prescribing PrEP to their patients. In contrast, generalists have expressed a need for more training before prescribing antiretroviral medications [18]. Sexually transmitted diseases (STDs) clinicians are likely to provide care to a population enriched with people at greatest risk for acquiring HIV; however, STD clinics may not be geared towards delivering the longitudinal care that would be required for PrEP provision. The solution may be to (a) provide basic training about PrEP to all clinicians who may have contact with people at risk of becoming infected, including primary care providers; (b) offer more comprehensive training to practitioners who have more frequent contact with people at highest risk or who are interested in becoming local experts in HIV preventive care; and (c) encourage providers who prefer not to prescribe PrEP to refer appropriate patients to expert colleagues. Some clinicians may also believe that condoms and other behavioral interventions should be prioritized over chemoprophylaxis, which could impact their willingness to prescribe PrEP. To address this potential barrier, trainings for providers should include the rationale that biobehavioral prevention (i.e. combining behavioral and pharmacological interventions) is needed given persistently high rates of HIV infection despite longstanding promotion of condom use.

The high cost of daily TDF–FTC, over US$10,000 annually [12], could limit access to PrEP for many people without insurance. Financial constraints could also be a major barrier to implementing PrEP in government-funded or -subsidized health systems. Gilead Sciences, the manufacturer of TDF–FTC, has a drug assistance program for uninsured patients in the US and will provide TDF–FTC at no cost to qualified people [47]. For those people with insurance, most third-party insurers will cover the cost of TDF–FTC given it is FDA-approved to be prescribed as PrEP, and several state Medicaid formularies have declared that they will cover the cost of PrEP for their beneficiaries [48, 49]. In addition to cost, stigma associated with using PrEP could prevent some people from utilizing this intervention. Some participants in PrEP efficacy studies in Africa reported that they were reluctant to take study medications provided to them because of fears that others would believe that they were HIV-infected [50]. Vocal rhetoric from organizations that oppose widespread use of PrEP, such as the AIDS Healthcare Foundation [51], have received substantial amounts of media attention in the US [52], which could be expected to dissuade some potential consumers from initiating PrEP. Efforts to de-stigmatize PrEP will be important to create a safe environment for people to seek and initiate PrEP.

4 Novel Solutions

Recent advances in the pharmacology of antiretroviral medications could potentially overcome some of the barriers to successfully implementing daily oral TDF–FTC as PrEP, such as adherence challenges, costs, possible toxicities from systemic exposure, and potential selection of drug-resistant viral strains among those who become infected with HIV while using PrEP.

Studies are testing whether oral TDF–FTC is efficacious when used according to a non-daily schedule, which could reduce costs and systemic exposure and possibly improve adherence among people who have episodic risky behaviors and prefer not to take daily pills. A study of episodic use of TDF–FTC among MSM in France, Quebec, and Berlin (Ipergay) randomized participants to use two tablets of TDF–FTC or placebo prior to exposure, then one tablet 24 h later, with the last tablet taken 48 h after the sex act. The study was stopped early after interim analyses found that TDF–FTC was protective against HIV acquisition. However, the level of efficacy, medication adherence, and the patterns of sexual risk among study participants are not expected to be presented until 2015 [53]. These results will be important to determine whether they were using TDF–FTC in an episodic versus daily or near-daily manner. Additional studies are assessing the pharmacokinetics and acceptability of fixed-interval use of TDF–FTC (i.e. twice weekly) plus post-exposure dosing (the ADAPT study) [54], which could decrease overall pill burden and drug exposure compared with daily use. An open-label study of daily TDF–FTC as PrEP among 1,225 men and transgender women who have sex with men (iPrEx OLE) found that none of the participants who took four or more pills weekly became HIV-infected during the study, which represented high levels of protection given an HIV incidence rate of 4.7 infections per 100 person-years if drug was not detected [15]. The findings from iPrEx OLE suggest that daily TDF–FTC may be 'forgiving' in terms of missed doses, which could encourage some people to initiate daily TDF–FTC who might not otherwise utilize this intervention if strict adherence was essential.

Additional oral antiretroviral medications with other mechanisms of action than TDF–FTC are being evaluated for use as PrEP. Maraviroc, an entry inhibitor that inhibits CC chemokine receptor 5 (CCR5) on host CD4 + T cells, has an excellent safety profile and concentrates on genital tissues [55]; it is being tested as a PrEP agent alone or in combination with TDF or FTC in a safety and acceptability study [56]. This agent would be attractive for use as PrEP as it is not typically used as a first-line agent for treating HIV infection [21]; therefore, any potential selection of drug-resistant viral strains among those who become infected while using maraviroc as PrEP would be unlikely to impact initial HIV treatment regimens.

Two phase III studies among African women at risk for HIV infection have tested the safety and efficacy of a topical intravaginal gel containing tenofovir [13, 57]. In one of these studies (CAPRISA-004), participants were instructed to apply the gel within 12 h before sex and another dose within 12 h after sex [57], whereas in the other study (VOICE), women were instructed to apply the gel on a daily basis irrespective of their sexual behaviors [13]. Both studies found the gel to be safe and well-tolerated but only the study of pericoital dosing demonstrated efficacy (39 %), which may have been due to differences in adherence or the pharmacology of daily versus pericoital dosing [57, 58]. A third study (FACTS-001) is testing the pericoital dosing regimen with this gel and could act as a tiebreaker [59], such that successful demonstration of efficacy could allow for licensure and production of this product for public use. Topical gels have also been formulated for rectal use, which could be utilized by MSM or women who engage in receptive anal sex and prefer to use topical rather than oral forms of PrEP [60]. An expanded safety and acceptability study of rectal tenofovir is underway among MSM in the US, Peru, Thailand, and South Africa.

Intravaginal rings that elute antiretroviral medications and could be left in situ for prolonged periods (e.g.

1 month), similar to contraceptive rings that are currently prescribed in clinical practice, could offer the benefits of other topical formulations (e.g. limited systemic drug exposure) without the potential adherence challenges associated with pericoital or daily application. Intravaginal rings containing dapivirine, a non-NRTI (NNRTI), alone or with maraviroc, were shown to be safe and well-tolerated in a pilot study [61], although only dapivirine achieved adequate levels in genital tract tissues [62]. Two efficacy studies of dapivirine-containing rings are underway and should be able to report their findings in 2016. Earlier phase studies are currently evaluating rings containing tenofovir or darunavir, a protease inhibitor [63].

Topically-applied, rapidly-dissolving films containing antiretroviral medications are also being tested. In a pilot study, a film containing dapivirine was shown to achieve drug concentrations in vaginal tissues similar to those measured after 28 days of using an intravaginal ring containing dapivirine [64]. Some women in the study did not accurately place the self-administered strips in the vagina, therefore the strips are being modified to facilitate proper placement for future studies [64].

A promising method for delivering antiretroviral medications for chemoprophylaxis or treatment of HIV infection is through parenteral injections of long-acting medications, which could overcome adherence barriers for people who may not be able or willing to take daily medications but who could present to care on an intermittent basis for medication dosing. Long-acting crystalline nanoformulations of rilpivirine (rilpivirine LA), an NNRTI, and cabotegravir, an integrase strand transfer inhibitor, have been developed and tested in animal models and early-phase human studies. In a study of HIV-uninfected volunteers, single doses of rilpivirine LA were well-tolerated, achieved peak concentrations after approximately 1 week, and had prolonged plasma and genital exposure, with measurable levels in both compartments at day 84 [65]. One participant who became infected with HIV while using the lowest dose of rilpivirine tested during the study was found to have sustained low levels of drug and selection of a viral strain resistant to rilpivirine and other NNRTIs [66], which underscores the importance of optimizing drug levels when utilizing long-acting agents for chemoprophylaxis. Another preclinical study demonstrated significant protection against vaginal retroviral challenge after a single dose of rilpivirine LA in a mouse model, although protection waned by 3 weeks post-injection [67]. An additional preclinical study with healthy volunteers demonstrated that rilpivirine LA achieved greater tissue concentrations in rectal versus vaginal or cervical compartments, and that viral suppression in an ex vivo explant model was achieved only in rectal tissue [68]. Given the lack of viral suppression in vaginal tissue in this model, further studies are being planned to optimize dosing of this agent for multiple mucosal compartments. For cabotegravir, studies with macaques demonstrated that schedules of drug administration correlating to quarterly dosing in humans offered high levels of protection against viral challenge [69], and phase II safety studies with doses at 12 week intervals are underway [70]. Notably, rilpivirine and cabotegravir do not have significant pharmacokinetic interactions with each other, raising the possibility that these two agents could be co-administered as PrEP or HIV treatment [71].

The concept of co-formulating preventive agents for the purpose of HIV prevention has been extended to include multipurpose technologies that can meet multiple sexual and reproductive health needs of consumers, in particular women who may benefit from preventing HIV infection, other sexually transmitted infections (e.g. herpes simplex virus), and unintended pregnancy [72]. Multipurpose products may be long-acting, such as injections or rings, or 'on demand', such as topical gels or diaphragms (or other barrier protection) co-administered with gels. Multipurpose products are generally in the early stages of development, but phase I studies of some products, such as an intravaginal ring containing a contraceptive agent (levonorgestrel) and tenofovir, are underway [63, 73].

5 Conclusions

In 2010, UNAIDS described its striking goal of revolutionizing HIV prevention and ultimately "getting to zero" new HIV infections worldwide [74]. For perhaps the first time since the beginning of the HIV epidemic over 3 decades ago, there are realistic expectations that substantial reductions in HIV incidence can be achieved if novel bio-behavioral approaches to HIV prevention can be successfully implemented on a global scale. PrEP is likely to decrease HIV transmission among those who can achieve sufficient levels of adherence, and experiences with PrEP use among early adopters appear to be positive, offering encouraging evidence that wider implementation of oral PrEP among those at greatest risk for HIV acquisition may be possible. For people at risk of HIV acquisition who are not able to benefit from using daily oral TDF–FTC for various reasons, whether due to inability or unwillingness to adhere to this regimen or preferences to use alternative approaches, additional dosing regimens, such as episodic use of TDF–FTC and novel agents with innovative routes of delivery, may be available in the next few years. Hopefully, a diverse array of effective chemoprophylaxis options could facilitate broad uptake by fulfilling the product preferences of all individuals who may benefit from PrEP. Stigma and insufficient training of healthcare

practitioners could jeopardize the success of PrEP programs, therefore it will be important to devote resources to these social and provider-related barriers while seeking advances in pharmacology. If many of the people at greatest risk for HIV acquisition can routinely access and utilize PrEP, and if HIV-infected individuals can initiate antiretroviral treatment early in the course of their infection, then these combined bio-behavioral strategies could have the capability of greatly reducing HIV incidence worldwide.

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