Pre-exposure Prophylaxis for Human Immunodeficiency Virus

The Past, Present, and Future

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KEYWORDS

• Pre-exposure prophylaxis • Implementation • Adherence • HIV prevention
• Biomedical intervention

KEY POINTS

- Our knowledge of pre-exposure prophylaxis (PrEP) as a means to prevent human immunodeficiency virus (HIV) acquisition has increased greatly over the decade.
- Evidence from clinical trials conducted among multiple high-risk populations suggests that oral PrEP, if adhered to, can be effective in reducing the risk of HIV acquisition among HIV-uninfected individuals.
- The key issues with PrEP use that have arisen as a result of these trials warranting further research include adherence, risk of drug resistance, and behavioral disinhibition.
- Studies further informing PrEP utilization are ongoing to address issues such as alternate dosing strategies and delivery methods, long-term side effects, and effectiveness in real-world settings.
- PrEP implementation is underway; future studies and activities will need to focus on optimizing PrEP regimens and adherence, increasing education and uptake among high-risk populations and providers, and establishing systems to monitor and evaluate PrEP use.

INTRODUCTION

Human immunodeficiency virus (HIV) prevention research has rapidly advanced over the last decade, with several large-scale research studies demonstrating that antiretrovirals (ARVs) can be used not only for the prevention of mother-to-child transmission, post-exposure prophylaxis, and treatment as prevention (TasP) but also for

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pre-exposure prophylaxis (PrEP). PrEP for HIV prevention involves the use of ARV medications, optimally delivered in concert with risk-reduction counseling and behavioral interventions, such as condom provision and use, to prevent HIV infection among those who are HIV uninfected but at high risk for infection. PrEP entails having an HIV-uninfected individual take ARVs orally or topically (either vaginally or rectally) to prevent sexual or parenteral infection with HIV.[1,2]

The concept of PrEP is not new and has been used as a prevention method for a variety of illnesses, including prevention against rabies[3] and malaria[4] among those traveling to endemic areas. PrEP was considered as a strategy to reduce the number of new HIV infections given the continued high HIV incidence rates both nationally and globally. Globally, an estimated 2.5 million new infections occur every year[5]; in the United States, there are an estimated 50,000 new infections annually.[6] Without an effective HIV vaccine on the horizon, the need for high-impact HIV prevention tools is essential. These tools include interventions such as TasP for HIV-infected individuals; routine HIV testing and linkage to care; and biomedical interventions, such as male circumcision.[7]

Further research into PrEP will add to the toolbox of HIV prevention methods.

This article describes the prior research that informs our current understanding of PrEP, summarizes ongoing research in the area, and highlights key issues that must be addressed in order to optimize the use of this HIV prevention tool.

THE PAST: DEVELOPMENT OF PRE-EXPOSURE PROPHYLAXIS AS AN HIV PREVENTION INTERVENTION

Prior Evidence of Use of Antiretrovirals for Prevention

Proof of concept for the use of PrEP to prevent HIV infection stems from research conducted in both animals and humans. The use of PrEP and postexposure prophylaxis to prevent mother-to-child transmission of HIV has been proven to reduce the risk of transmission by as much as 99%.[8–10] Similarly, the use of postexposure prophylaxis in situations in which a person has had a high-risk sexual or parenteral exposure, or a high-risk occupational exposure, has been shown to be effective with an 81% reduction in transmission.[11] This proof of concept led to the first HIV PrEP trials using animal models.

Animal Trials

The biological plausibility of using ARVs as PrEP for HIV prevention was first examined using animal models as early as 1995. These animal studies also assisted in understanding issues regarding which drugs would be efficacious, drug delivery, and dosing. Among the many ARVs available, tenofovir disoproxil fumarate (TDF), a nucleoside reverse transcriptase inhibitor, has been widely studied for use as both oral and vaginal PrEP. This ARV is generally well-tolerated in HIV-infected persons and has minimal side effects.[12] The combination of tenofovir (TDF) and emtricitabine (FTC) (Truvada) has also been extensively studied for use with PrEP and has been used in many of the animal and clinical trials conducted to date.

The first few nonhuman primate studies assessed the efficacy of injectable TDF for PrEP. In 1995, Tsai and colleagues[13] published data that found that 4 weeks of daily injections of TDF starting 48 hours before, 4 hours after, or 24 hours after intravenous simian immunodeficiency virus (SIV) challenge resulted in 100% protection in macaques. In 1998, Van Rompay and colleagues[14] also concluded that 2 injectable doses of TDF 4 hours before and 20 hours after oral SIV challenge resulted in 100% protection among newborn macaques.

Although the initial injectable PrEP animal studies found 100% protection, early studies examining daily oral dosing with TDF followed by oral or rectal exposure did not. A series of studies found either no or partial efficacy after oral exposure[15,16] or delayed infections after rectal exposure.[17] Not until 2008 did studies looking at FTC in combination with oral TDF begin to show efficacy in reducing the risk of infection. In 2008 and 2010, studies were published that demonstrated that daily oral and intermittent oral PrEP with FTC and TDF/FTC was efficacious, providing either partial or complete protection.[18–20] These findings demonstrated not only that TDF/FTC was able to provide a high level of protection but also that TDF/FTC could be used in lieu of TDF for PrEP, thereby lowering the risk of potential drug resistance in the event of seroconversion.[19] Finally, studies of vaginal delivery of 1% TDF gel applied topically before exposure were also shown to be fully protective.[21]

Hence, these animal studies provided evidence that either TDF or and TDF/FTC could be used to prevent infection; given through injections; taken orally either daily or intermittently; and, most importantly, were efficacious in providing protection from oral, rectal, and vaginal exposure.

Randomized Clinical Trials Among Humans

These nonhuman primate study findings coupled with other confirmatory animal studies[22] supported the introduction of clinical trials of PrEP among humans. Since 2011, results from phase I, II, and III clinical trials have focused on different medications, delivery methods, and high-risk populations. Many of these studies have confirmed the efficacy of ARVs for HIV prevention among high-risk populations, including men who have sex with men (MSM), high-risk heterosexual men and women, serodiscordant couples, and most recently among injection drug users (IDUs) (**Table 1**).[23–28]

Following safety evidence provided by phase I and phase II studies of PrEP among HIV-uninfected persons using TDF and TDF/FTC,[22,29] several landmark studies demonstrated the efficacy of PrEP in reducing HIV transmission. Five key studies have paved the way for future use of PrEP: the Center for AIDS Program of Research in South Africa (CAPRISA) 004, Pre-exposure Prophylaxis Initiative (iPrEx) trial, TDF2, Partners PrEP, and the Bangkok Tenofovir study. The CAPRISA 004 trial sought to assess the safety and efficacy of using a 1% vaginal gel formulation of TDF among heterosexual women in Africa.[23] Participants used the gel both before and after coitus. After 30 months of follow-up, it was determined that the use of the TDF gel reduced the risk of infection by 39% when compared with the placebo arm. Subsequent as-treated analyses found that among women taking greater than 80% of doses, the efficacy increased to 54%, although these post hoc analyses should be interpreted cautiously. Thus, the CAPRISA study was able to confirm that a vaginal gel for PrEP could be used safely and effectively by women for HIV prevention.

The iPrEx trial was one of the first to examine the efficacy of daily oral TDF/FTC use for PrEP among MSM and among transgender women compared with placebo. Approximately 2500 participants were enrolled from multiple countries and followed for a median of 21 months. In as-treated analyses, daily oral TDF/FTC was found to reduce the risk of infection by 44% among participants in the TDF/FTC arm, with further as-treated analyses indicating that among those taking pills on 90% or more of days, the efficacy increased to 73% and was more than 90% in those with detectable drug levels.[26]

The TDF2 study, conducted in Botswana, sought to assess the efficacy of oral TDF/FTC as PrEP among heterosexual men and women. Participants were randomized to receive either daily oral TDF/FTC or placebo. Taking daily TDF/FTC reduced the risk of

Table 1
Summary of completed PrEP trials

Study Name	Study Start Date	Target Population and Sample Size	Study Locations	Study Regimen	Overall Efficacy (%) (95% CI)	Efficacy Among Adherent Population[a] (%)
Bangkok Tenofovir Study	2005	IDUs (N = 2413)	Thailand	Oral TDF	49 (10–72)	74
CAPRISA	2007	Heterosexual women (N = 889)	South Africa	Vaginal TFV	39 (6–60)	54
TDF2	2007	Heterosexual men and women (N = 1219)	Botswana	Oral TDF/FTC	62 (22–83)	78
iPrEx	2007	MSM and transgender women (N = 2499)	Brazil, Ecuador, Peru, South Africa, Thailand, United States	Oral TDF/FTC	44 (15–63)	73–90
Partners PrEP	2008	Serodiscordant heterosexual couples (N = 4758)	Kenya, Uganda	Oral TDF Oral TDF/FTC	TDF: 67 (44–81) TDF/FTC: 75 (55–87)	86–90
FEM-PrEP	2009	Heterosexual women (N = 2120)	Kenya, South Africa, Tanzania	Oral TDF/FTC	6 (−52 to 41)	18–25
VOICE	2009	Heterosexual women (N = 5029)	Uganda, South Africa, Zimbabwe	Oral TDF Oral TDF/FTC	TFV: 15 (−20 to 40) TDF: −49 (−129 to 3) TDF/FTC: −4 (−49 to 27)	Study stopped for futility

Abbreviations: CAPRISIA, Center for AIDS Program of Research in South Africa; CI, confidence interval; iPrEx, Pre-exposure Prophylaxis Initiative; TFV, 1% tenofovir vaginal gel; VOICE, Vaginal and Oral Interventions to Control the Epidemic.

[a] Adherence was determined using different outcomes according to each study protocol.

HIV infection by 62% and increased to 78% among those confirmed to have received drug in the prior 30 days.[24] When one previously undiagnosed HIV-infected participant receiving TDF/FTC developed drug resistance, the TDF2 study results highlighted the important potential for drug resistance among seroconverters and the need to identify these people as early in their infections as possible.

The Partners PrEP study was conducted in Kenya and Uganda among HIV-1 serodiscordant couples. Participants were randomized to one of three study arms: daily oral TDF, daily oral TDF/FTC, or matching placebo.[27] Final analysis showed a 67% reduction in the risk of HIV transmission among the TDF arm and a 75% reduction among the TDF/FTC arm with no issues regarding safety or tolerability.[27] When assessing efficacy among those with detectable TDF drug levels, efficacy was 86% and 90% among the TDF and TDF/FTC arms, respectively.[30]

Finally, the Bangkok Tenofovir study in Thailand was the only study to date to evaluate the use of PrEP among IDUs.[31] A unique feature of this study was that study participants received oral TDF or placebo via directly observed therapy, rather than independently. Primary analysis found a 49% reduction in HIV infection among the participants receiving TDF compared with a 74% reduction among those observed while taking their medications who had detectable TDF drug levels.[25]

Although these landmark studies support the efficacy of oral PrEP among MSM, heterosexuals, men, women, and IDUs, as well as vaginal PrEP among women, 2 other large PrEP studies have shown little to no efficacy among women. The Vaginal and Oral Interventions to Control the Epidemic (VOICE) study, which enrolled women living in Southern Africa, randomized women into one of 5 study arms. These arms included daily vaginal gel with and without TDF, daily oral TDF, daily oral TDF/FTC, and daily matching oral placebo. Initial analysis found that neither the daily oral nor the vaginal TDF arms reduced the risk of HIV infection, and final analyses found that the daily oral TDF/FTC arm was also not efficacious in reducing the participants' risk of HIV infection.[32] Since publication of these findings, additional analyses determined that adherence, as measured by product use, was very low among study participants and may have explained these disparate results.

Similar to the VOICE trial findings, the FEM-PrEP study sought to assess the efficacy of PrEP among African heterosexual women, randomizing participants to receive either daily oral TDF/FTC or placebo.[28] The study was terminated prematurely after interim analyses found similar rates of HIV infection among both study arms. Poor adherence, as in the VOICE trial, was thought to explain the lack of efficacy, as low levels of plasma TDF were measured among women who became infected during the study period.[33] These studies underscore the important role of adherence in both researching and implementing PrEP.

Implementation of Pre-exposure Prophylaxis

With the results from most of the phase III trials showing efficacy, in July 2012, the US Food and Drug Administration (FDA) approved licensure of TDF/FTC for daily oral use as PrEP among HIV-uninfected persons at high-risk for infection.[34] Although other ARVs have been evaluated for use as for PrEP, TDF/FTC is currently the only approved ARV with this indicated use. This instance was the first time that an ARV for HIV has been approved for both prevention in uninfected persons and for treatment of HIV. In response to the availability of this new biomedical prevention intervention, the US Centers for Disease Control and Prevention has issued guidance documents for clinicians considering prescribing PrEP to MSM, IDUs, and heterosexuals at high risk for HIV.[35–38] The World Health Organization has also issued guidance for the use of PrEP among serodiscordant couples, MSM, and transgender women who have sex with men.[39]

Multiple demonstration projects are underway to assist in the scale-up of PrEP as an HIV prevention method in the United States and in Africa; these include open access programs to support PrEP use provided by the pharmaceutical company that makes Truvada,[40] HPTN 073,[41] and various locally administered agency-based programs.[42]

Lessons Learned from the Past

Safety

All of the aforementioned studies have shown acceptable levels of safety and tolerability. Most common short-term side effects reported in these studies have included nausea, headaches, and weight loss[24,26–28]; however, monitoring for longer-term side effects, such as hepatic toxicity, kidney toxicity, and bone density loss, will need to be conducted.

Resistance

Poor adherence when using ARVs for PrEP can increase one's risk of infection with resistant strains if a person seroconverts and can subsequently limit one's future treatment options.[43] Reassuringly, when participants on the studies referenced seroconverted, drug resistance among incident cases was relatively rare. As few as none and as many as 3 participants were reported to develop resistance,[12,24,26,27,44] usually to FTC, although it is important to remember that these studies were not statistically powered to assess the development of resistance.

Adherence

Adherence has often been described as the Achilles heel of PrEP, with both the VOICE and FEM-PrEP studies emphasizing the essential role that adherence plays in ensuring the efficacy of using ARVs for PrEP.[45] As discussed, among five key PrEP clinical trials, efficacy was notably higher among the more adherent participants when compared to the overall study population.[24,26–28,46–49] For example, in iPrEX, the overall efficacy was 44%; but among those with detectable drug, the efficacy increased to 92%.[26] Similarly, the FEM-PrEP study showed that the overall efficacy was a mere 6%, possibly because of low adherence.[28]

For many of these studies, post hoc, as-treated analyses should be interpreted cautiously, as they violate assumptions of intention-to-treat analysis and, thus, may reflect underlying differences between persons who adhere to medications and those who do not, rather than the intrinsic benefits of the medication itself. Therefore, going forward, when prescribing PrEP, education, assessment of a patient's ability to adhere to treatment, as well as follow-up safety monitoring visits will be critical in reducing the risk of HIV acquisition and development of resistant infection. Studies, described hereafter, are underway to further study interventions to increase adherence among PrEP users.

Behavioral disinhibition

With the availability and use of PrEP, concerns have been raised regarding behavioral disinhibition/risk compensation (eg, having more high-risk sex partners or engaging in more unprotected and higher-risk sex acts because one is taking PrEP).[50,51] PrEP is a part of a combination prevention method; therefore, all persons receiving it through clinical trials also receive risk-reduction counseling and are encouraged to use condoms. None of the studies described earlier have observed any significant behavioral disinhibition, yet this may present a real concern among persons using PrEP in nonclinical trial settings. Adherence to PrEP regimens needs to be a focus area as PrEP is scaled up in community settings; ensuring adequate complementary behavioral education and services alongside PrEP delivery will also be critical.

THE PRESENT: ASSESSMENT OF NEW REGIMENS, DELIVERY MECHANISMS, AND FEASIBILITY

The issues presented in the previous section regarding PrEP safety, the development of viral resistance among seroconverters, adherence, and behavioral disinhibition inform many of the studies currently in progress. Even as PrEP is rapidly translated into practice, research continues to further our knowledge of this biomedical prevention strategy.[52–54] Current studies are designed to identify prevention regimens more effective than TDF/FTC with less viral resistance potential as well as to develop new modes of administration that overcome barriers to adherence.[55–65] Further, several open-label demonstration projects are being conducted that aim to characterize the correlates of PrEP uptake in key affected populations.[41,42] This section describes examples of ongoing research that leverage past successes of PrEP and strive to expand opportunities for PrEP use into the future.

New Pre-exposure Prophylaxis Regimens

Given the use of TDF/FTC in many first-line regimens for HIV-infected persons, one key concern is identification of a PrEP agent for which the development of resistance among seroconverters, however few there are, would have less impact. Maraviroc (MVC) was FDA approved in 2007 as the treatment of HIV following demonstration of virologic suppression among HIV-infected persons.[66] This CCR5 antagonist has been used safely among this population and found to have an acceptable safety profile, and it is currently not a first-line treatment regimen.[54,66–68] MVC was considered a potential agent for use as PrEP because of its biological mechanism of action. Unlike TDF and FTC, MVC surrounds the CCR5 coreceptor, allowing MVC to interrupt viral binding early in the HIV lifecycle. Early primate studies demonstrated that MVC prevented simian HIV (SHIV) infection against rectal HIV-1 challenges as well as when it was used as a microbicide agent against vaginal challenges, although more recent studies of MVC among macaques indicated no HIV prevention activity against rectal SHIV compared with controls, even in the presence of adequate blood levels.[19,67,69–71] Other studies have shown protection against vaginal introduction of SHIV in macaques using MVC,[72–74] though results using intravaginal rings (IVR) among primates have been mixed.[75,76] These characteristics in combination with its ability to concentrate high levels of drug in the cervicovaginal and rectal tissues relative to plasma levels make MVC a potentially powerful PrEP agent to explore in humans. MVC has been studied among 450 HIV-uninfected persons with rheumatoid arthritis,[77] but this was for short-term (12 weeks) use only and not among a population identified as at high risk for HIV. However, its favorable safety results contributed to another ongoing clinical trial in the United States. In 2011, the National Institutes of Health–funded HIV Prevention Trials Network (HPTN) launched HPTN 069, a phase II, randomized, placebo-controlled, double-blinded, multisite study of MVC as PrEP, comparing 3 arms: MVC versus MVC+TDF versus MVC+FTC versus TDF+FTC (**Table 2**). This study, initially open only to men and transgender women (male at birth), expanded eligibility in 2013 to include biologically born women. Data from HPTN 069, will characterize the safety and tolerability of MVC among an HIV-uninfected population at an elevated risk for HIV and determine whether this potentially promising PrEP agent will move forward to phase III efficacy trials.[68]

Novel Formulations

In addition to the search for additional PrEP agents that are effective, better tolerated, and with low potential to develop resistance, as well as not competing with first-line

Table 2
New PrEP agents under study in 2014

Agent	Description of Drug	Methods of Delivery Under Study
Maraviroc	CCR5 antagonist	Oral; vaginal ring
Dapivirine	Non-nucleoside reverse transcriptase inhibitor	Vaginal ring
GSK1265744/LA	Integrase strand-inhibitor; long-acting analogue to dolutegravir	Oral; injectable (long acting)
TMC-278/LA	Long-acting formulation of rilpivirine	Oral; injectable (long acting)

treatment regimens as does TDF/FTC, a key goal among current research is the development of formulations to overcome barriers to adherence. As described earlier, all of the studies evaluating PrEP as prevention against sexual HIV acquisition,[24,27,28,49] and even the directly observed therapy administration to IDU,[25,46] were undermined by poor adherence. As a result, new long-acting formulations that are either injectable or, for women, used as IVR hold promise to overcome barriers to PrEP adherence. Multiple products showing promise in this regard are currently in the pipeline (see **Table 2**). For example, the recently FDA-approved integrase strand-inhibitor dolutegravir (Tivicay) has been shown to be an effective treatment among both ARV-experienced and ARV–naïve HIV-infected patients.[55–57,59–64] With its favorable safety profile and characteristics amenable to formulation as a long-acting agent (eg, potency, solubility, and melting point), this long-acting analogue to dolutegravir, GSK1265744LA, is potentially seen as an ideal candidate for long-acting PrEP, either as a monthly or a quarterly injection.[55–57,59–64] In addition to its physical properties, GSK1265744LA has been shown to be highly effective as PrEP when tested among macaques in a recent trial of SHIV prevention following rectal challenge.[55,56] A phase IIb randomized trial of the safety and tolerability of this agent is expected to begin among low-risk men and women in 2014 in 2 separate complementary studies in the United States, South America, and sub-Saharan Africa.

Another long-acting agent, TMC-278LA, is the long-acting formulation of (marketed as Edurant alone and together with TDF/FTC in Complera) a non-nucleoside reverse transcriptase inhibitor approved for use in the United States by the FDA in 2011. This agent has similarly been shown to be safe, tolerable, and have a favorable profile for long-acting delivery.[57,58,62] This treatment has been used effectively among HIV-infected persons, including as the first-line treatment of treatment-naïve individuals.[62] Small-scale, phase I studies have shown TMC-278LA to be well tolerated when administered intramuscularly.[58,62,78,79] This agent, too, is slated to begin a phase IIb randomized trial of the safety and tolerability among low-risk men and women in 2014 in the United States and sub-Saharan Africa.[80] The availability of long-acting formulations, particularly those that need only be administered quarterly, will offer significant adherence benefits compared with daily use.

IVRs offer another formulation of PrEP that will be useful in overcoming adherence barriers for women. These flexible rings do not require insertion by a health care provider, as they can be inserted by women monthly.[53,54,79] Benefits of the ring when compared with a long-acting injectable include the potential for simultaneous administration of PrEP and hormonal contraceptive; the ability to remove the ring in the event of changing HIV risk profiles; and, in the event of allergic reaction or side effect, increased ability to halt the dosing.[81] Previous studies have indicated efficacy at preventing vaginal SHIV infection after challenge with dapivirine, though the IVR with MVC has been less effective in primate trials.[81]

Open-Label Investigations

Perhaps as critical to the PrEP conversation as are new formulations is the question of scale-up. PrEP is one of the first available biomedical HIV prevention interventions; as such, few data exist regarding optimal methods of implementation among those at highest risk of HIV. Simply the availability of PrEP does not ensure uptake, particularly among persons at the highest risk of HIV who may not have access to health care or costly prescriptions.[82–88] In addition to ongoing clinical trials of new and currently approved PrEP agents described earlier, investigations are being conducted to characterize the way PrEP is disseminated outside of the ideal clinical trials environment.

Several investigations of open-label PrEP are currently ongoing in the United States. These investigations include iPrEx open label extension (OLE), the optional, open-label follow-on study to the iPrEx study[89]; HPTN 073, offering open-label TDF/FTC to black MSM in concert with a client-centered case management intervention[41]; and local demonstration sites exploring provision of PrEP, largely in urban centers.[90–92] These studies generally explore correlates of PrEP uptake, adherence behavior, sexual and other HIV-related risk behavior while taking PrEP, and myriad characteristics that will eventually inform wider distribution of PrEP. Outside of research trials and demonstration sites, there are few ways to obtain PrEP free of charge, but there are pharmaceutical company-sponsored assistance programs[40] and copay programs for PrEP[93] available. In addition, private insurance as well as that through the Affordable Care Act[1] will pay for or subsidize PrEP prescriptions with varying degrees of preauthorization and documentation. Despite these offerings, the number of PrEP prescriptions in the United States since FDA approval of TDF/FTC remains quite low.[94,95]

THE FUTURE: PRE-EXPOSURE PROPHYLAXIS IMPLEMENTATION

In the previous section, the authors provided an overview of the current research efforts to assess new PrEP regimens, novel PrEP formulations, and the feasibility of scaling up PrEP in high-risk populations in nonclinical trials settings. In this section, the authors address 4 areas that will need to be considered when strategizing about the scale-up of PrEP on a population-wide basis: (1) optimization of PrEP regimens, (2) delivery of PrEP, (3) engagement of high-risk populations; and (4) guidelines, goals and monitoring, and evaluation.

Optimization of Pre-exposure Prophylaxis Regimens

The numerous clinical trials summarized earlier clearly indicate that even in the research setting, a substantial proportion of persons who might benefit from PrEP are unable or unwilling to adhere to a daily oral regimen. Similar to other biomedical prevention behaviors, such as oral contraceptives[96] or preventive vaccines,[4,97] adherence to daily regimens or to prevention guidelines involve the complex interplay between knowledge, attitudes, and behavior. Taking daily medication to prevent HIV acquisition requires numerous behavioral steps. Perception of self-risk must be sufficient to take a pill daily, even if behavioral risks are not present each day, because of the need to maintain adequate blood levels.[26] An individual's assessment that the medication is worth taking despite the side effects, as well as change in acceptance of medication-related risks over time because of the unknown long-term impacts of taking PrEP,[45,47,98] may result in varying adherence over the life cycle. Overcoming concerns about stigma if possession of the medications alone discloses high-risk behavior or the concern that having ARVs makes others think that patients are HIV infected are also barriers to adherence.[48,99] Finally, even with appropriate knowledge, self-risk assessment, and the means to obtain and take the medication, daily

adherence can be a struggle[45–48]; many people do not adhere, even with no frank reasons for nonadherence.

Additionally, the impact of PrEP regimens on the development of ARV resistance in persons who become HIV infected while taking PrEP will also need to be considered. Monitoring provided by a clinical trial environment differs substantially from a community-based care approach. For example, study participants in trials are generally tested for HIV monthly or every 8 weeks, whereas in real-world settings, testing is recommended every 3 months. Persons on PrEP who do seroconvert are at an increased risk of resistance the longer the duration of treatment on PrEP continues after infection because of the difference in treatment regimens and doses prescribed for infection versus prevention. Reconciling clinical trials' standards with care delivery in real-world settings with regard to appropriate monitoring will be an important area of focus as PrEP is made more widely available.

Concurrently, the safety of longer-term PrEP administration will need to be considered, as current research studies have followed those taking PrEP for only 2 to 3 years. The IPrEx OLE study is continuing to follow PrEP users taking TDF/FTC and will soon be able to provide information on longer-term safety and efficacy; similarly long-term follow-up studies both within and outside of clinical trial settings will need to be conducted as new, longer-acting PrEP regimens are developed.

Lastly, the targeting of PrEP use during periods of risk will continue to emerge as an important issue. PrEP scale-up has been compared with that of birth control,[96] in that women may elect to use oral or injectable birth control methods during periods of time when they do not desire to get pregnant. Similarly, persons at risk for HIV may elect to use PrEP for short periods of time during high-risk activity (eg, multiple sexual partners), for longer periods of time (eg, serodiscordant relationships), or may cycle on and off PrEP. This usage is also similar to models such as malaria prophylaxis, which can be used for a short duration (travel to malaria-endemic areas) or for longer durations (eg, living in malaria-endemic areas).[100]

Delivery of Pre-exposure Prophylaxis

Challenges to delivery and scale-up of PrEP have been identified, largely because of the issues around payment coverage for the drugs,[101] uncertainties of prescribing among many community-based noninfectious disease physicians (where most HIV-uninfected persons are seen for care),[102,103] minimal access to studies or free demonstration projects,[42] and challenges in engaging and treating high-risk populations who are likely most in need of the prevention intervention that PrEP represents.[82,104,105] First, there are issues regarding which clinical providers will prescribe PrEP and monitor its use by patients. Most HIV-uninfected persons who will be eligible for PrEP are seen by community-based noninfectious disease physicians who may be unaware of PrEP guidelines, feel uncomfortable discussing sexual or drug use behavior with patients, and do not have substantial experience prescribing ARVs.[102,106–108] Alternatively, PrEP could be delivered by infectious disease specialists with expertise in HIV and ARVs; but their capacity and willingness to provide PrEP for large numbers of HIV-uninfected persons may vary by provider. Another challenge presaged by the minimal availability of free or discounted PrEP is the transition into community-based access following the discontinuation of subsidized PrEP. Future programs will need to overcome this challenge and prospectively identify procedures for roll-off from clinical trials and open-label demonstration projects once these programs end.

Additionally, there are important cost, insurance coverage, and access considerations that will also need to be considered if PrEP is to be implemented on a wider basis given the high cost of ARVs. Although cost-effectiveness studies have indicated

that PrEP is cost-effective in areas with high HIV prevalence, generalized epidemics, and among high-risk populations,[101,109–114] the longer-term costs of HIV testing and monitoring will also need to be considered.[101] At present in the United States, financial coverage for PrEP depends on one's health insurance or willingness to self-pay; it will be important to monitor the impact of the Affordable Care Act on coverage for PrEP as well as changing private insurance paradigms for coverage of PrEP. Currently, there is limited access to PrEP through research studies and demonstration projects,[42] and Gilead Sciences, which manufactures Truvada, has developed a patient assistance program to assist patients who seek PrEP but do not have insurance coverage.[40]

Globally, there are country-specific issues related to PrEP access, including payment options and the development of national PrEP guidelines. In addition, issues related to resource allocation have been raised regarding supporting PrEP implementation both domestically and globally when there are still many untreated HIV-infected persons in need of ARV therapy.[115] The World Health Organization has issued guidance that, for serodiscordant couples when the HIV-infected partner may not yet be eligible for ARV treatment as per country guidelines, PrEP can be considered for the uninfected partner for 6 months as a bridge to treatment.[39] Moreover, the use of TasP is now established as an important component of HIV prevention programs both domestically and globally, which could potentially modulate enthusiasm for directing limited resources toward PrEP.

Engagement of High-Risk Populations

Despite the efficacy of PrEP in reducing the individual risk of HIV acquisition, many potential users in high-risk populations remain unaware of the potential benefits of PrEP and how to access this intervention.[116,117] Educational initiatives are being developed for persons at high HIV risk who may benefit from PrEP, including mobile phone applications, Web sites to assess one's risk for HIV, adherence interventions,[118] and the issuance of PrEP guidance documents for interested participants and providers by state health departments.[119,120]

Stigma remains a considerable barrier to PrEP provision, in the context of prescribing and using PrEP as well as adherence. Because ARV use for prevention and treatment can easily be confused, uninfected persons may be reluctant to use PrEP as friends and family members may think they are HIV infected.[45] In addition, the use of PrEP also signals high-risk sexual or drug use behavior and may suggest gay or bisexual orientation among men, drug use in men and women, and nonmonogamy in couples. This problem may be obviated by clinic-based injections when long-acting formulations become available, but daily regimens and IVRs will not eliminate these factors. For oral PrEP, changes in packaging that distinguish the use of PrEP for prevention from treatment may ultimately facilitate acceptance of and adherence to PrEP, much as oral contraceptives benefit from packaging that enables daily adherence. Risk compensation is a frequent issue that emerges in discussions of PrEP scale-up, as the prevention benefits of PrEP as a biomedical intervention can be mitigated by behavioral factors, such as an increase in numbers of sexual partners or a decrease in condom use.[121]

Consideration of issues related to gender will also be important as PrEP use becomes more widespread to ensure that this prevention modality meets the needs of women. In the United States, women have been underrepresented in PrEP studies and demonstration projects, although women are included in the Centers for Disease Control and Prevention's PrEP guidelines and the FDA approval of TDF/FTC for PrEP.[34,36] Globally, women have been well represented in PrEP trials; but caution will be required translating lessons learned outside of the United States to women

in the United States, just as the converse is true for MSM. The complex relationship for women regarding PrEP in the context of pregnancy prevention, pregnancy, and desired family building will also necessitate further exploration.[122,123]

Guidelines, Goals and Monitoring, and Evaluation

The use of oral PrEP for individuals at high risk of HIV infection has been shown to be a safe and effective HIV prevention intervention. Scaling the use of PrEP to a population-based level,[124] however, will be an ongoing public health challenge that will require awareness of numerous issues, several of which are described earlier. Moving forward, a higher degree of granularity and regular updating of PrEP guidelines will be needed as new ARVs are demonstrated to be safe and effective for PrEP use; longer-acting PrEP formulations become available; different patterns of intermittent PrEP use are evaluated; PrEP uptake increases in various high-risk populations; and the role of PrEP is further evaluated in discordant couples in which the HIV-infected partner is virologically suppressed on ARVs. For example, more data will be needed with regard to how to use PrEP over the life cycle: as behavioral risk profiles change, guidelines for how PrEP use should change will be necessary. Similarly, for discordant couples in which the HIV-infected partner is adherent to ARV and virologically suppressed, more data will be needed to discern whether the addition of PrEP is cost-effective and warrants added medication risks to the uninfected partner. Moreover, although it may be premature at present, the development of local, regional, and global quantifiable goals for PrEP use will be useful to promote the scale-up of PrEP use to impactful levels, especially if long-acting PrEP formulations become available. Lastly, as PrEP use becomes more widespread,[125] innovative monitoring and evaluation systems will need to be developed for PrEP uptake, adherence, ARV resistance, safety, and efficacy. As PrEP becomes more widely available and people become more aware about its benefits, research inquiries into these more nuanced facets of PrEP deserve exploration.

SUMMARY

In the past decade, enormous progress has been made in the development of PrEP as an HIV prevention intervention, with the safety and efficacy of PrEP now demonstrated in MSM, IDUs, and heterosexuals. Current research is ongoing to assess new PrEP ARV regimens, alternative and long-acting PrEP delivery mechanisms, and the feasibility of implementing PrEP in high-risk populations. In the years ahead, the HIV prevention field will continue to address several critical issues, including the optimization of PrEP regimens, how best to support the delivery of PrEP on a population-level scale, engagement of high-risk populations, the updating of PrEP guidelines, and the establishment of PrEP-related goals and monitoring and evaluation systems.

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