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Clinical Treatment Options Infectious Diseases: Update on PrEP Implementation, Adherence, and Advances in Delivery

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Opinion statement

Pre-exposure prophylaxis (PrEP) is an effective and evidence-based HIV prevention option and is recommended for individuals with substantial risk for HIV infection [1]. Randomized controlled trials have demonstrated that daily oral PrEP dramatically reduces the risk of HIV infection when it is taken as directed. Concerns regarding widespread emergence of antiretroviral resistance attributable to PrEP and behavioral disinhibition have to date not been observed in clinical trials and open-label demonstration projects. PrEP has great potential as part of an HIV risk reduction strategy, and barriers to wider implementation including community education, prescriber availability, and elimination of financial barriers should be aggressively pursued. Adherence is critical to PrEP efficacy and has varied across study populations; developing and refining ways of measuring and supporting adherence is essential to the success of PrEP. Evaluation of long-acting medications and alternative formulations for PrEP is underway and may lead to the wider implementation and impact of PrEP.

Introduction

Pre-exposure prophylaxis (PrEP) is an HIV prevention strategy involving the use of antiretroviral medications for HIV-uninfected individuals who are at risk for HIV acquisition initiated before exposure. PrEP effectiveness has been established through large randomized controlled trials of daily oral medication for sexually active men who have sex with men (MSM) as well as heterosexual men and women, and intravenous drug users demonstrating risk reductions of 44–75 % compared with placebo [2••, 3••, 4••, 5•]. The United States Food and Drug Administration subsequently approved daily oral fixed-dose combination tenofovir-emtricitabine (TDF/FTC, marketed as Truvada) for HIV prevention, and the Centers for Disease Control and Prevention released comprehensive guidelines for PrEP prescribing in May 2014 [1, 6••].

PrEP demonstrates great promise as a component of combination prevention strategies. Data continue to emerge reinforcing the safety and efficacy of the intervention, and details regarding behavioral changes, adherence, optimal counseling strategies and follow-up are now becoming available. Questions regarding the optimal implementation strategy for this intervention remain, with numerous PrEP demonstration projects currently underway to attempt to clarify the location, personnel, and resources required for PrEP provision. Additionally, clinical trials are underway to assess different medications, dosing strategies, and delivery mechanisms for PrEP that may alter the landscape for biomedical prevention in the near future. In this review, we will summarize emerging literature relevant to PrEP implementation including adherence, risk compensation, uptake and delivery, and strategies for long-acting or intermittent dosing of PrEP medication that are currently under investigation.

Antiretroviral medication for PrEP

The scientific basis for antiretroviral use for prevention initiated prior to sexual exposure arises from non-human primate studies in which tenofovir and emtricitabine, two drugs with favorable pharmacokinetics in rectal and vaginal mucosa, reduced infection risk in macaques by 70–100 % when administered prior to mucosal simian immunodeficiency virus (SIV) exposure [7–11]. Initial large clinical trials therefore generally assessed TDF, with or without combination FTC. These randomized controlled clinical trials in humans have provided evidence that daily antiretroviral-based oral PrEP, as part of a comprehensive prevention strategy, is safe and effective for MSM and heterosexual men and women as well as intravenous drug users at risk for HIV infection [2••, 3••, 4••, 5•]. Both TDF and TDF/FTC regimens have been shown to be effective when used, with somewhat higher (but not statistically significant) protection with TDF/FTC observed in the Partners PrEP trial [12]; however, TDF/FTC is the only regimen currently approved by the United States Food and Drug Administration for HIV pre-exposure prophylaxis [6••].

Side effects and monitoring

Combination TDF/FTC is well tolerated. The most common side effects are mild gastrointestinal complaints occurring in the first 1–2 weeks of beginning medication and usually improving after this point [2••, 4••, 5•, 6••]. Renal tubular effects of TDF have been observed in large trials of HIV-positive individuals receiving this medication for the treatment of infection [13, 14], but only a mild decline in creatinine clearance has been observed in studies using this medication

for PrEP and this effect reverses upon discontinuation of the drug [15]. TDF/FTC PrEP is not recommended for individuals with a baseline creatinine clearance of less than 60 mg/dL, and baseline and interval renal function monitoring is advised for all patients receiving this medication for PrEP [1]. A small but statistically significant decrease in bone mineral density is also observed in the first 24–36 weeks after starting PrEP [4••, 16, 17]; the clinical importance of this decrease is unclear, as no excess fractures have been observed in the PrEP treatment arm of the completed randomized controlled studies [4••, 16].

Despite the well-established safety profile of TDF/FTC, concern regarding side effects is a common reason for declining to initiate or electively discontinuing PrEP [18•, 19] and a common concern on the part of providers who are hesitant about PrEP prescribing [20, 21]. Careful assessment of putative side effects and counseling and support regarding these events are important to avoid unnecessary PrEP discontinuation among individuals who remain at risk for HIV infection.

Resistance

Unrecognized early/acute HIV infection at the initiation of PrEP accounts for the vast majority of cases of drug resistance identified in clinical trials to date (Table 1) [2••, 4••, 5•, 22]. Adequate clinical and laboratory screening for early HIV infection at the time of PrEP initiation is essential to avoid resistance and to initiate effective combination antiretroviral therapy for the treatment of infection [1]. Resistance to drug emerging after PrEP has been established is much less

Table 1. Antiretroviral resistance among active-arm seroconverters in PrEP trials

PrEP trial	Resistance in acutely infected ppts at baseline (active arm)	Resistance during follow-up (active arm)
iPrEx [4••, 22]	• 2/2 acutely infected ppts with resistance: 1 M184V (standard seq.) 1 M184I (standard seq.)	•No resistance detected by standard seq. among 48 active arm seroconverters • 2 ppts with minor variant M184I 1 detected by AS-PCR 1 by 454 seq.
Partners PrEP [2••, 23]	• 3/12 acutely infected ppts with resistance 1 K65R/K70E in TDF group (standard seq.) 1 M184V in TDF/FTC group (standard seq.) 1 M184V in TDF/FTC group (454 seq.)	• No resistance detected by standard seq. in 51 active arm seroconverters • 4 ppts with minor variant resistance 3 in TDF/FTC arm: 2 M184V; 1 M184IV and K65R 1 in TDF arm: M184I (unlikely selected by PrEP exposure)
TDF2 [5•]	• 1/1 acutely infected ppt with resistance: K65R, M184V, and A62V (standard seq.)	• No resistance reported in 9 active arm seroconverters using standard and ultrasensitive (Qiagen) sequencing
FemPrEP [24, 32•]	• 3/6 ppts with first evidence of infection at the first post-enrollment visit 2 M184V 1 M184I	• No resistance detected by standard seq. in 27 active arm seroconverters 1 seroconverters with minor variant resistance: M184I
BKK TDF study [3••]	• No acutely infected ppts in active arm	• No TDF resistance (K65R, K70E) among 15 seroconverters in active arm

Standard seq. Standard consensus sequencing, *Ppt* participant, *AS-PCR* allele-specific polymerase chain reaction, *454 seq* 454 deep sequencing

common, likely because most infections occur in the absence of detectable drug levels to drive resistance. PrEP-related mutations were detected with ultra-deep sequencing in 4 of 51 active-arm seroconverters infected after enrollment in the Partners PrEP study, 2 of which had detectable drug levels after HIV acquisition and mutations associated with the drugs they were assigned. Overall, detectable drug levels were predictive of identification of resistance [23]. Among 48 iPrEx active-arm participants with incident infections, none had clinically detectable resistance and only 2 had minor variant resistance to FTC at <1 % frequency [22]. In the Preexposure Prophylaxis Trial for HIV Prevention among African Women (FemPrEP) study, FTC resistance was detected by clinical assays in 4 seroconverters in the active arm of the study, with an additional case of minor variant resistance to FTC identified using more sensitive sequencing techniques; these rates of resistance are thought to be similar to those found among transmitted infections in the geographical area of the study [24]. Modeling studies suggest that PrEP is unlikely to contribute substantially to prevalence of drug-resistant virus in the community in comparison to resistance developed during the treatment of chronic HIV infection [25].

Risk compensation

Substantial behavioral changes while receiving PrEP (risk compensation or risk disinhibition) have not been observed in the randomized controlled trials to date [2••, 4••, 5•, 18•, 26]. Number of partners and episodes of condomless sex decreased during the course of the iPrEx study and the open-label extension (iPrEx OLE) of this study [4••, 24, 27]. An analysis of sexual behavior of participants in the Partners PrEP study likewise did not find evidence for increases in condomless sex during the blinded study or after release of results [26]. All PrEP clinical trials are conducted with dedicated risk reduction counseling as well as provision of condoms and comprehensive sexual health care; adaptation of these comprehensive prevention services may be challenging in some non-research implementation sites. In one survey of potential PrEP recipients, 35 % of young MSM indicated intent to decrease condom use with PrEP [28], but such dramatic increases have not been observed in any PrEP setting to date. Making PrEP available could facilitate engagement of individuals at risk for HIV and uptake of other prevention practices (prevention synergy), including frequent HIV testing, provision of condoms, long-term counseling regarding status disclosure and condom use, and treatment of sexually transmitted infections [18•, 29]. As risk behavior in placebo-controlled trials may not reflect sexual practices in more real-world settings, evaluation of sexual behavior in open-label PrEP programs is being planned in a number of PrEP demonstration projects.

Adherence

PrEP effectiveness is directly related to medication adherence. In the iPrEx study of PrEP for MSM and transgender women, only 9 % of individuals seroconverting during the study had detectable (any) drug levels at the visit, compared with 51 % of HIV-negative controls [4••]. Although overall PrEP efficacy was 44 % in the study, among participants with drug-detectable drug levels, PrEP efficacy was estimated to be more than 90 % [4••, 30]. The Partners

PrEP study, evaluating PrEP among discordant couples, demonstrated 67–75 % protective efficacy overall and also reported high levels of drug detection [2••]. The Vaginal and Oral Interventions to Control the Epidemic (VOICE) and FemPrEP trials, both large trials of PrEP for heterosexual women, failed to show PrEP effectiveness [31, 32•]. Analysis of serum drug levels from the VOICE trial demonstrated detectable drug in fewer than 23 % of women in the active arm of the study. In contrast, self-reported adherence was 80–90 % [31]. Extrapolating from clinical trial data and controlled pharmacokinetic studies, an estimate of protective effect with various levels of adherence may be formulated. Analysis of TDF and FTC drug levels from the iPrEx and STRAND studies approximated 76 % protection for 2 doses of oral TDF/FTC weekly, 96 % for 4 doses weekly, and 99 % for 7 doses weekly [33•]. In the open-label extension of iPrEx, no participants became infected with drug levels consistent with taking ≥4 doses/week. These data suggest that less than daily dosing may provide some protection against infection, although daily dosing may help facilitate adherence through building a pill-taking routine and also afford some forgiveness for missed pills [18•], and currently, oral PrEP with TDF/FTC is only recommended for daily use.

Due to the inconsistent relationship between self-reported adherence and objective measures such as drug levels, most PrEP research studies include multiple adherence parameters: self report, pill counts, and plasma, peripheral blood mononuclear cell (PBMC) levels, hair, and/or dried blood spot (DBS) drug levels have been commonly measured. Plasma levels provide the ability to estimate short-term (2–7 days) adherence, while PBMCs provide information on medium-term (7–14 days) adherence [34–36] Drug levels in DBS and hair reflect longer term exposure to TDF/FTC and may be more feasible to collect and process in real-world settings [37].

Adherence in the clinical setting, when patients are aware that they are receiving an active medication that is proven to be effective when taken, may well be different from adherence in a clinical trial setting when benefit is unknown [38•]. PrEP demonstration projects and extensions of previous trials, in which participants are provided PrEP in an open-label fashion, are beginning to provide some data regarding longitudinal adherence in these settings. Recently reported data from the iPrEx open-label extension provides evidence that adherence is complex, with the most common pattern being initial adherence followed by discontinuation rather than intermittent use, and that while adherence is higher among those with highest sexual risk for infection, those discontinuing did also have ongoing behavioral risk for infection [18•, 38•].

As therapeutic drug monitoring is not currently recommended or practiced as part of routine PrEP prescribing, adherence to PrEP in real-world settings can be challenging to assess or estimate. Maintaining a neutral approach to questioning regarding adherence may help to reduce inflated adherence estimates due to desire to please or to avoid extended counseling and may then allow discussion regarding new approaches that may improve adherence [38•, 39].

Supporting PrEP adherence

As adherence is crucial to PrEP effectiveness in the clinical setting, discussion regarding planned strategies for optimizing adherence is an important part of initial and follow-up counseling when initiating PrEP. In a qualitative study of

the iPrEx participants, coordinating timing of medication dosing with another daily routine was helpful to adherence [40]. Ready access to medication in a keychain or other portable holder also facilitated adherence for some participants. Disruption in routine and not having medication available are consistently identified barriers to adherence [29, 40–42]. Technological support for PrEP adherence, such as text, email, and SMS messaging, to remind or provide support for individuals receiving PrEP are also currently under investigation as tools to encourage adherence [43].

PrEP studies conducted with discordant couples have demonstrated the highest levels of adherence, emphasizing the importance of partner support in supporting adherence [41, 44]. High levels of adherence and efficacy in the Partners PrEP study may be partially explained by inclusion of stable discordant couples, for whom PrEP provided a relief from the "discordance dilemma" and who also provided substantial support for PrEP taking [44]. In a Partners PrEP sub-study focused on adherence, some decline in adherence over time was observed [45]. Additionally, adherence <80 % was more likely in younger participants, those with less sexual activity, and those with frequent alcohol use [45]. In the FemPrEP study, effectiveness was impacted by low adherence [32•, 41]. Analysis of adherence factors indicated that risk perception impacted adherence, with motivation increased for those with higher risk perception [46]. Community perception of PrEP, stigma associated with taking antiretroviral medications, and partner support (or lack of support) also impacted adherence across studies, emphasizing the need to consider not only individual-level but also partner and community factors [19, 41, 46–48].

PrEP implementation: opportunities and challenges

Several PrEP demonstration projects and implementation programs are underway to evaluate the uptake, adherence, sexual behaviors, safety, and/or effectiveness of PrEP when delivered in more real-world contexts. In the open-label extension (OLE) of the iPrEx trial, approximately three quarters of HIV-negative participants who returned for study participation elected to take PrEP, with higher uptake among those reporting condomless receptive anal sex and having evidence of prior herpes infection [18•] HIV incidence was lower among those receiving PrEP vs. those who chose not to receive PrEP (1.8 vs. 2.6/100 person years), and higher PrEP drug concentrations were associated with higher levels of protection [18•]. An interim analysis of the open-label PROUD study in the UK which involved randomization to either immediate or delayed initiation of PrEP found that PrEP was highly protective in those receiving PrEP, and it was recommended that PrEP be offered to all study participants immediately [49].

While studies tracking pharmacy claims suggest that few patients in the USA are being prescribed PrEP [50, 51], interest and uptake of PrEP among individuals with behavioral risk for HIV is high when offered as part of demonstration projects and without charge [18•, 52]. In the US Demo Project evaluating PrEP delivery in STD clinics and a community health center, almost half of eligible referred clients, many of whom had not heard of PrEP and 87 % of those who were self-referred to the project elected to take PrEP [52, 53].

As PrEP requires prescription and safety monitoring by medical practitioners, healthcare providers play a critical role in successful PrEP implementation. Several studies among US providers found knowledge and support of PrEP to be high, particularly among HIV specialists, but prescribing of PrEP to be quite low across clinical groups [20, 21, 54–56]. Concerns expressed by providers include safety, efficacy, adherence, antiretroviral resistance, behavioral disinhibition, cost, and operational challenges of delivering PrEP in busy clinical settings [54–56]. Despite CDC guidance on PrEP, there are significant differences in the real-world practice of PrEP, including deciding who is eligible for PrEP, how persons are followed up, and how PrEP is discontinued [21]. Recently, a national clinician consultation PrEPline (855-448-7737) has been established to provide support to clinicians prescribing PrEP [57], and numerous groups are developing resources for clinicians to address barriers in scaling up PrEP delivery, including clinical practice guidelines [1] and tools to provide education around PrEP to patients [58], facilitate taking a sexual history [59], identify appropriate PrEP candidates [60], and prescribe and monitor PrEP safely [61]. Cost of medication is a real or perceived barrier to starting PrEP in many settings [55, 62]; commercial insurance frequently covers PrEP medication but may involve high copayments [63, 64]. Pharmaceutical patient assistance programs, Medicaid, and some specialized governmental assistance programs are available to assist with payment for PrEP in the USA [65, 66]. HIV infection disproportionately affects historically stigmatized groups as well as populations with lower socioeconomic status and decreased access to medical care [67–69]; engaging people who are at risk for HIV with appropriate and accessible information regarding PrEP as a prevention option, enabling access to PrEP providers, and removing economic barriers to biomedical prevention methods are necessary to ensure that PrEP implementation occurs in an equitable manner that minimizes disparities and maximizes impact [70].

Alternative dosing strategies for PrEP

While the first generation of PrEP trials evaluated daily oral dosing of TDF/FTC, PrEP strategies that involve intermittent or on-demand dosing of oral PrEP medication are currently under investigation. The IPERGAY study for MSM in France and Canada involves taking two doses of medication in the 24 h prior to anticipated sex and one each in the 2 days following sex; this strategy produces blood levels thought to be protective and was stopped early due to a significant reduction in infection in the study arm compared with placebo [71]. Preliminary adherence data indicate drug detection levels of 82–86 % in the active arm [72], and additional data will be forthcoming. The UVRI Uganda Research Unit Study compared acceptability and adherence to daily and intermittent PrEP for discordant heterosexual couples, with intermittent dosing involving twice weekly dosing with an additional post-coital dose. More than 90 % adherence to fixed doses was reported by bottle monitoring device, but only 45 % adherence to post-coital dosing [73]. In a placebo-controlled study comparing daily oral PrEP to fixed intermittent plus post-coital dosing for MSM and female sex workers in Kenya, a similar pattern was seen with 83 % median

adherence to daily dosing by Medication Event Monitoring System (MEMS) cap monitoring versus 55 % for fixed intermittent doses and 26 % for post-coital doses. However, MEMS cap monitoring may have underestimated intermittent and post-coital doses due to the practice of removing doses for post-coital dosing away from home and difficulty with accurate recording of sexual activity [74]. Other studies, such as the US HPTN 067/ADAPT, to evaluate the feasibility of intermittent and on-demand oral PrEP are also underway.

Innovation in drug delivery and long-acting medication

Antiretroviral compounds and formulations allowing less frequent dosing are in development and may have the potential to positively impact adherence and acceptability of PrEP. The paradigm of long-acting injectable prophylaxis that is acceptable and effective has been established with progestogenic contraception [75]. An international survey of potential PrEP users and a survey of young MSM in New York City indicated that long-acting injectable formulations were acceptable and preferred over oral daily PrEP by up to 80 % of those surveyed [76, 77], while a similar survey in a cohort of Thai MSM indicated that daily oral PrEP was preferred over injectable forms [78].

GSK744, an injectable long-acting integrase inhibitor with the possibility of dosing every 3 months, demonstrated efficacy in prevention of rectal and vaginal SIV infection in macaques, and a phase IIa trial evaluating tolerability and acceptability of this compound for HIV-negative men is underway [79, 80]. TMC278-LA, a long-acting injectable form of the non-nucleotide reverse transcriptase inhibitor (NNRTI) rilpivirine with potential for use as PrEP, has also completed phase I trials, and a phase II trial in HIV-uninfected women is planned [80–82]. Additionally, dapivirine and maraviroc containing vaginal rings remaining in place for 28 days have demonstrated safety and acceptability in phase I human trials, and a dapivirine ring is currently under evaluation in human efficacy studies [83]. These products and other long-acting agents have the potential to impact adherence and offer many potential advantages over oral medication requiring daily dosing. Challenges with long-acting injectable agents include injection site reactions, follow-up for HIV testing and re-dosing of medication, and theoretical concerns that individuals stopping injections will experience prolonged suboptimal levels of medication that may lead to a greater risk of resistance will require investigation as these promising technologies become available [84].

Conclusion

PrEP is rapidly emerging as an important part of comprehensive HIV prevention programs and has a potential to impact HIV incidence. Consistently, adherence to medication is evident as the most important factor in realizing the benefits of PrEP [38•, 42]. As PrEP moves toward wider implementation, improvements in understanding of adherence factors, and innovation in PrEP outreach to improve uptake and availability for all groups at risk for HIV infection will be required to decrease disparities in PrEP uptake and to maximize impact of this intervention.

Compliance with Ethics Guidelines

Conflict of Interest

Gilead Sciences donated a study drug to the US PrEP demo project, of which Liu is the protocol chair, Susanne Doblecki-Lewis is a co-investigator and site medical director, and Stephanie Cohen is a site co-PI.

Human and Animal Rights and Informed Consent

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

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