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Current Concepts for PrEP Adherence:

In The PrEP revolution; from clinical trials to routine practice

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Abstract

Purpose of review—This review describes 1) the current understanding of adherence to oral PrEP, 2) methods for adherence measurement, 3) approaches to supporting PrEP adherence, and 4) guidance for defining PrEP adherence goals within the larger context of HIV prevention.

Recent findings—PrEP adherence has generally been higher in recent trials, open-label extensions, and demonstration projects compared to the initial clinical trials; potential explanations include known PrEP efficacy and different motivations to take PrEP. Recent studies have explored adherence monitoring through electronic pill containers, short message service (SMS), and drug concentrations in hair and dried blood spots. The few PrEP adherence interventions developed to date include combinations of enhanced counseling, feedback of objective adherence measurement, and SMS. Conceptualization of PrEP adherence is evolving. The goal is not 100% adherence indefinitely, as it was in clinical trials. PrEP adherence should be defined with respect to HIV exposure, which varies over time by sexual behavior and use of other prevention strategies.

Summary—PrEP adherence beyond clinical trials has generally been high enough to achieve reliable HIV prevention. Future efforts to measure and support PrEP adherence should focus on the context of risk for HIV acquisition, accounting for dynamic behaviors and choices among HIV prevention options.

Keywords

pre-exposure prophylaxis; adherence

Introduction

Former US Surgeon General C. Everett Koop famously said, “Drugs don’t work in patients who don’t take them.” Pre-exposure prophylaxis (PrEP) against HIV infection is no

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exception. Six clinical trials yielded PrEP efficacy estimates of 0–75%, primarily due to differences in adherence amongst the studies (1–6).

As PrEP moves from clinical trials into routine practice, adherence will determine how effective PrEP is at preventing HIV. All of the recently published reviews and opinion pieces comment on its role (7–13). Many importantly emphasize the differences between adherence in randomized, placebo-controlled trials and adherence in the setting of known efficacy. This article highlights the promising evidence, as well as indicates populations that warrant particular attention.

Limitations in the reliability of self-reported PrEP adherence became apparent during the initial clinical trials, paralleling the experience with antiretroviral therapy (ART) adherence (14). Several recent papers present comparisons of multiple adherence measures in those trials. This article summarizes those findings so as to inform the best approaches for future research and potentially clinical care.

Effective counseling is needed to support all who desire to use PrEP for HIV prevention and targeted intervention is important for those who struggle with adherence. This article reviews PrEP adherence interventions developed to date and presents recommendations for further research and best practices for clinical implementation.

Finally, recent literature has been exploring different ways of conceptualizing PrEP adherence. PrEP is not meant for life; high adherence is needed during periods of use when an individual is at risk for HIV acquisition. This article comments on the necessary steps to achieve this critical alignment, which refines the relationship between adherence and effectiveness.

Current understanding of adherence to oral PrEP

As shown in Table 1, participants in recent PrEP trials, open-label extensions and demonstration projects have generally had higher adherence compared to participants in the initial clinical trials (i.e., those completed or stopped by 2013). In studies with comparison arms, efficacy/effectiveness has been correspondingly high.

For example, iPrEx was a randomized controlled trial of daily tenofovir/emtricitabine (TDF/FTC) among men who have sex with men (MSM) in Latin America, the US, South Africa, and Thailand (3). Adherence was 51% by detection of tenofovir in plasma and efficacy was 44%. The PROUD study is an open-label randomized wait-listed trial of daily TDF/FTC involving MSM in England (16). Initial results presented in early 2015 showed that enough pills were prescribed to cover 86% of the days participants would be taking PrEP if everyone’s adherence had been 100%; efficacy was correspondingly high at 86%. Similarly, IPERGAY is a randomized trial of placebo versus “on demand” TDF/FTC (i.e., doses before and after sexual events) among MSM in France and Canada (17). Adherence to an on demand regimen is difficult to assess and is dependent on the frequency of sexual behavior (23). That said, recently presented results indicated that the overall median number of pills taken per month was 16 according to pill counts. In an assessment of 1,212 sex acts reported by 319 participants in IPERGAY, only 43% indicated that PrEP was taken before and after

sex as prescribed and 25% of participants did not use PrEP at all. Despite these findings, efficacy was again 86%, suggesting that those most at risk of HIV acquisition may be the ones taking PrEP when it is needed. PROUD and IPERGAY plus the other studies listed in Table 1 show that PrEP can effectively prevent HIV among MSM. An important exception to this trend, however, has been seen with young MSM. Project PrePARE assessed the feasibility and acceptability of PrEP among MSM aged 18–22 years old and found detectable tenofovir in only 20% of participants at week 24 (24). In the follow-up study of open-label PrEP in a similar population, <34% had drug levels consistent with 4+ pills per week at week 48 (20).

Adherence was notably low in the two initial clinical trials focusing on African women—FEM-PrEP and VOICE (4, 6). Adherence to daily PrEP was 21–37% in the former and 28–29% in the latter, as determined by drug detection; neither study showed efficacy. The ADAPT study is an open-label comparison of daily versus non-daily TDF/FTC, and results of women from the South African site were also presented in 2015 (21). Adherence in the daily arm was 79% as measured by an electronic monitor (i.e., a pill bottle that records openings). While the study did not comment on effectiveness, these findings are highly encouraging that African women can adhere to PrEP.

Among the initial clinical trials, adherence and efficacy were highest among serodiscordant couples in East Africa. The Partners PrEP Study found adherence in this population to be 82% by drug detection; efficacy was 67% for TDF alone and 75% for TDF/FTC (1). The Partners Demonstration Project involves a “bridge” of PrEP for the HIV-uninfected partner for six months, while the HIV-infected partner initiates ART. Preliminary findings indicated adherence of 86% by drug detection and 96% reduction in incidence when compared to counterfactual simulations (22). These findings clearly indicate that PrEP works well for HIV prevention when it is taken.

The high PrEP adherence seen with most populations may be attributable to numerous factors, such as the known efficacy of PrEP (10). Motivations may also have differed. For instance, individuals may have participated in the initial clinical trials to gain certain benefits, such as free, high quality health care, rather than to take PrEP (25). In the more recent studies, individuals may have enrolled because PrEP is the right HIV prevention choice for them. Additionally, experience from the initial clinical trials showed the importance of disclosure of PrEP use and support from a partner (26). The extent of this support in more recent studies is not known, but warrants consideration. Other potentially impactful factors may include cultural setting (e.g., community support) and attitudes toward healthcare (e.g., trust of providers) (10).

Methods for adherence measurement

Measurement of adherence is challenging and no gold standard exists; the strengths and weaknesses of each measure have been reviewed elsewhere (27). In brief, self-report is generally considered an overestimate due to multiple biases (e.g., social desirability, recall), but is readily and inexpensively obtained. Objective measures are likely more accurate, but are more expensive and have limited feasibility outside of research settings. The

performance of multiple measures for HIV treatment adherence has been well studied (28, 29). While many of those findings likely apply to PrEP adherence, HIV-uninfected individuals may be differently motivated to report or otherwise modify adherence behavior (e.g., taking medications only before a visit in which a drug level will be measured) for HIV prevention compared with HIV-infected individuals taking lifesaving ART. Recent analyses have compared various adherence measures employed in the PrEP clinical trials, with a goal of informing which measures should be used in future studies, demonstration projects, and clinical care.

In iPrEx, the Partners PrEP Ancillary Adherence Study, and FEM-PrEP, self-reported adherence measures were not found to be useful in distinguishing among participants with and without detectable tenofovir (30–32). In the TDF2 study (33), however, detectable drug concentrations were modestly associated with self-report as well as pill counts, and drug <100% adherence.

SMS offers a promising approach to improve self-report. Questions may be administered frequently, thus reducing recall bias, and the relative anonymity compared with face-to-face interviewing may reduce social desirability bias. SMS was used in the Partners PrEP Study to measure (34) both adherence and concurrent sexual behavior, and similar work is ongoing within the Partners Demonstration Project (35).

Electronic monitoring with MEMS caps is being employed in numerous ongoing demonstration projects (36, 37) and offers a means for determining day-to-day patterns of adherence, which may be used for alignment of adherence and risk for HIV acquisition (see below). In the Partners PrEP Ancillary Adherence Study, MEMS adherence significantly distinguished among participants with detectable tenofovir in plasma (31). Correlation, however, was imperfect, suggesting potential inaccuracies in some of the MEMS data and/or assay error. A wireless version of electronic monitoring called Wisepill is also available and is being used in the Project PrEPARE and ADAPT studies (19, 21). This technology enables real-time adherence monitoring and can be paired with interventions for specific missed doses and/or used for enhanced counseling (see below).

Drug detection is the only adherence measurement that documents ingestion and was widely employed in PrEP clinical trials, primarily using plasma and peripheral blood mononuclear cells (PBMC) (1–6, 38). Alternative approaches to drug detection include hair and dried blood spots (DBS). Both reflect longer-term windows of exposure (i.e., weeks to months versus 7 and 14 days with plasma and PBMC, respectively) and can be more easily transported for central laboratory processing than plasma or PBMC. Acceptability has generally been high, although concerns have been raised about hair collection in some populations (39, 40). Both tenofovir and emtricitabine concentrations have been evaluated; due to differences in their half-lives, the combination of both drugs can give an idea of recent versus steady-state dosing (41, 42). Strong correlation between dosing frequency and tenofovir levels in hair has been demonstrated (43). Additionally, high correlation between hair and DBS has been shown with data from iPrEx OLE (44); significant correlations were also seen between hair and both plasma and PBMC in the intermittent PrEP pilot RCT conducted by the International AIDS Vaccine Initiative (IAVI) (38).

In sum, the objective adherence monitoring approaches explored in recent studies are promising as alternatives to self-report. Importantly, differences in motivation for participation in clinical trials compared with open-label extensions, demonstration projects, and clinical care may allow for better self-report and should be explored, potentially including cognitive testing for measures that may perform well in a given population (45). Future studies should also validate the self-report obtained via SMS against objective adherence measures. Efforts to decrease the cost of wireless electronic monitoring and drug concentration monitoring will be critical for more widespread use. Point-of-care testing would also increase utility for drug concentrations and could be used to inform counseling (see below).

Approaches to supporting PrEP adherence

Despite the well-acknowledged role of adherence in PrEP efficacy, few PrEP adherence interventions have been developed and evaluated (see Table 2). Many lessons may be learned from the large literature exploring ART adherence interventions (49, 50); however, relevant factors may differ significantly for prevention (e.g., motivations, tolerance of side effects, availability of support). Formative work among US MSM suggest key components of a behavior adherence intervention for PrEP should be motivations to use PrEP, barriers to PrEP use, facilitators of PrEP use, sexual decision-making in the context of PrEP, prospective PrEP education content, and perceived effective characteristics of PrEP delivery personnel (51).

Most PrEP adherence interventions involve enhanced counseling. One approach, called LifeSteps, is based on cognitive behavioral therapy and includes problem solving and motivational interviewing techniques. It was used in the Partners PrEP Ancillary Adherence Study (46) and more recently in Project PrEPARE, which randomized MSM to Life-Steps or supportive counseling (19). Adherence was monitored by Wisepill, and sexual behavior was assessed via daily SMS. Most participants demonstrated levels of PrEP adherence consistent with protective benefit with both types of counseling.

Another enhanced counseling intervention, called Next-step counseling, was used in iPrEX, and iPrEX OLE (47). Although not assessed for effectiveness, an analysis of counseling sessions found that the most commonly reported facilitator of PrEP adherence was matching dose taking with a routine daily event (86%), and the most commonly reported challenge was disruption in routine (37%) (52). Next-step counseling was also combined with feedback of plasma drug levels and MEMS adherence in a study of US MSM (53). Additional targeted counseling was planned for individuals with low tenofovir levels; however, preliminary evidence indicated that nearly all participants had levels consistent with steady-state daily dosing for at least 48 hours before specimen collection.

A recent study explored the acceptability of drug level feedback in iPrEx OLE (54) and found it was well received. In most cases, it enhanced open discussion of missed doses, and participants reported a desire for greater specificity, particularly quantitative drug levels needed for protection. Provision of tenofovir drug levels to VOICE participants in Uganda

as adherence feedback was found to be safe and ethical without a sense of victimization (55).

Ongoing research is evaluating SMS and smart phone apps as a promising approach to adherence support. A study involving iPrEx OLE participants (48) adapted an SMS-based intervention previously shown to increase ART adherence and virologic suppression rates in HIV-infected individuals (56). Preliminary results showed statistically significant improvements in a pre-post design. Other groups are exploring similar SMS-based interventions, including the demonstration project called California Collaborative Treatment Group Consortium/ALERT (Active Linkage, Engagement and Retention to Reduce HIV).

Future research on PrEP adherence interventions should include more studies involving women and especially adolescents, for whom adherence may be a particular challenge. Given the high levels of adherence seen for many in recent trials, open-label extensions, and demonstration projects, general counseling may be sufficient for most PrEP users. Enhanced counseling can be targeted to those who are struggling and could be facilitated through technology (e.g., two-way SMS). Real-time electronic monitoring and/or drug concentration feedback in combination with targeted counseling is particularly appealing for research and should be considered for wider use if costs decrease.

Guidance for defining adherence goals within a larger context of HIV prevention

Unlike ART, PrEP is not intended for lifelong use; it is needed during seasons of potential HIV exposure. The goal for PrEP adherence should therefore be an alignment with this risk, rather than 100% use for an artificially defined period, such as the duration of a clinical trial. A recent paper introduced the term “prevention-effective adherence” to explore this concept, which accounts for dynamic behavior, circumstances, and use of alternative HIV prevention tools (e.g., condoms, use of ART by known HIV-infected partners) over time (27). Importantly, high PrEP adherence in the absence of risk for HIV acquisition is not advantageous to the PrEP user (e.g., potential side effects, time needed to pick up refills) or to society (e.g., cost of unnecessary medication). These factors are impeding the rollout of PrEP in all settings and are particularly important for those with limited resources, which may be hesitant to implement PrEP if it is not targeted efficiently.

Prevention-effective adherence depends on the ability to understand risk for HIV acquisition, which may be difficult. The low PrEP adherence seen in VOICE and FEM-PrEP despite high incidence of HIV infection suggests women may have particular challenges. However, adherence was higher among women in FEM-PrEP who did rate their risk as high (57). Risk perception may also be a challenge for adolescents, given typical neurocognitive development (58) and the adherence challenges discussed above. Importantly, as noted earlier, the high efficacy seen in IPERGAY despite variable adherence patterns suggests that individuals may indeed be able to align their risk and adherence well.

Future research should explore the concept of risk perception in an effort to help individuals understand it and motivate adherence accordingly. Commonly used questions like, “What is

your chance of getting HIV in the next [time frame]?" may not be meaningful. Other factors, such as pleasure (59), future orientation (60), comparative risk (61), and affect (62), have been associated with risk taking for HIV and other conditions, and should also be explored further. Varying degrees of risk attitudes (e.g., tolerance or aversion) should also be considered (63). Assessment of life aspirations and how prevention of HIV via effective PrEP adherence fits into that picture may be another promising approach. Importantly, like adherence generally, risk perception will need to be studied outside of clinical trials, because any self-determinations of HIV risk may include the risk of placebo and/or concerns about drug efficacy.

It is also important for PrEP users to know how much PrEP is enough PrEP. Current recommendations indicate that PrEP should be used on a daily basis (64, 65); however, a pharmacokinetic modeling study using data from iPrEx indicated that four doses a week may be sufficient to achieve 96% efficacy (66). This concept of "doses per week" may be easier for individuals to understand and achieve. The high efficacy associated with "on demand" dosing in IPERGAY adds support for alternate dosing regimens. Further research is needed, though, given the lower adherence seen with intermittent compared with daily regimens in the IAVI trial, as well as the ADAPT study. Additionally, recent pharmacokinetic studies suggest women may need a higher number doses per week to achieve similar levels of protection (67, 68). Knowing the level of "forgiveness" is important for the decision to take PrEP. The expectation of perfection may dissuade many for whom PrEP could be a highly effective prevention option. Additionally, those unable to achieve sufficient dosing may need guidance toward other prevention options, such as condoms.

Conclusion

Experience with recent trials, open-label extensions, and demonstration projects suggests that PrEP adherence may be higher in many populations than that seen in the initial clinical trials. Promising adherence measures include SMS and wireless electronic monitoring, as well as hair and dried blood spots for longer-term objective adherence assessments. Adherence intervention may be best achieved through targeted, enhanced counseling, as facilitated by technology and/or adherence feedback where feasible. Efforts should be geared to the needs of those selecting PrEP and helping them align PrEP use with periods of risk for HIV acquisition, thus achieving patterns and levels of adherence that provide effective protection against HIV.

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Key points

- PrEP adherence has generally been higher in recent trials, open-label extensions, and demonstration projects compared to the initial clinical trials; potential explanations include known PrEP efficacy and different motivations to take PrEP.
- More PrEP adherence data are needed for women and adolescents outside of clinical trials to determine the need and nature of adherence interventions.
- Future efforts for PrEP adherence should focus on methods to align HIV risk and adherence to the prevention choice most appropriate for a given individual.

Table 1

Adherence and efficacy in clinical trials, open-label extensions, and demonstration projects. The initial clinical trials (i.e., completed or stopped by 2013) are shaded in light gray.

	Study design	N	Adherence	Efficacy/Effectiveness
Men who have sex with men (multiple geographic regions)				
iPrEx (3)	Placebo controlled RCT of daily TDF/FTC	2,499	51% by drug detection	44% (95% CI 15, 63%; p=0.005)
iPrEx OLE (15)	Single arm OLE of daily TDF/FTC	1,603	71% by drug detection	49% (95% CI −1, 74%)
PROUD (16)	Randomized wait-listed trial (randomization to immediate versus 12-month delayed daily TDF/FTC)	545	86% of days participants would be taking PrEP if everyone's adherence were 100%	86% (95% CI 62, 96%; p=0.0002)
IPERGAY (17)	RCT (placebo versus on demand dosing of TDF/FTC)	400	Median 16 pills/month by pill count; 43% optimal use, 25% suboptimal use by ACASI	86% (95% CI 39, 99%, p=0.002)
The Demo Project (18)	Demonstration project of daily TDF/FTC	557	95–100% with detectable drug 73–92% with 4+ doses/week	–
Project PrEPARE* (19)	Pilot RCT of counseling intervention (all received daily PrEP)	55	84% with drug levels consistent daily use	–
Project PrEPare* (20)	Demonstration project of daily TDF/FTC in young MSM	200	34% of participants had drug levels consistent with 4+ doses/week	–
Women in Africa				
FEM-PrEP (6)	RCT of placebo versus daily TDF/FTC	2,120	37% by drug detection	6% (95% CI −52, 41%; P=0.81)
VOICE (4) (oral arms only)	RCT of daily TDF versus TDF/FTC versus placebo	3,019	28–29% by drug detection	TDF: −49% (95% CI −129, 3%); TDF/FTC: −4% (95% CI −49, 27%)
ADAPT (21)	Open-label comparison of daily versus non-daily TDF/FTC	179	79% (daily), 63% (time driven), 53% (event driven) by drug detection	–
Serodiscordant couples in Africa				
Partners PrEP Study (1)	RCT of TDF versus TDF/FTC versus placebo	4,758	82% by drug detection	TDF: 67% (95% CI 44, 81%; p<0.001) FTC/TDF: 75% (95% CI 55, 87%; p<0.001)
Partners Demonstration Project (22)	Demonstration project involving TDF/FTC and ART	1,013	86% by drug detection	96% (95% CI 81,99%; p<0.0001)
Heterosexual men and women in Africa				
TDF2 (5)	RCT of TDF/FTC versus placebo	1,219	84% by clinic pill count	62% (95% CI 22, 83%; P=0.03)

RCT=randomized controlled trial, OLE=open-label extension, ACASI=audio computer-assisted self-interview, TDF=tenofovir, FTC=emtricitabine, ART=antiretroviral therapy.

*These studies were independent despite similar names.

Table 2

PrEP Adherence Interventions. Data from initial clinical trials (i.e., completed or stopped by 2013) are shaded in light gray.

Study	Intervention type	Description	Effect
Partners PrEP Ancillary Adherence Study (46)	Enhanced counseling (Life Steps)	Flexible number of sessions addressing barriers and facilitators, included an optional couples component	Mean adherence during the month before the intervention was 76%, and increased significantly to 84% in the month after the first intervention session (p<.001).
Project PrEPARE (19)	Enhanced counseling (Life Steps) with adherence and sexual behavior feedback	Four weekly sessions that addressed barriers and facilitators; adherence was measured with Wisepill and sexual behavior was assessed with SMS	No benefit; high adherence seen for all participants
iPrEx OLE (47)	Enhanced counseling (Next-step)	Two-parts exploring contextual facilitators, barriers and individualized needs for enhancing sexual health promotion, PrEP adherence, and the desire to continue PrEP	–
iText (48)	mHealth	SMS-based support system	For the mean number of missed doses, RR=0.5 (95% CI 0.3–0.8, p=0.008) by pill count and RR=0.5 (95% CI 0.3–0.9, p=0.023) by self-report