

Adherence to Preexposure Prophylaxis: Current, Emerging, and Anticipated Bases of Evidence

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Despite considerable discussion and debate about adherence to preexposure prophylaxis (PrEP) for human immunodeficiency virus (HIV), scant data are available that characterize patterns of adherence to open-label PrEP. The current evidence base is instead dominated by research on adherence to placebo-controlled investigational drug by way of drug detection in active-arm participants of large randomized controlled trials (RCTs). Important differences between the context of blinded RCTs and open-label use suggest caution when generalizing from study product adherence to real-world PrEP use. Evidence specific to open-label PrEP adherence is presently sparse but will expand rapidly over the next few years as roll-out, demonstration projects, and more rigorous research collect and present findings. The current evidence bases established cannot yet predict uptake, adherence, or persistence with open-label effective PrEP. Emerging evidence suggests that some cohorts could execute better adherence in open-label use vs placebo-controlled research. Uptake of PrEP is presently slow in the United States; whether this changes as grassroots and community efforts increase awareness of PrEP as an effective HIV prevention option remains to be determined. As recommended by multiple guidelines for PrEP use, all current demonstration projects offer PrEP education and/or counseling. PrEP support approaches generally fall into community-based, technology, monitoring, and integrated sexual health promotion approaches. Developing and implementing research that moves beyond simple correlates of either study product use or open-label PrEP adherence toward more comprehensive models of sociobehavioral and socioecological adherence determinants would greatly accelerate progress. Intervention research is needed to identify effective models of support for open-label PrEP adherence.

Keywords. study product adherence; PrEP adherence; social science; behavioral science.

The last several years has witnessed a surge of research addressing preexposure prophylaxis (PrEP) for human immunodeficiency virus (HIV), and a number of reviews are available [1–8]. The focus of this review is to provide the current evidence base for PrEP adherence with a specific emphasis on current knowledge and

remaining gaps, highlighting the areas for improvement and contribution from sociobehavioral science. This review is sectioned into data concerning study product adherence in the context of randomized controlled trials (RCTs) testing PrEP safety and efficacy with placebo-controlled blinded methods, and data concerning open-label PrEP. Our contention is that adherence to experimental study drug and PrEP (an antiretroviral medication with known HIV prevention benefits) will not be identical or interchangeable, although their degree of separation is difficult to determine relying on currently available literature. This gap will be addressed through emerging data that unpack factors influencing study product use and through demonstration project data regarding rates of adherence and longevity (or persistence) with PrEP. Anticipated data coming from roll-out, demonstration projects, and trials using open-label

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Table 1. Major Preexposure Prophylaxis Trials

Study	Efficacy	Estimated Adherence by Drug Concentration
PP-TDF/FTC [10]	75%	75%–80%
PP-TDF [10]	67%	67%–80%
TDF2 –TDF/FTC [14]	62%	80%
BKK-TDF [11]	49%	67%
iPrEX –TDF/FTC [12]	44%	51%
CAPRISA–TDF Gel BAT24 [9]	39%	38%–98%
VOICE-TDF Gel Daily [13]	14.7%	22%
FemPrEP–TDF/FTC [15]	6%	37%
VOICE-TDF/FTC [13]	–4%	29%
VOICE-TDF [13]	–49%	28%

Abbreviations: BKK, Bangkok Tenofovir Study; CAPRISA, Centre for the AIDS Programme of Research in South Africa; FTC, Emtricitabine; iPrEX, Iniciativa Profilaxis Pre-Exposición; PP, Partners PrEP; TDF, Tenofovir disoproxil fumarate; TDF2, Botswana TDF/FTC Oral HIV Prophylaxis Trial; VOICE, Vaginal and Oral Interventions to Control the Epidemic.

PrEP will shift the landscape of the evidence base in the near future. Issues to consider as we shape research, practice, and policy agendas are reviewed.

Rates and Correlates of Study Product Adherence in Placebo-Controlled RCTs

Across the major PrEP RCTs (Table 1 [9–15]), the association between efficacy and estimated adherence (detectable drug) is clear and approximates a sigmoid dose-response curve [16]. Larger effects were reported by trials with higher proportions of participants with drug detected, leading many to conclude that the drugs work if taken [17]. Reports to date from these trials suggest multiple levels of ecologic influences on adherence to study product.

Individual Demographic and Behavioral Factors

Reports from PrEP RCTs have identified a number of individual-level demographic and behavioral variables associated with study product adherence. Discrete correlates of product adherence have included older age, sex (female), marriage (vs not being married or in polygamous marriages), higher socioeconomic status, higher education level, absence of heavy or binge alcohol use, and sexual activity [13, 18–21]. The most consistent correlate across studies to date appears to be age, such that younger trial participants indicate worse study product adherence than older trial participants.

Risk and Risk Perception

Risk perception may importantly contribute to study product adherence in PrEP RCTs. The FEM-PrEP trial reported that 70% of participants perceived themselves to be at low risk for HIV infection [15], and this trial received early discontinuation due to futility. It may be that the perceived risk of HIV infection

among these participants was too low to promote use of study product. Conversely, the highest levels of product use in PrEP RCTs were observed within the Partners PrEP trial, where adherence to study product in a substudy approached 100% [19]. Qualitative interviews with trial participants revealed the belief that adherence to study product helped reduce anxiety over the risk of HIV transmission in their serodiscordant relationships [22]. Even though all trials strongly advise participants not to rely on the product provided to prevent HIV infection (eg, active drug is under investigation and received product is potentially placebo), beliefs in the possible efficacy of the study product may remain, and have been described as misconceptions given all of the information provided to participants *not* to develop such beliefs (eg, prevention misconception [23]). Nonetheless, in situations where risk is substantial and options for mitigating risk are minimal, use of study product may increase one's sense of doing "something" proactive either for themselves or for possible prevention strategies that could be available to them in the future. These insights widen the ecologic circle of possible influences on study product adherence beyond individual-level demographic and behavioral factors to psychosocial concerns, such as beliefs in product effectiveness, perceived risk of HIV infection, relationship context, and relationship dynamics.

Acceptability

Acceptability of either the delivery strategy (eg, pills, gel) evaluated or of the presence of a biomedical clinical trial more generally in the community likely influence product use. Results from 2 major trials in sub-Saharan Africa, each focused exclusively on women in highly endemic areas, have raised questions about the acceptability of certain drug delivery strategies as a potential determinant of study product adherence in certain settings or populations. Both FEM-PrEP [15] and the Vaginal and Oral Interventions to Control the Epidemic (VOICE) studies [13] had null or negative efficacy (Table 1) and reported drug exposure levels that suggested that a sizable proportion of their participants did not use the study drug. Emerging work on temporal patterns of drug detection suggests that a proportion of trial participants in these trials never had drug detected over any available assessment. Adherence refers to one's patterns of use for a regimen that he or she has adopted or engages with, and persistence refers to the length of time one engages with a regimen [24]. If some trial participants never started the regimen in the first place, then this would be more akin to notions of product uptake and adoption than product adherence or persistence. With high retention and engagement in other aspects of the study, selective nonengagement with the study product is an inconsistency that warrants better understanding.

Although higher rates of study product adherence were observed among women enrolled in the Botswana TDF2 PrEP

trial [14], as well as those in the Partners PrEP trial [10], some have suggested that low study product uptake and use in trials may signal regional differences in the acceptability of drug delivery strategies used (eg, pills, gel, ring). Regional differences in the percentage of participants with detectable drug levels have been noted in several prevention studies (eg, *Iniciativa Profilaxis Pre-Exposición [iPrEx]* [12], *Microbicide Trials Network 001 [MTN001]* [25]), with higher rates of detection in the United States than elsewhere. Whether these differences may reflect regional or population differences in the acceptability of using biomedical agents for HIV prevention or a particular delivery system (eg, pills, gel) is presently unclear. Efforts to identify alternative delivery systems that increase the available delivery options for PrEP could be helpful. Current efforts include alternatives for delivery (eg, *ASPIRE [A Study to Prevent Infection With a Ring for Extended Use]* trial of dapivirine ring [26], long-acting agents [27, 28], and combined multipotent approaches [eg, combined birth control and antiretrovirals for prevention] [29]).

An emerging perspective regarding study product use and nonuse in HIV prevention trials calls attention to larger socio-cultural phenomena that may signal conflict between communities and the presence of biomedical research. Detailed qualitative work [30] in communities hosting microbicide trials has identified 3 major themes from interviews conducted among female participants, partners, and community members in South Africa; “malicious whites” (reflecting a discourse of prevention trials being foreign, as well as local beliefs that study drugs or procedures may infect women with HIV or otherwise violate personal rights by selling blood or body parts, and overall lack or reciprocity between the trial and the community), “greedy women” (reflecting perceptions of community members that women participating in these trials were self-centered, invested in self over family, and intentionally deceitful to both the study team and the community), and “virtuous volunteers” (reflecting a discourse supporting trial participants and their participation as a contribution to the safety of the community) [30]. The authors position each theme into the social, cultural, and historical context of the community that continues to carry a disproportionate burden of disease and economic disparity in the context of changing socioeconomic structures and gender roles. Understanding the relative contribution of cultural and community perspectives on clinical trials and biomedical agents to low study product uptake and adherence is critically important in setting agendas for ongoing and future research [31].

Correspondence Between Study Product Adherence and PrEP Adherence

Much of the existing literature uses the term “PrEP adherence” when discussing study product adherence. We use the term

“study product adherence” to refer to adherence in the context of blinded RCTs, and reserve the term “PrEP adherence” to describe adherence in the context of open-label effective PrEP use. This distinction reflects important differences between these 2 contexts, and it can be helpful as the field increasingly moves from trial results to open-label findings over the coming years.

The fact that a sizable proportion of participants in some PrEP trials did not show adequate adherence to study product has cast considerable doubt on the potential effectiveness of PrEP for impacting the HIV epidemic in real-world use. Although we recognize these concerns, we simply do not yet know whether open-label PrEP adherence will show patterns similar to those seen in blinded RCTs, or whether determinants of study product adherence will be generalizable to individuals who are seeking out and opting to use open-label PrEP as a prevention strategy.

Many factors differ between one’s engagement with an open-label PrEP regimen and a regimen that is provided in the context of an investigational controlled research trial. Some considerations argue for lower rates of open-label PrEP adherence relative to study product adherence. Typically, the intensive adherence support and monitoring included in clinical trials (eg, those provided in PrEP trials [19, 32]) are thought to produce higher, rather than lower, rates of adherence when contrasted to real-world efficaciousness (see [33]). Alternatively, open-label PrEP adherence may actually exceed study product adherence. Motivation to adhere to study product vs an active drug regimen with known prevention benefits would likely have different underlying drivers. For example, one adaptation of an information-motivation-behavioral skills model [34] to study product use suggested that research engagement beliefs (positive attitudes toward contributing to HIV prevention research and understanding of and trust in clinical trials) are more relevant to study product use than individual health promotion beliefs [35]. Applications of socioecological models to product use are emerging that similarly position use and nonuse within larger community and cultural belief structures concerning clinical trials [36]. To date, few decision-making or health promotion models articulated to study product use have been proposed and fewer rigorously evaluated, which is a gap that sociobehavioral science should work to address.

PrEP Adherence and Uptake

The evidence base regarding adherence rates or determinants in the context of open-label PrEP is very limited at present. Grant et al [37] presented data on drug detection levels in the open-label extension (OLE) of the iPrEx study. In this study, former iPrEx RCT participants were offered open-label PrEP, and were told that they could also choose to continue to engage in the research and receive HIV testing, sexually transmitted infection testing and treatment, condoms, and safer sex promotion counseling without PrEP. Among the former iPrEx

participants eligible for PrEP ($n = 1451$), 72% opted to receive PrEP, a high rate of acceptance. These PrEP adopters were older and reported lower educational attainment and more recent condomless receptive anal intercourse than nonadopters. Drug detection data confirmed that 72% had detectable drug levels, compared with the estimated 51% with drug detection in the RCT phase, suggesting that adherence to open-label PrEP in this population could exceed that observed in the prior efficacy trial. In the open-label extension, to date, drug detection was more common among participants who were older, who held higher attained education, and who had drug detected in the RCT phase (active arm participants). More comprehensive data concerning factors supporting PrEP adherence in iPrEx OLE are being collected using mixed-methods approaches. Data collection for the study concluded at all sites in January 2014.

Mera and colleagues from Gilead Sciences presented a poster recently that characterized utilization data specific to Truvada for PrEP in the United States from January 2011 to March 2013 [38]. Of the 1774 individuals starting PrEP across 49 states in 700 different cities, the median age was 37, 48% were women, and prescribing tended to be from non-infectious disease clinicians who did not appear to also prescribe Truvada for treatment. Geographically, 18% percent of PrEP prescriptions originated in the Midwest, 24% in the West, 24% in the Northeast, and 32% in the South. Although the total number of PrEP initiators may appear low, slow uptake would be expected given that PrEP is not advertised and penetration of knowledge about the availability of PrEP in at-risk communities has been driven heavily by grassroots efforts rather than organized health promotion campaigns to date.

The next several years will include a substantial expansion of the evidence base characterizing uptake, adherence, and persistence with PrEP. A number of demonstration projects have launched among men who have sex with men (MSM) in the United States, and several are planned for heterosexual men and women. Factors influencing PrEP adherence are being collected in these projects, including knowledge, personal and interpersonal attitudes and beliefs, perceived risk of HIV infection and efficacy to mitigate risk, and barriers and facilitators of PrEP adherence. These efforts to move beyond basic demographic correlates (eg, age, education) to more comprehensive sociobehavioral models will provide a deeper understanding of PrEP uptake and adherence, and identify areas for intervention. PrEP demonstration projects are also monitoring use of other prevention strategies, including condom use, to evaluate if and how PrEP use may influence prevention practices other than PrEP. It is possible that PrEP use could either decrease engagement with other prevention practices (risk compensation or safety offset) or increase their use (prevention synergy).

Supporting PrEP Adherence

Strategies leveraged in clinical trials to support study product use have included theory based one-on-one and group education and counseling that use principles of motivational interviewing [39] and cognitive behavioral therapy [40, 41], either targeted to those struggling with adherence [19] or provided as part of each clinical visit [32]. In a number of demonstration projects in the United States, adherence is similarly supported through standard and targeted strategies. A unique aspect of open-label use of effective PrEP is the potential to combine PrEP adherence discussions with other non-PrEP HIV prevention strategies. Doing so in PrEP efficacy RCTs is not possible, as the participant cannot and should not rely on use of the study-provided placebo-controlled pills, gel, or ring for HIV prevention. In addition, real-world PrEP use is expected to be a time-limited approach for many. Persistence with PrEP in practice is not technically necessary when situations change and HIV risk decreases or other effective prevention strategies are preferred. This is contrasted to study product use, which requires persistence through the full length of the trial to determine safety and efficacy. Appropriate cycling on and off of PrEP is another area where adherence to recommendations will play an important role in avoiding potential negative outcomes of cycling onto PrEP without confirmation of HIV-negative status.

Consistent with Centers for Disease Control and Prevention and World Health Organization clinical guidelines [42–45], all demonstration projects have some form of adherence education and/or counseling, which have been characterized loosely into community-level, technology-based (eg, texting, mobile apps, websites), monitoring-based (eg, providing information about drug detection, intensification of intervention based on drug detection), and integrated prevention strategies [8]. Integrated sexual health promotion counseling [46] and comprehensive care [47], where the focus is on personalized prevention plans and overall health, rather than adoption of and adherence to a single prevention strategy (eg, PrEP), is an innovative approach unique to open-label PrEP projects.

Efforts to engage community continue to be needed. An individual's choices and behaviors are best understood when contextualized by community and cultural systems and structural access according to a number of sociobehavioral and socioecological models. PrEP uptake and use may be particularly challenged in the context of community disapproval or any emergent "PrEP user stigma" (where PrEP users are portrayed as lacking accountability and disregarding the safety of self and others). Many demonstration projects and grassroots efforts are targeting community awareness and discussion around PrEP. How this may impact individual behaviors is an important area of research focus.

Within the decade to come, results from a number of open-label PrEP studies are anticipated. These include, but are not limited to, projects investigating intermittent PrEP adherence

(the Alternative Dosing to Augment PrEP Pill Taking [ADAPT] Study: HPTN067 [HIV Prevention Trials Network] [48]), PrEP adherence in young MSM in the United States (ATN110/113 [Adolescent Trials Network]), black MSM in the United States (HPTN073 [47]) and among MSM in the United Kingdom (PROUD [Pre-exposure Option for reducing HIV in the UK] study [49]); follow-on and extension studies offering former PrEP RCT participants active open-label PrEP (Partners PrEP, iPrEx OLE, TDF2); and the impact of delivery of microbicide gel from research or family clinics (CAPRISA008). These will combine with a host of demonstration projects to provide much-needed information on rates and determinants of PrEP adherence. There is additionally a strong need for controlled research that directly tests the viability and impact of PrEP adherence support interventions, which may vary in terms of their timing (at initiation vs at each visit), targeting (provided to all or only those indicating nonadherence), and modality.

Conclusions

The current evidence base for sociobehavioral issues germane to PrEP predominantly comprises data collected in the context of investigational RCTs. Emerging evidence suggests that many factors may distinguish study product use in RCTs from open-label effective PrEP adherence. Although the current evidence base does not yet include characterization of open-label PrEP uptake, adherence, or persistence, emerging evidence presented in recent conferences suggests that some correlates of study product use (eg, age, education) may similarly predict adherence to open-label PrEP. Gaining a more nuanced understanding of factors influencing PrEP should be a behavioral research priority, particularly in the United States as individuals start to avail themselves of this prevention innovation outside of research projects. Anticipated evidence from demonstration projects, open-label PrEP studies, follow-on projects, and RCT extensions will provide a much needed dramatic widening of our knowledge base in the next several years. Information continues to emerge relative to both placebo-controlled study drug use and PrEP use, and we recommend being clear in presentation of results about which adherence is being presented (either adherence to study product or adherence to PrEP), reserving the term PrEP adherence for open-label effective PrEP. Either model should push beyond discrete demographic correlates to more comprehensive psychological and socioecological models of adherence determinants, which will identify targets for adherence support interventions. Critical questions requiring transdisciplinary attention include how/if PrEP competes with or synergizes other prevention strategies, how many adopters insufficiently adhere to PrEP, and which kinds of support appear effective, cost-effective, and feasible for implementation in care environments that are not experienced in prescribing ART. When added to calls for more research with

adolescents, women, and transgendered women, as well as methodologies for monitoring and quantifying PrEP adherence, the emerging sociobehavioral evidence base for PrEP should provide substantial guidance for research and practice communities alike.

Notes

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