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Optimizing Pre-Exposure Antiretroviral Prophylaxis Adherence in Men Who Have Sex with Men: Results of a Pilot Randomized Controlled Trial of “Life-Steps for PrEP”

Kenneth H. Mayer^{1,2,*}, Steven A. Safren^{1,3,*}, Steven A. Elsesser^{1,4}, Christina Psaros⁵, Jake Tinsley¹, Mark Marzinke⁶, William Clarke⁶, Craig Hendrix⁶, S. Wade Taylor^{1,7}, Jessica Haberer⁵, and Matthew J. Mimiaga^{1,8}

¹The Fenway Institute, Fenway Health, Boston, MA

²Beth Israel Deaconess Medical Center, Harvard Medical School, Harvard T.C. Chan School of Public Health, Boston, MA

³University of Miami, Miami, FL

⁴Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA

⁵Massachusetts General Hospital, Harvard Medical School, Boston, MA

⁶Johns Hopkins University, Baltimore, MD

⁷Wheelock College, Boston, MA

⁸Brown University, Providence, RI

Abstract

Introduction—Antiretroviral pre-exposure prophylaxis (PrEP) has been demonstrated to decrease HIV acquisition in multiple efficacy trials, but medication adherence is critical, and was suboptimal in several studies.

Methods—Fifty HIV-uninfected at risk men who have sex with men (MSM) were randomized to a cognitive behavioral intervention condition or a time and session-matched comparison counseling intervention. The experimental intervention entailed four nurse-delivered initial and two booster sessions based on Life-Steps, an ART treatment adherence intervention. The comparison condition provided information and supportive counseling. The primary analyses compared adherence (Wisepill and tenofovir plasma levels) at 3 and 6 months.

Corresponding author: Kenneth H. Mayer, MD, Infectious Disease Attending and Director of HIV Prevention Research, Beth Israel Deaconess Medical Center, Professor of Medicine, Harvard Medical School, Medical Research Director, The Fenway Institute, Fenway Health, 1340 Boylston St, Boston, MA 02215, kmayer@fenwayhealth.org, t. 617.927.6087 f. 617.267.0764.
*co-primary authors

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COMPLIANCE WITH ETHICAL STANDARDS:

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Results—Fifty-eight MSM were screened to enroll 50 participants. Median age was 38.2 years old, 86% were white; 64% had completed college. Wisepill adherence was high in both groups, and not statistically different. Plasma tenofovir levels were significantly higher in the intervention group at six months using mean substitution analysis (i.e. computing missing variables) ($p=0.037$), however, in the completer analyses (i.e. using only those completing all study visits), there were no statistically significant differences between randomization conditions.

Conclusions—Medication adherence was high across a cognitive-behavioral (Life-Steps) and time-matched counseling intervention for PrEP adherence, with some evidence suggesting superiority of Life-Steps in this pilot RCT. Further evaluation in a fully powered efficacy trial is warranted to assess the robustness of this intervention.

Keywords

Pre-Exposure Antiretroviral Prophylaxis; Medication Adherence; HIV; MSM

INTRODUCTION

Although the global HIV pandemic has been decreasing in some settings (1), HIV prevalence and incidence among men who have sex with men (MSM) has continued to grow in most countries where it has been tracked (2,3). Daily co-formulated tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) has been shown to be effective in decreasing HIV incidence in at risk MSM in several clinical randomized controlled trials when used as pre-exposure prophylaxis (PrEP) (4-6). In the iPrEx trial, a multinational study of 2,499 MSM and transgender women conducted in the U.S., Latin America, Thailand, and South Africa, HIV incidence among those randomized to TDF/FTC was 44% less than among those who received the placebo (4). Protection exceeded 90% in participants whose drug levels were consistent with taking the medication at least four times a week (7), indicating that PrEP adherence was most strongly associated with PrEP efficacy (8,9). However, only half of the iPrEx participants demonstrated consistent medication adherence. PrEP studies in other high-risk populations demonstrated the importance of consistent medication use to ensure optimal protection against HIV (10-14). In these initial placebo-controlled trials, participants were informed that they might be receiving a placebo and that the efficacy of PrEP had not yet been established, so the reasons for non-adherence might differ from real world use of medication demonstrated to have prophylactic efficacy.

Consistent antiretroviral medication adherence for HIV treatment has been a challenge for some people living with HIV despite the long established finding that non-adherence can result in significant morbidity and mortality (15, 16). Similarly, although PrEP can protect HIV-exposed persons from becoming infected if used consistently, anticipated side effects, psychiatric morbidity, substance use, risk misperception, and socially disruptive events (e.g., termination of a long term relationship or unstable housing) may contribute to suboptimal adherence to PrEP and HIV seroconversion (9,17). The intervention used in this study is based on prior research by our group to increase HIV medication adherence, the Life-Steps intervention (18-20). Life-Steps is a brief adherence intervention that uses general principles of cognitive-behavioral therapy (CBT) and problem-solving therapy (21, 22) and was used in two large-scale antiretroviral trials (23, 24), one of which focused on treatment as

prevention (23). Life-Steps also informed the adherence intervention used in an ancillary study to promote PrEP adherence in the Partners PrEP study, which enrolled serodiscordant couples in East Africa (25, 26). Life-Steps is a client-centered, scalable, counseling intervention, which has demonstrated success in improving antiretroviral medication adherence in people living with HIV (19). It involves the provision of education and also incorporates techniques drawn from motivational interviewing (27) and problem solving (28, 29 to maximize behavior change. In order to optimize the benefits of PrEP for high risk MSM a multidisciplinary investigator team conducted formative qualitative focus groups with PrEP-experienced and PrEP-naïve MSM (30), and used these findings and the framework of the adherence intervention used in the Partners PrEP trial (25) to fully adapt the “Life-Steps for PrEP” intervention for MSM initiating PrEP.

The present study was a pilot randomized controlled trial designed to preliminarily test “Life-Steps for PrEP” compared to an active, time and session-matched comparison condition. The primary study outcome was PrEP adherence, assessed via electronic real-time adherence monitoring (Wisepill™), as well as quantification of plasma tenofovir (TFV) levels between the two study conditions at three and six months. We also examined the frequency of condomless anal sex in both conditions to explore the degree to which rates condomless sex continued during PrEP coverage. The study team hypothesized that participants randomized to “Life-Steps for PrEP” would have enhanced PrEP adherence compared to those in the time and session-matched comparison condition.

METHODS

Design

The study was an open label two-arm, pilot randomized controlled trial of MSM presenting for PrEP at Fenway Health, the largest clinic providing primary care for sexual and gender minority patients in New England (31). Enrolled participants were equally randomized to either: 1) “Life-Steps for PrEP”, a nurse-delivered, CBT-oriented PrEP adherence intervention, or 2) a time and session-matched comparison condition.

Recruitment

Participants were recruited by community outreach by the staff of Fenway Health, a Boston community health center with expertise in sexual and gender minority health. Participants were recruited via advertisements on social media, including several sites where MSM meet sexual partners, and flyers posted within the waiting areas of Fenway Health’s clinical care sites.

Inclusion/exclusion criteria

Eligible participants were those assigned male sex at birth, 18 years of age or older, HIV-uninfected at screening (confirmed via HIV blood test), and at high risk for HIV acquisition, defined by having condomless anal sex (insertive or receptive) with an HIV-infected partner at least once in the prior three months, or condomless anal sex (insertive or receptive) at least three times in the last three months with at least two partners during the same time period. Participants also had to be able to understand study procedures and give informed

consent (evidenced by signature on the informed consent form), able to understand and speak English, and had to be medically cleared to take the study drug (normal hepatic, renal and hematological lab tests). Participants were excluded if they could not provide informed consent due to psychiatric or cognitive concerns, had been previously prescribed PrEP, had been prescribed any ARV in the past three months (i.e. post-exposure prophylaxis), had a history of, and/or, current medical conditions that would preclude taking the study drug, including the use of agents with significant nephrotoxic potential, were in an anti-HIV vaccine clinical trial, reported active alcohol or drug use that might interfere with study participation, or had other concerning conditions, based on opinion of investigators.

Procedures

The study protocol consisted of nine visits over the course of six months. Participants who were pre-screened by study staff and determined to be potentially eligible for the trial were invited to take part in a screening visit where eligibility was ultimately determined, based on interview and safety lab results. Eligible individuals were invited back the following week for the first of four weekly counseling sessions. The initial counseling session was the same for all participants and focused on introducing the program, rapport building, and providing educational information about PrEP. Participants were equally randomized to either the “Life-Steps for PrEP” intervention, or to the time and session-matched comparison condition. Participants in both study conditions were provided with a 6-month supply of study product over the course of the study. Participants received their first 30-day supply of study product at their first counseling session. Subsequent study visits consisted of three additional weekly counseling sessions and four follow-up visits at one, two, three, and six months after enrollment. The follow-up sessions at two and three months were booster sessions that included content specific to participant’s randomized condition. Study burden was equal across the two conditions.

Interventions

“Life-Steps for PrEP” condition—The experimental intervention, which has been described in greater detail previously (32), was derived from Life-Steps (18,19), and consisted of four weekly sessions and two booster sessions, which occurred two and three months after PrEP initiation. The intervention component of each visit lasted approximately 50 minutes. The first session included education about PrEP, a discussion involving the psychosocial context in which PrEP use would occur, a brief motivational interviewing exercise, and exploring the establishment of a regular dosing schedule. Session two began with an adherence check-in, then focused on understanding the clients’ experiences taking PrEP, and engaging in problem solving to address any reported barriers to adherence. Session three also began with an adherence “check-in” and then introduced sexual risk behavior education, identifying high-risk activities, and factors that could increase and decrease personal risk for HIV as well as other sexually transmitted infections. The session also involved a discussion about biological factors associated with HIV transmission (e.g., partners’ level of infectiousness, measured by plasma HIV RNA), and discussed ways to reduce their risk in the context of taking PrEP. Overall, the core components of the intervention focused on medication adherence, sexual behavior, and problem solving barriers to adherence. Session content was designed to be flexible, allowing patients to identify their

adherence support needs. Optional modules provided a framework to help interventionists work with participants who were experiencing substance abuse or mental health concerns that were adversely impacting PrEP adherence. In the final weekly session, the nurse-counselor discussed PrEP adherence goals and prior session content, and the patient's plans for continued PrEP use upon intervention completion. Booster sessions at months two and three were designed to offer an opportunity for the trained study nurse to monitor PrEP adherence via electronic real-time adherence monitoring in the absence of weekly support. Study nurses used booster sessions to review PrEP adherence over a longer time-span and to address barriers to adherence using problem-solving skills learned during the earlier sessions. For participants who identified no challenges to adherence, the study nurse used the booster session to review and refine the existing adherence plan and help them identify potential future barriers to adherence.

Information and supportive counseling—The time and session-matched comparison condition was comprised of informational and supportive counseling (ISP). Patients randomized to this condition met with a nurse-counselor on the same schedule as those randomized to “Life-Steps for PrEP” (four sessions over four weeks and two booster sessions), but their sessions did not focus on problem solving adherence challenges or other cognitive behavioral interventions. Each ISP session started with education around a particular health concern, such as sexual health, diet, or exercise. After this content was discussed, the interventionist spent the remainder of the session providing supportive counseling on a topic dictated by the participant. These patients were able to discuss general health concerns, including sexual health. They also could discuss nutrition and exercise, and if mental health concerns presented, they were referred to appropriate care at the clinic where the study took place.

Training—Training for the interventions was conducted over two half day sessions. Training content focused on the fundamentals of using cognitive behavioral therapy and problem-solving therapy to support health related behavior change, as well as the intervention protocol. In addition to didactic information, a series of role-plays to illustrate key concepts were used.

Randomization—Randomization was done by the study coordinator, following a computer-generated algorithm, in blocks of four. Randomization allocation was implemented via sequentially numbered envelopes provided to the clinician by the study coordinator in order of enrollment. Due to the nature of the intervention (open label TDF/FTC), no medication blinding occurred.

Study Assessments

Demographics—Participants completed a basic questionnaire that assessed age, race/ethnicity, personal income, education attainment, and relationship status. Substance use self-report was corroborated by standardized assays (33).

PrEP adherence—Medication adherence was objectively assessed via Wisepill™, an electronic pill storage device that allows for real-time adherence monitoring by sending a

date and time stamp each time it is opened using a Subscriber Identity Module (SIM) card. These data were pulled from a central server by research staff using a secure web-based interface. We created a variable for each week that the participant had at least 80% adherence via real-time adherence monitoring. This criterion was used because at the time the protocol was developed, post-hoc pharmacokinetic analyses of iPrEx data found that no HIV seroconversions were seen in participants whose plasma drug concentrations were consistent with taking four or more tablets a week for MSM (7, 8). However, in two studies in women (11,12), PrEP was not found to be effective because of suboptimal adherence. We thought that without additional prospective clinical data for MSM, using a cut-point consistent with taking four pills a week could result in considering people fully protected who might not be, so we selected a higher adherence threshold to identify individuals whose adherence patterns were consistent with a very high level of protection.

Tenofovir plasma levels—Plasma samples were collected at the 3- and 6-month follow-up visits, and analyzed using well-established protocols (34) to corroborate real-time adherence monitoring information and self-reports. TFV was isolated via protein precipitation, and quantified via liquid chromatography-tandem mass spectrometry (LC-MS/MS). Calibration curves were generated via linear regression with $1/x^2$ weighting. The lower limit of quantification for TFV: was 0.51 ng/mL. Drug levels of 52 ng/ml or greater were consistent with daily use (34). The threshold values defining the 3 adherence categories, ≤ 0.5 ng/mL (consistent with not more than once weekly use), 0.5 to 52.0 ng/ml (once weekly to daily use) and ≥ 52.0 ng/mL (daily use), are based on median TFV plasma concentrations at steady-state when taken under direct observation in HPTN 066 (34).

Sexual behavior—Sexual behavior was assessed via: 1) an audio computer-assisted self-interview (ACASI) at each follow-up visit, and 2) a daily text message. In the ACASI, participants were asked about the number of times they engaged in anal intercourse, the HIV status of their partners (HIV-infected, HIV-negative, and HIV- unknown status), and the number of times when condoms were used/not used. For texts, a daily SMS was sent to participants initiating the day they started taking PrEP. In response to this text message, participants could indicate if they engaged in any anal or vaginal sex, and if condoms had been used. “Overall protection” from HIV acquisition was defined as either 80% or greater adherence to PrEP medication as determined via real-time adherence monitoring or no condomless sex in a given week.

Data Analysis—The distributions of all variables were assessed, as were the autocorrelations across time between all study variables and the primary outcomes. Dependent variables were examined to determine which distributional models were most appropriate for subsequent statistical procedures. We examined the equivalence of the random assignment of groups with regards to key baseline characteristics, including socio-demographics and sexual risk-related variables. The primary analyses compared adherence (defined by the real-time adherence monitoring and quantity of TFV detected in blood). For all analyses, two-tailed tests of significance were used, with significance at $\alpha = 0.05$. The original power analysis took into consideration that this was a preliminary study, with limited power for efficacy, and primary emphasis on feasibility and potential estimation of

an effect size. Accordingly, comparisons at any given time point (e.g. the 3 or 6 month assessment) yielded 65% power to detect a medium effect size in study planning. However, the adherence outcome was based on a repeated measures analysis, and for a two-tailed p-value of .05, and a medium effect size (approximately 10% difference in the slope), 25 participants per arm would have resulted in 87% power. Generalized linear models (GLM) were fit to analyze longitudinal data for each analysis. The GLMs were estimated using generalized estimating equations (GEE) with robust standard error estimates (35, 36). All analyses followed an intent-to-treat model, analyzing participants in the study arm to which they were assigned, regardless of fidelity to assigned study condition. Additionally, analyses using mean substitution for the imputation of missing data for the drug detection levels were conducted to obtain a more complete understanding of the data, as this was a pilot RCT. Completer analyses were conducted in parallel with mean substitution analyses to compare levels of significance value using only data from participants who completed all study visits.

RESULTS

Participants were recruited between November, 2012 and December, 2013 (Figure 1), with the last follow-up assessment being June 2014. Eight potential participants were not enrolled in the study: 4 because of having an exclusionary medical condition; 1 because of taking contraindicated medication; 1 because of recent post-exposure prophylaxis use, 1 being found to be HIV-infected at the screening visit; and 1 being lost to follow-up prior to enrollment visit. Demographics are depicted in Table 1. The median age of the participants was 38.4 years, with the vast majority aged between 25 and 50. The vast majority were white (86%), had at least some college education (88%), were fully employed (70%), and 44% earned more than \$60,000 per year. At baseline, there were no statistically significant differences between those in the intervention and comparison condition with regard to age, education, income, race/ethnicity, excessive alcohol use, or drug use (Table 1).

Twenty participants assigned to the comparison condition (80%) and 19 assigned to the intervention (76%) completed the 6-month visit (Figure 1). The major reasons for non-completion included perceived study burden (N=4, 1 in comparison, 3 in intervention arm), relocation (N=3), elevated creatinine (N=2), other adverse event (N=1), and concern about others' perception of PrEP use (N=1, intervention arm). Three serious adverse events (SAEs) were identified. These SAEs occurred in the active comparison condition and included hospitalizations for the following reasons: appendicitis, bowel obstruction, and panic attack that were not related to study product use. The study product was generally safe and well-tolerated, though two participants did develop changes in renal function, which resolved after product discontinuation, and several participants reported mild and transient gastrointestinal symptoms, primarily flatulence or diarrhea, though only one participant discontinued product use because of symptoms. There were no social harms that emerged due to participation in the trial, however one participant discontinued PrEP because of personal concerns of others' perceptions regarding his PrEP use. None of the participants became HIV-infected during the course of the study.

PrEP adherence via real-time adherence monitoring

For 824 out of 1,028 total weeks of follow-up (80.2% of total study time), participants had achieved adherence of 80% or higher as measured by real-time adherence monitoring (Wisepill™). While the comparison condition had fewer observed weeks with at least 80% adherence than the intervention condition (77% vs. 83%), there were no significant differences in the odds of subjects achieving adherence of 80% or greater between the conditions (OR: 0.7, 95% CI: 0.3-1.7, $p=0.48$).

Plasma tenofovir levels

Individuals randomized to the intervention condition did not have significantly higher TFV levels compared to the control condition at 3 months, but at 6 months their levels were significantly higher than the control group ($p=0.037$) (Table Two) using mean substitution for the imputation of missing data and intent-to-treat analyses. By 6 months, 84% of the intervention group continued to have drug levels consistent with daily TDF/FTC use, while only 63% of the comparison group had similar levels ($p=0.03$) using mean substitution for the imputation of missing data (Table Three). However, in the completer analyses, there were no differences between the control and intervention condition.

Substance use

The use of recreational drugs during the study, as measured at 3 and 6 months by self-report and drug assays, was high in both the comparison (66.7%) and CBT groups (75%), ($p=0.56$).

Condomless anal sex

There were no significant differences in amount of condomless sex between the intervention and comparison condition (OR: 0.9, CI: 0.6-1.2, $p=0.47$), assessed as weeks with <100% condom use measured by daily text messages (61% vs. 58%).

Overall protection

Defined as either 80% or greater adherence to PrEP medications via real-time adherence monitoring or no condomless sex in a given week, the overall protection rate in the sample was 932 out of 1028 total weeks of follow-up (90.7%). There were no significant differences in number of protected weeks between the intervention and comparison condition (OR: 1.1, CI: 0.4-3.0, $p=0.9$). During the final week of participation, 41.7% of the participants in the entire sample reported no condomless sex via text messages, 52.8% reported condomless sex and had drug levels consistent with daily PrEP use, and only 5.4% reported condomless sex and had drug levels consistent with less than daily PrEP use.

DISCUSSION

Men who have sex with men (MSM) are disproportionately affected by HIV, with high HIV incidence rates globally (1-3). Although some behavioral interventions have been shown to have a modest impact on decreasing HIV risk (37), sustained impact on HIV incidence in MSM has been limited. The use of TDF/FTC for HIV chemoprophylaxis is an important

addition to prevention tools available to stem the epidemic, but medication adherence is essential to ensure that PrEP is effective (38). The first PrEP study in MSM, iPrEX, found that about half the participants consistently took TDF/FTC, and preventive efficacy was directly related to medication adherence, as measured by blood levels (7), also seen in other PrEP studies (5,6, 10-14). Maintaining protective levels of PrEP adherence in the real world may be challenging for many MSM, given high levels of concomitant behavioral health concerns (e.g. substance use, depression) (39) and adverse social environments (3, 38-43).

The current study suggests that a modest investment of resources in structured staff training and tailored patient counseling may be effective in optimizing the promise of PrEP. Building on our team's experience in developing behavioral interventions to enhance medication adherence for HIV-infected patients (HAART) (17, 18), we tailored a CBT-focused intervention, "Life-Steps," for HIV-uninfected MSM initiating PrEP, and report on the pilot data in this paper. The intervention was individually tailored and allowed participants to focus on specific factors in their lives that they anticipated impeding optimal PrEP adherence. In hopes that the features would make it scalable should it be found to be efficacious (32), the intervention was manualized, and delivered by a trained nurse. Although at the 3 month visit, plasma tenofovir levels were comparable between the time and session-matched comparison condition and the CBT intervention group, by 6 months, the participants in the CBT group had significantly higher tenofovir levels in intent-to-treat analyses, with a greater likelihood that their drug levels reflected daily PrEP taking. Overall, Wisepill™ adherence and protected time (either taking pills or using condoms) were high in both study intervention conditions. These findings suggest that the time-matched control condition, involving 6 sessions of general counseling might also have affected participants' adherence behaviors. Further studies involving larger samples that could involve a more "real world" control condition (i.e. usual clinical practice) may be helpful in determining the true added benefit of the Life-Steps for PrEP intervention.

The TFV drug concentrations suggest that high sustained (6 month) levels of adherence to a daily regimen in the intervention was demonstrated, compared to the time-matched control condition. It could be argued that the differences in adherence reflected by the TFV levels were not clinically meaningful, since a post-hoc analysis of the iPrEX trial (7) and the results of the iPERGAY study (6) suggest that for MSM, maintenance of TDF/FTC levels consistent with taking at least 4 pills a week would confer a very high level of protection against HIV. However, since it is possible that PrEP adherence outside of the controlled setting of a clinical trial may attenuate over time, the demonstration of increased adherence in the CBT group could be associated with longer term, sustained adherence, warranting further study.

Additionally, the participants in the current study were not selected because they had PrEP adherence problems or were at risk for PrEP adherence problems, hence PrEP adherence interventions should be studied in individuals who have greater room for improvement (e.g. those who are depressed, using substances, and/or encounter structural challenges, like housing instability). These findings may suggest that the modest investment in time (4 hours over a month) by a nurse may be cost-effective, since the retail cost of TDF/FTC is about \$15,000 a year in the US, and the life time cost of HIV infection can be many hundreds of

thousands of dollars if a person who fails PrEP subsequently becomes infected, and then requires daily HAART (44). The improved adherence in the CBT arm is also notable since many of the participants continued to engage in condomless sex and used disinhibiting recreational drugs, which could enhance PrEP-users risk for HIV seroconversion. By trying to match the amount of contact the nurse interventionist had with study participants in the control condition, some subtle support for PrEP adherence could have been introduced, since the study visits entailed contact with the clinical setting where PrEP was being provided and interactions with empathic health professionals. The determination of the least intrusive level of intervention and participant contact is a challenge for this type of intervention study that invariably requires clinical assessment, and the use of study instruments to assess participants' behavior between study visits, whether randomized to the behavioral intervention or the matched control condition.

Although this trial provides suggestive, preliminary evidence that a nurse-delivered, structured, CBT-based intervention could improve PrEP adherence and clinical outcomes, further refinement is needed before a definitive recommendation can be made based on this work. Because this was a pilot study, the sample size was small, limiting the robustness of the findings, and the ability to generalize the observations to a wider population of PrEP users. Regarding the small sample size, it is possible that the lack of statistical differences in adherence and the mixed results for tenofovir levels when doing completer versus mean substitution analyses may be due to limited power. This is a particular issue when a time-matched control group is used (as was the case in this study), as well as including anyone wanting to be in the trial versus restricting study entry based on low adherence at the start. It is possible, for example, that motivated PrEP users were also ones to be interested in the study, and therefore were predisposed to be adherent. Additionally, the same nurse delivered both the experimental and control conditions. Although we monitored for possible contamination via clinical supervision, it is possible that the general counseling skills attained via study participation may also play into the difficulties in seeing differences between study arms. With all of this in consideration, the study was not fully powered to determine an effect; these initial data provide strong preliminary evidence in support of the intervention's efficacy, but requires further testing in a fully powered randomized controlled efficacy trial.

Another limitation of the study may be the use of plasma monitoring of tenofovir drug levels as biomarker to corroborate self-reported adherence and Wisepill use. Plasma monitoring can be more readily influenced by recent pill ingestion than measures of intracellular drug (e.g. PBMCs) or tissues reflecting cumulative exposure (e.g. hair), making it susceptible to the "White Coat" effect, i.e. participants taking pills when they knew they were being evaluated at study visits. This seems less likely since the Wisepill readout and plasma levels were highly correlated. Another concern may be the use of a greater than 80% weekly pill taking threshold for optimal adherence, based on an overly conservative assessment of the iPrEX data. Subsequent post-hoc analyses suggest that participants whose drug levels were consistent with taking 4 or more pills per week had over 90% protection (7), so there may be more forgiveness for missed doses of tenofovir-emtricitabine for PrEP than envisioned when the study was conceptualized several years ago.

Most (86%) of the sample was Caucasian, highly educated, and the median age was 38.4 years, which may limit generalizability to racial and ethnic minorities, or younger populations where the U.S. HIV epidemic among MSM is spreading most rapidly (45, 46) and adherence may be more of a challenge for this developmental period. While daily text message surveyed sexual activity and not adherence specifically, this daily text message may have served as a form of reminder and adherence intervention in itself (47). Similarly, use of the real-time adherence monitoring to actively track pill taking may have increased adherence or sustained high baseline adherence in both arms thus diminishing our ability to show an effect of the intervention (48). While retention was generally high, 3 out of the 4 participants who reported study burden as the primary reason for leaving the study were randomized to the intervention condition. This might suggest that not everyone will perceive a need for intervention. More work could be done to identify who will most benefit from these types of interventions. Moreover, the intervention might need further cultural tailoring for MSM living in other parts of the world, or those whose risk is from an HIV-infected primary partner, and may need to incorporate other elements when addressing PrEP for high-risk heterosexuals (e.g. contraception, harm reduction for parenteral substance users, etc.). Recent studies have suggested that individuals with less than perfect PrEP medication adherence may attain high levels of protection (6, 7), but it is not known whether optimal protection might still be achieved by counseling at risk MSM to try to take TDF/FTC on a daily basis.

For PrEP to have a population-level impact in reducing HIV incidence among MSM globally, long-term patterns of adherence must be supported at the time of PrEP initiation. This is very analogous to the role that evidence-based behavioral interventions can have in enhancing medication adherence in HIV-infected patients on highly active antiretroviral therapy (HAART), leading to improved virologic suppression rates (18). Accordingly, further studies of PrEP adherence interventions in general, and this intervention in particular, are warranted.

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Figure 1.
Consort Diagram of Study Flow

Table I

Socio-demographics of Study Participants at Screening

	Total Sample (n = 50)	CBT (n = 25)	ISP (n = 25)	p value (assessing differences by condition)
	Mean (SD) or %			
Age	38.24 (12.6)	40.16 (12.95)	36.60 (11.25)	$p = 0.18$
Race/Ethnicity				$p = 0.06$
White	86%	76%	96%	
Black/African American	2%	0%	4%	
Hispanic/Latino	8%	16%	0%	
Other	4%	8%	0%	
Education				$p = 0.99$
High School Graduate	12%	12%	12%	
Some College	24%	24%	24%	
College Graduate	22%	20%	24%	
Some Graduate Work/ Graduate Degree	42%	44%	40%	
Employment				$p = 0.65$
Employed Full-time	70%	76%	64%	
Employed Part-time	20%	16%	24%	
Unemployed	8%	8%	8%	
Other	2%	0%	4%	
Income				$p = 0.51$
<\$11,999	12%	8%	16%	
\$12,000-\$23,999	12%	8%	16%	
\$24,000-\$59,999	32%	40%	24%	
>\$60,000	44%	44%	44%	
Alcohol, binge drinking past month (5 drinks)				
Yes	62%	60%	64%	$p = 0.78$
No	38%	40%	36%	
Recreational Drug Use, any past month				$p = 0.56$
Yes	64%	60%	68%	
No	36%	40%	32%	

Table II

Plasma Concentration of Tenofovir at 3 and 6 Months

3 Month Visit		6 Month Visit	
Randomization	Mean [Tenofovir] (SD)	Randomization	Mean [Tenofovir] (SD)
Control	131.0 ng/ml (119.6)	Control	101.0 ng/ml (84.1) ^a
Intervention	166.6 ng/ml (121.7)	Intervention	157.8 ng/ml (131.6)

^a $p = 0.037$ compared to intervention group at 6 months, using mean substitution for the imputation of missing data

Table III

Plasma Tenofovir Levels, Stratified by Dosing Pattern

3 Month Visit			6 Month Visit		
TFV Doses in past week ^a	Adherence Category Percent ^b		TFV Doses in past week ^a	Adherence Category Percent ^c	
	Intervention (n=20)	Control (n=21)		Intervention (n=19)	Control (n=19)
None	0%	4.8%	None	0%	5.3%
<7	10%	14.3%	<7	15.8%	31.6%
7	90%	81%	7	84.2%	63.2%

^a Number of doses per week estimated by plasma tenofovir levels:

- <0.5 ng/ml = None
- 0.5 - 52 ng/ml = <7
- >52.0 ng/ml = 7

^b p = NS between intervention and control p = 0.03 using mean substitution for the imputation of missing data