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Factors Associated with Adherence and Concordance Between Measurement Strategies in an HIV Daily Oral Tenofovir/ Emtricitabine as Pre-exposure Prophylaxis (PreP) Clinical Trial, Botswana, 2007-2010

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Abstract

This study examined study product adherence and its determinants in the Botswana oral pre-exposure prophylaxis efficacy trial. Among the 1,219 participants, the mean adherence by pill count and 3-day self-report was 94 % for each. In multivariable models, pill count adherence was significantly associated with adverse events (nausea, dizziness, vomiting) (RR 0.98 95 % CI 0.98–1.00; $p = 0.03$) and side effect concerns (RR 0.98 95 % CI 0.96–0.99; $p = 0.01$). Self-reported adherence was significantly associated with having an HIV-positive partner (RR 1.02 95 % CI 1.00–1.04; $p = 0.02$) and Francistown residence (RR 0.98 95 % CI 0.96, 0.99; $p = 0.0001$). Detectable drug concentrations showed modest associations with self-report and pill count adherence, and drug levels were higher among those self-reporting 100 % adherence than those reporting <100 %. Most common adherence barriers involved refill delays and other logistic challenges; cellphone alarm reminder use was the most common facilitator.

Keywords

Oral pre-exposure prophylaxis (PrEP); Adherence; HIV prevention

Introduction

A series of landmark clinical trials have demonstrated that daily oral pre-exposure prophylaxis (PrEP) can be highly efficacious in preventing HIV acquisition. The Botswana trial, known as the TDF2 trial, showed that a regimen containing tenofovir disoproxil fumarate and emtricitabine (TDF/FTC, known by the brand name Truvada®) was 62.2 % efficacious in preventing HIV infection among at-risk young men and women [1]. Other prevention trials have similarly established proof of concept for daily oral PrEP among samples of adult heterosexual African men and women in serodiscordant partnerships (partners PrEP trial) [2], among men who have sex with men (MSM) and transgender women who have sex with men (iPrEx trial) [3, 4].

Trials of daily oral PrEP regimens indicate that the efficacy of PrEP for HIV prevention may be importantly influenced by adherence. Among a subset of Partners PrEP participants who received active drug, plasma drug concentration assays showed detectable drug in 31 % of participants who seroconverted, compared to 82 % of a matched sample of participants who remained uninfected [2]. A similar pattern was observed in the TDF2 trial, where detectable TDF/FTC drug concentrations were found in 50 % (2 of 4) of participants who became HIV infected, compared to 80 % (55 of 69) for tenofovir (TFV) and 81 % (56 of 69) for emtricitabine (FTC) of a matched sample that did not seroconvert [1]. Data from PrEP trials conducted to date collectively show a dose–response pattern, in which greater product

adherence corresponds to higher PrEP efficacy [5, 6]. The FEM-PrEP trial among at-risk adult women in Kenya, South Africa, and Tanzania showed low adherence and was unable to demonstrate a protective effect [7]. Likewise, the vaginal and oral interventions to control the epidemic (VOICE) study among adult women in South Africa, Zimbabwe and Uganda was unable to demonstrate efficacy due to adherence challenges [8]. The data and outcomes from these PrEP trials suggest that study product adherence may represent the “Achilles heel” for PrEP as an HIV prevention strategy [5, 9].

The assessment of adherence has proven challenging in daily oral PrEP trials. PrEP trials have used combinations of self-reported adherence, pill counts, dispensation (or time-to-refill) measure, and drug concentrations in blood plasma [10]. There have been reports that study product adherence showed modest or transient declines over time in some trials [3, 13]. Results to date generally indicate that self-reported measures over-estimate adherence relative to other measures [10, 11]. Data from the VOICE trial was particularly concerning because self-report and pill count measures indicated high adherence while plasma drug levels suggest that product non-use was common [12]. Self-reported study product adherence nonetheless showed significant moderate to high correlations with pill count adherence in the iPrEx and Partners PrEP trials [13, 14], and self-report adherence also significantly predicted drug concentrations in iPrEx [13]. Understanding the patterns, interrelationships, and validity of various measures of study product adherence in PrEP trials represents an important issue; proper adherence documentation is needed to provide evidence for the safety and efficacy of any HIV biomedical intervention and to appropriately interpret the outcomes of prevention trials [15].

Limited research has examined determinants of study product adherence in oral PrEP clinical trials. Determinants reported to date have been largely limited to demographic and individual-level behavioral factors [10, 11]. Factors quantitatively associated with poor adherence in more than one oral PrEP trial included younger age, heavy alcohol use, and certain sexual risk practices and partner characteristics [11, 16, 17]. Partners PrEP participants who reported no sex showed lower adherence [16], and iPrEx participants reporting recent unprotected sex with an HIV-positive partner showed higher adherence [17]. iPrEx additionally observed significantly higher study product adherence among individuals reporting low side effects [17], as well as among U.S. (vs. non-U.S.) participants [18]. When asked why doses were missed, oral PrEP trial participants often report reasons such as forgetting [18–20], travel and schedule disruptions [18–22], and insufficient medication supply due to missed clinic visits [10, 23]. Qualitative studies conducted within oral PrEP trials additionally indicate that relationship problems [24], social costs [25], and concerns about HIV-related stigma [19–21] can impede adherence. Adherence facilitators may include use of reminder devices such as cellphone alarms [18, 19, 22, 24], the integration of doses into daily routines [18, 21], and social support from friends and family [19, 21, 24].

Data from the TDF2 trial provides an opportunity to advance the emerging research literature regarding the validity of adherence measures in PrEP trials, as well as factors associated with product adherence. Information derived from the TDF2 clinical trial may also help inform the implementation of PrEP delivery in real-world settings. The purpose of

this article is to (a) describe adherence measures used in TDF2 (pill count, self-report) and compare them with available drug concentration data, (b) identify factors associated with study product adherence, and (c) identify salient barriers and facilitators to study product adherence from the perspective of trial participants.

Methods

Between 2007 and 2010, we conducted TDF2, a Phase III, randomized, double-blind, placebo-controlled PrEP efficacy trial among sexually active, heterosexual, young adults in Botswana [1]. Data presented here examine demographic, behavioral, and psychosocial factors associated with adherence for the participants enrolled in the TDF2 study. A detailed description of the trial methodology is provided in the trial outcomes paper [1]. Ethical approval for the trial was granted in Botswana by the Human Research Development Committee (HRDC) under the Ministry of Health Ethics, and in the U.S. by the institutional review board at the Centers for Disease Control and Prevention in Atlanta, Georgia. This trial is registered with ClinicalTrials.gov number NCT00448669.

Sample Recruitment and Eligibility Criteria

Sexually active young adult men and women were recruited and randomized 1:1 to once-a-day TDF/FTC or to placebo. Persons were eligible to take part in the trial if they were: 18–39 years of age, citizens of Botswana, sexually active in the past 3 months, not pregnant, HIV uninfected, and able and willing to provide written informed consent.

Study Procedures

Baseline demographic and behavioral data were collected by a face-to-face interview and audio computer-assisted self-interview (ACASI) in the participant's preferred language (English or Setswana). Monthly visits were scheduled in 30-day intervals to dispense study product, conduct adherence and behavioral assessment, HIV testing, and clinical evaluation. In addition to the monthly visit procedures, quarterly visits included risk-reduction counseling, blood samples for clinical safety monitoring (chemistry), and blood specimen storage for consenting participants. At semi-annual visits, ACASI was used to collect behavioral and psychosocial measures. Participants were advised to return to the clinic in the event of an illness or due to study pill-related concerns.

The same procedures and content for medication adherence counseling were used at the two sites and monitoring was conducted by an external group to ensure compliance. All participants received medication adherence counseling based on current interventions used in Botswana [26]. The adherence counseling, which included basic education about study medications (dose and dosing schedule, how TDF/FTC might work, recognizing and handling side effects, refills and drug storage), was conducted at the end of each study visit. In addition, adherence counseling also focused on discussing beliefs about and attitudes toward taking the study product, and on social and medication-related concerns and expectations, including pill-sharing requests from friends and family. At each monthly follow-up visit, study counselors reviewed the study participant's self-reported medication adherence. Persons with 100 % adherence were congratulated and encouraged to continue

adhering to the study product. Persons reporting less than 100 % adherence, were asked to talk about barriers they experienced in adhering to the daily dose of the study medication, to identify strategies that they could use to overcoming medication-adherence barriers, and to create a plan for optimizing adherence.

Adherence Measures

Two primary measures were used to characterize trial participant adherence to the study product: self-report and pill count. The self-report measure was collected at each monthly visit through a face-to-face interview based on the Adult AIDS Clinical Trials Group Adherence Questionnaire [27]. Participants were asked to recall if they had missed a dose of the study product during the past three days and to report the reason for the missed dose(s). To assist with recall, they were asked to consult a self-kept paper-and-pencil diary record regarding doses taken and missed. No electronic device was used to monitor diary or medication use.

The pill count adherence measure was determined by counting the number of pills returned at every monthly visit. Participants received a 30-day supply of study medication at enrollment, and were asked to take one pill every day and to return all unused pills to the study clinic at their next monthly visit. Pills were counted and re-dispensed with a new 30-day supply.

Drug Level Data

Plasma drug concentrations analyses were conducted using participants randomly selected as part of a case–control sub-study to assess the drug level among HIV seroconverters and non-seroconverters [1]. Twenty-three participants seroconverted while taking part in the TDF2 trial. Nineteen out of the 23 had been assigned to the placebo study arm and four were assigned to TDF/FTC. For each of these 23 seroconverters, we randomly chose three samples from the non-seroconverters who were assigned to the TDF/FTC arm who were matched on time in study, sex, and study site. Drug level samples for seroconverters were collected before or near the estimated date of infection, and drug level samples for the matched non-seroconverters were selected around the same study visit. The analysis presented here involves the four seroconverters assigned to TDF/FTC and 69 TDF/FTC matched controls, which yielded drug level measurement data for 73 participants in the TDF/FTC treatment arm. Given that emphasis was on assessing the correspondence between drug levels and adherence measures rather than on efficacy, we used all cases and control participants in the TDF/FTC group. Drug concentrations for tenofovir and emtricitabine were measured using the plasma levels of TDF/FTC in the blood via an ultra-performance liquid chromatograph mass spectrometry assay (lower limit of detection, 0.3 ng per milliliter for both TFV and FTC).

Additional Measures

Demographic information (gender, age, educational status, marital status, employment, and city of residence) was collected at baseline. Sexual behaviors in the past 30 days (sex with a main partner, sex with casual partner, and sex with anyone who has HIV) were assessed at baseline and at monthly follow-up visits. HIV and pregnancy (women only) tests were

performed at each monthly visit. Perceived study arm assignment (TDF/FTC or placebo) was assessed at baseline and semi-annual visits. At monthly visits, participants were also asked to identify strategies that facilitated or barriers that prevented daily pill-taking.

Documentation of adverse events was based on both clinical observation and self-report, and occurred throughout the study. Documentation of one or more of the three most significant adverse events (nausea, vomiting or dizziness) in TDF2 [1] was used to define the adverse events variable used in this analysis.

Psychosocial data were collected via ACASI on attitudes toward the study as well as on pregnancy intentions every 6 months. Information on alcohol and recreational drug use were also collected via ACASI every 6 months. During the study exit interview, participants were asked via CAPI about their concerns with taking the study pill and side effects was listed as one of the response options.

Data Analysis

The demographic, behavioral, psychosocial, and biomedical variables were summarized as percentages, and measures of adherence were summarized by mean and standard deviation by treatment assignment. We compared the correlations between pill count and self-reported adherence measures and also tested for time trends in both measures.

To identify factors associated with daily study product adherence, we conducted unadjusted and adjusted generalized estimated equations analyses. Separate models were constructed with monthly pill count and 3-day self-report adherence measures as the outcome variables. The unadjusted models used demographic, behavioral and psychosocial variables as covariates. The adjusted analyses included the following demographic variables: age, gender, education, marital status and city of residence as common factors. Additionally, psychosocial or behavioral factors with p value <0.1 in the unadjusted models were also included. Relative risks (RR), risk differences (RD) and 95 % confidence intervals (CI) were calculated for all models.

The relationship between TFV/FTC detection and the adherence measures (pill count and self-report) was explored through correlation coefficients and linear models. In the correlation analysis, the TFV and FTC drug-level data were dichotomized using the limit of detection (LOD). The pill-count data and self-report data were dichotomized at a cut point of 0.90 to indicate high/low adherence.

We explored linear models using a $\log_{10}$ transformation for TFV and FTC drug levels as the outcome in separate models and the pill count and self-report adherence measures as predictor variables in addition to the demographic, behavioral and psychosocial variables (described previously). Our linear model treated LOD values as censored and values greater than or equal to LOD as the observed value. All model estimated values were back-transformed to the original scale for TFV and FTC and interpreted as an estimate of the geometric mean (GM). All statistical analyses were performed using SAS software version 9.3 (SAS Institute, Cary, NC, USA).

Trial participant responses to open-ended questions regarding (1) reasons for missed doses of study product and (2) strategies used to assist with study product adherence were exported from the SAS database and analyzed in Microsoft Excel using an inductive content analysis approach. Because responses were generally brief (ranged from a single word to a short sentence), it was determined that Excel rather than qualitative data analysis software program would be sufficient for performing the analysis and would permit re-merging of codes with the larger SAS trial dataset. The inductive analysis process involved three careful readings of the English translations of all responses for the two open-ended questions, sorting and categorizing responses to develop and refine an analysis codebook containing code names and brief code definitions, and applying codes to all responses by one analyst, which was then followed by review of the coding by a second analyst to ensure correct coding of all responses. Codes (24 unique barriers and 5 unique adherence strategies) were enumerated to identify the most common types of responses provided to the two questions. In addition, trends in types of responses provided by study visit were assessed.

Results

Study Sample

Out of 2,533 persons screened, 1,345 met all study eligibility criteria. One hundred twenty-six persons eligible to take part in the study declined enrollment. Of the 1,219 enrolled, 611 were randomized to the TDF/FTC group and 608 were assigned to the placebo group. The demographic characteristics of study participants by trial arm are shown in Table 1. Median participant age was 25 years. Most participants in the 21–29 age group had completed secondary education, were single, and were unemployed. No statistically significant differences were observed in terms of gender, age, education, marital status, employment status, or city of residence by trial arm.

At baseline, approximately two-thirds of participants in each of the study arms reported a single sexual partner during a past 30-day period; 94 % of participants reported ever having a main partner and 56 % reported ever having a casual partner. When asked at baseline, more than 50 % reported alcohol use in a past three-month period. After six months, 11 % reported recreational drug use since the beginning of the study. Over the 36-month study period, approximately 10 % of participants self-reported having an HIV-positive sexual partner. See Table 1 for further details on the study participants.

Pill Count and 3-day Self-Report

Over the 36-month study period, the pill count measure showed a mean of 94.06 (95 % CI 93.85–94.32) and a median of 100 %. The self-report measure showed a mean of 94.26 (95 % CI 93.87–94.64) and a median of 100 %. No significant differences were observed between the pill count measure and the self-report measure. For the pill count, monthly values of adherence did not significantly decline over time ($p = 0.45$). Mean pill count adherence was 93.85 % during the first six months of study participation and 94.19 % during the last six months of study participation. The minimum mean value of monthly pill count adherence (89 %) was observed in the last month of the trial period. Monthly values of adherence declined over time for the self-report measure ($p = 0.01$). Mean self-report

adherence was 94.64 during the first six months of study participation and 92.97 during the last six months of study participation. The minimum mean value of monthly self-report adherence (78 %) was observed towards the end of the study in month 35. The correlation between pill count and self-report adherence was found to be weak but statistically significant ($r = 0.053$, $p < 0.0001$).

Predictors of Pill Count and 3-day Self-Report

We found few statistically significant bivariate associations between participant demographic characteristics and the pill count or 3-day self-report adherence measures (see Table 2). City of residence was associated with both the pill count and self-report, with higher adherence observed among participants from Francistown. Being married was significantly associated with greater self-reported adherence.

Greater pill count-based adherence was observed in participants who were sexually active with a casual partner, sexually active with a main partner, and/or reported an HIV-positive sexual partner in the past 30 days, had no concerns about study drug side effects, and did not use alcohol or drugs. Greater self-report adherence was observed in participants who were sexually active with a main partner, had an HIV positive sexual partner, and did not use alcohol or drugs. Women having no intention of being pregnant had greater adherence for both pill-count and self-reported adherence measures.

In a multivariable model (see Table 3), greater pill count adherence was significantly associated with a lack of concern about side effects and not experiencing any of the three common adverse events. Greater self-reported adherence was significantly associated with having resided in Francistown and having an HIV-positive sexual partner.

Drug Level Data

For the drug concentration analysis conducted with four seroconverters and 69 matched controls in the active drug arm of the trial, the phi-coefficient for the association between pill count adherence and detectable drug was 0.20 and 0.16, respectively, for TFV and FTC. The phi coefficient for self-report adherence and detectable drug was 0.28 for both TFV and FTC.

Results for the linear regression model of TFV and TDF are presented in supplemental file S1. The overall GM and 95 % CI for TFV was 24.3 ng per milliliter (ng/mL) (12.6, 46.8), and for FTC it was 72.1 ng/mL (29.7, 175.0). Linear regression models predicting drug level revealed that self-report adherence and site were statistically significant. The GM for TFV and FTC in Francistown [53.8 ng/mL (23.4, 124.0) and 213.5 ng/mL (71.7, 635.7)] were higher than in Gaborone [9.8 ng/mL (3.9, 24.9) and 24.2 ng/mL (7.2, 81.3)]. The GM ratio (GMr) for Francistown versus Gaborone are 5.50 ($p = 0.008$) for TFV and 8.82 ($p = 0.009$) for FTC. The self-report data were dichotomized using the self-report cut-point of <1.0 and 1.0. This cut-point was chosen because 64 of the 69 participants with available self-report data had a value of 1.0 and the five other participants had either 0 or 1/3 recorded for self-report. Those who self-reported <100 % adherence showed a GM of 2.0 ng/mL (0.17, 23.0) for TFV and 2.5 ng/mL (0.09, 67.1) for FTC, whereas those who self-reported 100 %

adherence showed a GM of 36.2 ng/mL (19.4, 67.5) for TDF and 122.5 ng/mL (53.0, 283.1) for FTC. The GMr for self-report <100 versus 100 % are 18.1 (p = 0.025; TFV) and 48.6 (p = 0.025; FTC). Although the GMr for pill count <90 versus ≥90 % for TFV and FTC were not statistically significant (p = 0.11 and 0.088, respectively), due to our limited sample size, the GMr were substantial (3.74 and 6.60, respectively).

Adherence Barriers and Facilitators

From the open-ended question on reasons for missed doses, the most common explanation for non-adherence was running out of study product (n = 643; 48 % of the reasons). Other common reasons given were: losing pills (n = 160; 12 %), missing doses due to travel (n = 156 times; 12 %), forgetting to take the pill (n = 107; 8 %), and having a disruption in one's daily schedule (n = 77; 6 %). Less frequently mentioned was concern about side effects (n = 42 times; 3 %). Other less frequent reasons provided for non-adherence included disinterest in continuing with study participation or pill-taking, concerns about stigma, and confusion about the dosage schedule (1 %, collectively). In examining reasons for missed dosages over time, we found that this response pattern remained consistent (data not shown here).

In identifying strategies they used to improve adherence to study product in the past 30 days, the majority of trial participants (56 %) indicated that they had used a cell-phone alarm feature to remind them to take their pills. Other adherence strategies, such as relying on friends or integrating medication doses with daily tasks, were reported by few trial participants (1 %). Many trial participants (34 %) reported having no particular strategy to facilitate adherence.

Discussion

This study found high adherence to study product in the TDF2 trial as measured by pill count and self-reported adherence. Although self-report and pill count adherence may overestimate product adherence relative to drug concentrations, this study established that self-report adherence significantly predicted drug level in bivariate and controlled multivariate analyses. These findings establish some modest credence for the validity of the self-report measure. This study further identified factors predictive of self-report and pill count product adherence in the TDF2 PrEP trial, which constituted adverse events, concerns about side effects, having an HIV-positive partner, and site-level differences. Trial participants reported that travel and logistic barriers interfered with efforts to maintain adherence and study product reserves. Participants described electronic alarms as an important adherence facilitator, although approximately one-third of the trial sample reported using no strategy to facilitate adherence. These study findings and their implications for future PrEP trials and research are further discussed below.

The drug concentration analysis revealed a modest correlation between TDF/FTC drug level and self-report adherence (0.28) and a weaker relationship between drug levels and pill count adherence (0.20 and 0.16). Multivariate regression showed that drug level for TFV and FTC was associated with self-report adherence and site. Our small sample suggests that those who self-reported 100 % adherence had a higher amount of both TFV and FTC drugs in their system than those who self-reported less than 100 % adherence. There was also a

substantially higher amount of detectable TFV and FTC drug levels among those with pill counts ≥ 90 % versus those with pill counts <90 %, although this finding did not reach statistical significance in this small sample. These findings associating adherence pill count and self-report measures with drug levels diverge from results of the VOICE trial (12) and more closely match results from the iPrEX trial (13), which similarly reported that self-report and pill count evidenced modest but significant associations with drug level. All of these trials have nonetheless found adherence by self-report and other adherence measures to be higher than that indicated by drug detection [11]. It is widely acknowledged that self-report measures tend to overestimate adherence due to social desirability and recall biases [29, 30]. Pill count measures are also subject to various threats to validity, such as when social desirability concerns lead to “pill dumping” prior to scheduled study appointments [31]. Plasma drug concentrations present limitations as a proxy for adherence, as well; these include potential variation in drug pharmacokinetics, sample collection, and laboratory assays. Despite the limitations associated with each of these methods, the results reported here are reminders that these measures retain some correspondence, and further research to improve the collection and accuracy of inexpensive behavioral self-report measures are needed to aid future prevention trials and research.

This study did not find strong evidence for declines in adherence over the trial. Although self-report adherence significantly decreased, it was only approximately one percentage point lower in the final six months of study participation compared to the first six months. A similar pattern was observed in the Partners PrEP trial, which found modestly higher adherence during the first six months of study participation than the last six months [16]. The iPrEx trial reported that study product use decreased during the first year of use from 99 to 91 % on the basis of drug dispensation (time-to-refill) data, whereas self-reports and pill count measures showed increased adherence over the same interval [3]. iPrEx also observed that self-reported adherence showed a significant but transient decline in the active arm at 4 weeks, which may have been attributable to side effects associated with PrEP initiation [3].

The self-report and pill count adherence measures were very weakly correlated with one another, despite both showing high levels. This finding suggests that the measures could be assessing somewhat different constructs. Differences in the operationalization of these measures may account for their poor correspondence. The pill count measure assessed adherence based on returned pills not used over 30 days, whereas the self-report measure assessed adherence based on recall prompted by participants’ diary records over the prior three days. It may be that the longer assessment interval associated with the pill count measure helps to capture highly infrequent or episodic non-adherence (e.g., during weekends), relative to the shorter interval for the three-day self-report measure [28]. Trial participants did report missed doses due to travel and schedule disruptions in the adherence barrier data. This may have prompted intermittent gaps in adherence that might be better evidenced in the pill-count data than in the self-report data. A proper comparison would have utilized the same time frames for each measure.

Our findings show several factors associated with study product adherence in the trial. Demographic factors, such as age, were generally not associated with adherence by either pill count or self-report measure. Some PrEP trials have suggested age-related adherence

differences [11], but the uniformity of participant ages in the TDF2 trial may have precluded detection of differences in this regard. We found a relationship between site of residence and both pill count and self-report adherence that persisted in the multivariable model predicting pill count adherence. The drug level analysis additionally showed that mean drug levels varied by site. Site effects have been evident in prior trials, such as iPrEX, where U.S. participants showed higher adherence than non-U.S. participants [17]. Ready explanations for the site effects observed in this study are lacking. Clinics at both sites were centrally located and maintained the same hours of operation. An independent group monitored counseling to ensure consistency across the two sites. Available qualitative data (not reported here) also indicated no site differences in participant experiences around study visits, including duration, clinic wait times, or staff attitudes. It is possible that unmeasured ecologic factors may have played a role in the site differences.

Some behavioral and psychosocial factors were found to be associated with adherence. Similar to other oral PrEP trials, we found some relationships between partner characteristics, sexual practices, and adherence [16, 17]. Greater self-report and pill count adherence was observed in participants who were sexually active with a main partner, and who were aware that their main partner was HIV positive. These findings may indicate that individuals with greater perceived HIV transmission risk adhere more closely to study products in PrEP trials [10]; however, the magnitude of the observed differences for variables with statistical significance were generally small and not likely to be of strong clinical relevance. The Partners PrEP trial qualitative findings offer related insights in that serodiscordant couples' concerns about HIV transmission risk promoted adherence to study product, although relationship discord could undermine this effect [24]. Lastly, while our multivariable model did not show that alcohol use was related to non-adherence, we did find univariable effects. Studies of antiretrovirals found that an the association between alcohol use and poor adherence was explained by strategies participants used to avoid side effects that come with mixing HIV medications and alcohol [32, 33].

Both concerns about and actual experiences with side effects have been shown to be barriers to HIV prevention and treatment adherence [34, 35]. Participants self-reporting concerns about side effects (e.g., nausea and diarrhea) commonly associated with TDF/FTC showed lower pill count adherence in the multivariable model. These findings suggest that future PrEP trials and PrEP implementation efforts should recognize that concerns about and actual experiences of side effects may have a deleterious effect on adherence, and can therefore compromise the efficacy of PrEP for HIV prevention. Strategies to help individuals address PrEP adherence while experiencing side effects should be developed.

Trial participants commonly attributed missed doses to factors such as running out of pills, losing pills, or losing access to pills due to travel. Citizens of Botswana travel frequently, especially during weekends and holidays. These data suggest that any future programs to address PrEP adherence should develop messages and counseling that focus on pill management, such as the importance of ensuring timely refills of medication and strategies for staying adherent when traveling away from home. Our findings showed that trial participants rarely mentioned side effects as a reason for missed doses, in comparison to some of these other, more commonly cited concerns. Thus, it may be that participants

perceived or attributed the greatest adherence barriers to be schedules and difficulty remembering, rather than to avoiding medication doses due to perceived side-effects.

The most frequently reported strategy to help with taking daily study medication was the use of personal cell phone reminder alarms. To improve medication adherence, increased use of mHealth, a healthcare delivery method that relies on the use of mobile technology, is being implemented [36–39]. In addition to self-regulated cell phone alarms, mobile phone short message service, audiovisual reminders from electronic reminder devices and pager messages offer potentially effective tools for improving adherence; yet, long term effects [40] and uptake in resource-limited settings remain unclear [41]. Moreover, issues of intentional (deliberately missing or altering medication doses) and unintentional (forgetting) non-adherence that go beyond the scope of our study suggest that these technologies may be more effective if used exclusively for those who are unintentionally non-adherent [40, 42]. Although social support from friends and relatives are cited frequently in the treatment adherence literature [15] participants rarely reported using friends as reminders to take study medications. Non-reliance on one's social support system could have been related to concerns that others would assume that study participants were HIV infected because they were receiving HIV treatment medication. Consequentially, concerns about HIV-stigma may have prevented participants openly carrying or taking the study pills in public or when friends and family were nearby as study product packages were similar to the ARV containers used for HIV positive treatment. Lastly, while there may be synergies of study product use and oral contraceptive pill use for women that might facilitate adherence, we did not find evidence for this in our data (analysis not shown).

This study had several limitations. The trial was not designed to test a comprehensive model of adherence determinants, and so a limited number of factors could be tested in relationship to adherence. Additionally, drug-level data were only available on a small subsample of trial participants, limiting our ability to compare and test the relationships between drug detection and adherence as assessed by pill count or self-report. The study used a self-report adherence measure that has been repeatedly suggested in the literature to overestimate adherence relative to other adherence measures due to social desirability and recall issues. A self-report estimate over a longer time frame (7 days or 30 days) may better capture infrequent or episodic non-adherence. Finally, it is important to recognize that the analyses conducted here are derived from a placebo-controlled trial, so participants did not know whether they were taking active drug or placebo. Adherence in the context of a placebo-controlled trial is likely to be different from adherence in an open-label trial or real-world use of PrEP, because trial participants are unaware whether they are receiving active drug and whether the active drug is efficacious. Moreover, statistically significant factors such as site of residence and being married showed small effect sizes and may not be clinically meaningful [43]. Small effect size may be attributed to the relatively large sample along with the lack of variability in the distribution of adherence that probably produces tight "clumping of data".

In conclusion, further research is needed to understand optimal adherence measures and adherence determinants in biomedical HIV prevention trials. The development of improved behavioral adherence assessments and novel adherence biomarkers could advance the

sensitivity and specificity of adherence measures, which is critical to the interpretation of trial results. To improve adherence, support strategies in PrEP trials and real-world implementation should seek to address potential adherence barriers such as alcohol use, adverse events, side effect concerns, and logistic barriers to medication possession. Efforts to promote use of cellphone reminders may also provide a valuable tool for supporting adherence. These efforts may strengthen the ability of trials and demonstration projects to improve adherence to oral PrEP thereby strengthening the impact of this important new HIV prevention modality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. N Engl J Med. 2012; 367:423–34. [PubMed: 22784038]
2. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med. 2012; 367(5):399–410. [PubMed: 22784037]
3. Grant RM. Antiretroviral agents used by HIV-uninfected persons for prevention: pre- and post-exposure prophylaxis. Clin Infect Dis. 2010; 50:S96–101. [PubMed: 20397962]
4. Choopanya K, Martin M, Suntharasamai P, Sangkum U, Mock PA, Leethochawalit M, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (The Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2013; 381(9883):2083–90. [PubMed: 23769234]
5. Baeten J, Celum C. Oral antiretroviral chemoprophylaxis: current status. Curr Opin HIV AIDS. 2012; 7:514–9. [PubMed: 22964886]
6. Hendrix CW. Exploring concentration response in HIV pre-exposure prophylaxis to optimize clinical care and trial design. Cell. 2013; 155(3):515–8. [PubMed: 24243011]
7. Van Damme L, Corneli A, Ahmed K, Agot K, Lombaard J, Kapiga S, et al. Preexposure prophylaxis for HIV infection among African women. N Engl J Med. 2012; 367(5):411–22. [PubMed: 22784040]
8. Marrazzo J, Ramjee G, Nair G. Pre-exposure prophylaxis for HIV in women: daily oral tenofovir, oral tenofovir/emtricitabine, or vaginal tenofovir gel in the VOICE Study (MTN 003). 2013
9. Abdool Karim SS, Baxter C. Antiretroviral prophylaxis for the prevention of HIV infection: future implementation challenges. HIV Therapy. 2009; 3(1):3–6.
10. Muchomba FM, Gearing RE, Simoni JM, El-Bassel N. State of the science of adherence in pre-exposure prophylaxis and microbicide trials. J Acquir Immune Defic Syndr. 2012; 61:490–8. [PubMed: 22932322]
11. Koenig LJ, Lyles C, Smith DK. Adherence to antiretroviral medications for HIV pre-exposure prophylaxis: lessons learned from trials and treatment studies. Am J Prev Med. 2013; 44(1):S91–8. [PubMed: 23253769]

12. Marrazzo, J.; Ramjee, G.; Nair, G.; Palanee, T.; Mkhize, B., et al. Pre-exposure prophylaxis for HIV in women: daily oral tenofovir, oral tenofoviremtricitabine, or vaginal tenofovir gel in the VOICE study (MTN 003). Atlanta: CROI; 2013.
13. Amico KR, Liu A, McMahan V, Anderson P, Lama J, Guanira J, et al. Adherence indicators and PrEP drug devels in the iPrex study. CROI. 2011 Paper #95LB.
14. Haberer J, Baeten J, Celum C, Tumwesigye E, Krows M, Kidoguchi L, et al. Near perfect early adherence to antiretroviral PrEP against HIV infection among HIV serodiscordant couples as determined by multiple measures: preliminary data from the Partners PrEP Study. 2011
15. Stirratt MJ, Gordon CM. Adherence to biomedical HIV prevention methods: considerations drawn from HIV treatment adherence research. Curr HIV AIDS Rep. 2008; 5:186–92.
16. Haberer JE, Baeten JM, Campbell J, Wangisi J, Katabira E, Ronald A, et al. Adherence to antiretroviral prophylaxis for HIV prevention: A substudy cohort within a clinical trial of serodiscordant couples in East Africa. PLOS Med. 2014; 10:e1001511. [PubMed: 24058300]
17. Amico KR, Marcus JL, McMahan V, Goichochea P, Vargas L, Grant R, et al. Correlates of study product use among U.S. participants in the iPrEx randomized controlled trial of daily oral preexposure prophylaxis. 2013 Abstract no. TUPE310.
18. Amico KR. Adherence to preexposure chemoprophylaxis: the behavioral bridge from efficacy to effectiveness. Curr Opin HIV AIDS. 2012; 7(6):542–8. [PubMed: 22964887]
19. Minnis AM, Gandham S, Richardson BA, Guddera V, Chen BA, Salata R, et al. Adherence and acceptability in MTN 001: a randomized cross-over trial of daily oral and topical tenofovir for HIV prevention in women. AIDS Behav. 2013; 17(2):737–47. [PubMed: 23065145]
20. Hosek SG, Siberry G, Bell M, Lally M, Kapogiannis B, Green K, et al. The acceptability and feasibility of an HIV preexposure prophylaxis (PrEP) trial with young men who have sex with men. J Acquir Immune Defic Syndr. 2013; 62(4):447–56. [PubMed: 24135734]
21. Tangmunkongvorakul A, Chariyalertsak S, Amico KR, Saokhieo P, Wannalak V, Sangangamsakun T, et al. Facilitators and barriers to medication adherence in an HIV prevention study among men who have sex with men in the iPrEx study in Chiang Mai, Thailand. AIDS Care. 2012; 25(8):961–967. [PubMed: 23252473]
22. Van der Elst EM, Mbogua J, Operario D, Mutua G, Kuo C, Mugo P, et al. High acceptability of HIV pre-exposure prophylaxis but challenges in adherence and use: qualitative insights from a phase I trial of intermittent and daily PrEP in at-risk populations in Kenya. AIDS Behav. 2012; 17(6):2162–2172. [PubMed: 23080358]
23. Peterson L, Taylor D, Roddy R, Belai G, Phillips P, Nanda K, et al. Tenofovir disoproxil fumarate for prevention of HIV infection in women: a phase 2, double-blind, randomized, placebo-controlled trial. PLoS Clin Trials. 2007; 2:e27. [PubMed: 17525796]
24. Ware NC, Wyatt MA, Haberer JE, Baeten JM, Kintu A, Psaros C, et al. What's love got to do with it? Explaining adherence to oral antiretroviral pre-exposure prophylaxis for HIV-serodiscordant couples. J Acquir Immune Defic Syndr. 2012; 59:463–8. [PubMed: 22267018]
25. Van der Straten A, Stadler J, Montgomery E, Hartmann M, Magazi B, Mathbula F, et al. Women's experiences with oral and vaginal pre-exposure prophylaxis: the VOICE-C qualitative study in Johannesburg, South Africa. PLOS One. 2014; 9:e89118. [PubMed: 24586534]
26. Botswana Ministry of Health. Botswana national guidelines—HIV testing and counseling. 2009:25–32.
27. Chesney MA, Ickovics JR, Chambers DB, Gifford AL, Neidig J, Zwickl B, et al. Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: the AACTG adherence instruments. Patient Care Committee & Adherence Working Group of the Outcomes Committee of the Adult AIDS Clinical Trials Group (AACTG). AIDS Care. 2000; 12:255–66. [PubMed: 10928201]
28. Simoni JM, Kurth AE, Pearson CR, Pantalone DW, Merrill JO, Frick PA. Self-report measures of antiretroviral therapy adherence: a review with recommendations for HIV research and clinical management. AIDS Behav. 2006; 10(3):227–45. [PubMed: 16783535]
29. Paterson DL, Potoski B, Capitano B. Measurement of adherence to antiretroviral medications. J Acquir Immune Defic Syndr. 2002; 31

30. Turner BJ. Adherence to antiretroviral therapy by human immunodeficiency virus–infected patients. J Infect Dis. 2002; 185(Supplement 2):S143–51. [PubMed: 12001036]
31. Berg KM, Arnsten JH. Practical and conceptual challenges in measuring antiretroviral adherence. J Acquir Immune Defic Syndr. 2006; 1(43 Suppl 1):S79–87. [PubMed: 17133207]
32. Kalichman SC, Grebler T, Amaral CM, McNerey M, White D, Klichman MOCC, et al. Intentional non-adherence to medications among HIV positive alcohol drinkers: prospective study of interactive toxicity beliefs. J Gen Intern Med. 2013; 28(3):339–405. [PubMed: 23229910]
33. Kalichman SC, Amaral CM, White D, Swetsze C, Kalichman MO, Cherry C, et al. Alcohol and adherence to antiretroviral medications: interactive toxicity beliefs among people living with HIV. J Assoc Nurses AIDS Care. 2012; 23(6):511–20. [PubMed: 22421097]
34. Gebremariam MK, Bjune GA, Frich JC. Barriers and facilitators of adherence to TB treatment in patients on concomitant TB and HIV treatment: a qualitative study. BMC Public Health. 2010; 10:1471–2458. (Electronic).
35. Martin LR, Williams SL, Haskard KB, DiMatteo MR. The challenge of patient adherence. Ther Clin Risk Manag. 2005; 1(3):189. [PubMed: 18360559]
36. Thirumurthy H, Lester RT. M-health for health behaviour change in resource-limited settings: applications to HIV care and beyond. Bull World Health Organ. 2012; 90(5):390–2. [PubMed: 22589574]
37. Cole-Lewis H, Kershaw T. Text messaging as a tool for behavior change in disease prevention and management. Epidemiol Rev. 2010; 32(1):56–69. [PubMed: 20354039]
38. Pop-Eleches C, Thirumurthy H, Habyarimana J, Graff Zivin J, Goldstein M, de Walque D, et al. Mobile phone technologies improve adherence to antiretroviral treatment in resource-limited settings: a randomized controlled trial of text message reminders. AIDS. 2011; 25:825–34. [PubMed: 21252632]
39. Patil DA. Mobile for Health (mHealth) in Developing Countries: Application of 4 Ps of Social Marketing. J Health Inform Dev Ctries. 2011; 5(2):317–326.
40. Vervloet M, Linn AJ, van Weert JC, de Bakker DH, Bouvy ML, van Dijk L. The effectiveness of interventions using electronic reminders to improve adherence to chronic medication: a systematic review of the literature. J Am Med Inform Assoc. 2012; 19(5):696–704. [PubMed: 22534082]
41. Tomlinson M, Rotheram-Borus MJ, Swartz L, Tsai AC. Scaling up mHealth: where is the evidence? PLoS Med. 2013; 10(2):e1001382. [PubMed: 23424286]
42. Wroe AL. Intentional and unintentional nonadherence: a study of decision making. J Behav Med. 2002; 25(4):355–72. [PubMed: 12136497]
43. Stang A, Poole C, Kuss O. The ongoing tyranny of statistical significance testing in biomedical research. Eur J Epidemiol. 2010; 25(4):225–30. [PubMed: 20339903]

Table 1

Characteristics of participants, BotswanaTDF2 PrEP trial, 2007–2010

Characteristics		TDF/FTC n = 611	Placebo n = 608	*p*
Gender, n (%)	Male	331 (54.2)	331 (54.4)	0.93
	Female	280 (45.8)	277 (45.6)	
Age group (years), n (%)	18–20	10 (1.6)	15 (2.5)	0.34
	21–29	550 (90.0)	532 (87.5)	
	30–39	51 (8.3)	61 (10.0)	
Education, n (%)	Primary or less	20 (3.3)	20 (3.3)	0.996
	Secondary	446 (73.0)	445 (73.2)	
	Postsecondary	145 (23.7)	143 (23.5)	
Marital status, n (%)	Married	32 (5.2)	38 (6.3)	0.45
	Single	578 (94.6)	567 (93.3)	
Employment status, n (%)	Employed	245 (40.1)	235 (38.7)	0.61
	Unemployed	366 (59.9)	373 (61.3)	
City of residence, n (%)	Gaborone	326 (53.4)	325 (53.5)	0.97
	Francistown	285 (46.6)	283 (46.5)	
Perceived TDF/FTC randomization, n (%)	Yes	121 (20.1)	109 (18.4)	0.44
	No	480 (79.9)	484 (81.6)	
Casual partner[a], n (%)	Yes	339 (55.5)	345 (56.7)	0.66
	No	272 (44.5)	263 (43.3)	
Main partner[a], n (%)	Yes	580 (94.9)	562 (92.4)	0.07
	No	31 (5.1)	46 (7.6)	
HIV-positive partner[a], n (%)	Yes	58 (9.5)	65 (10.7)	0.49
	No	553 (90.5)	543 (89.3)	
Pregnancy occurrence[a], n (%) (women only)	Yes	48 (17.1)	53 (19.1)	0.54
	No	232 (82.9)	224 (80.9)	
Adverse events[a,b], n (%) (nausea, dizziness, vomiting)	Yes	190 (31.1)	124 (20.4)	< 0.0001
	No	421 (68.9)	484 (79.6)	
Total sex acts in past 30 days, n (%)	0	97 (15.9)	99 (16.3)	0.98
	1–2	119 (19.5)	119 (19.6)	
	3+	395 (64.7)	390 (64.1)	
Number of sex partners in past 30 days, n (%)	0	73 (12.2)	78 (13.1)	0.88
	1	410 (68.2)	405 (67.8)	
	2+	118 (19.6)	114 (19.1)	
Alcohol use in past 3 months, n (%)	Yes	359 (59.7)	340 (56.8)	0.30
	No	242 (40.3)	259 (43.2)	
Side effect concerns[c,d], n (%)	Yes	72 (18.9)	54 (14.1)	0.07
	No	309 (81.1)	329 (85.9)	
Recreational drug use[e], n (%)	Yes	38 (10.5)	43 (11.6)	0.64
	No	325 (89.5)	329 (88.4)	
Pregnancy intention[e], n (%) (women only)	Yes	60 (69.8)	43 (58.9)	0.15

Characteristics		TDF/FTC n = 611	Placebo n = 608	*p*
TDF everyday protect[e,f], n (%)	No	26 (30.2)	30 (41.1)	
	Agree	341 (86.7)	333 (83.3)	0.14
	Disagree	51 (13.0)	67 (16.7)	
HIV meds too strong[e], n (%)	Agree	244 (62.2)	208 (52.0)	0.004
	Disagree	148 (37. 8)	192 (48.0)	

[a] Data presented are for responses at any point during the study

[b] Collected monthly; Presence of nausea, dizziness, and vomiting only included here. Dizziness, nausea, and vomiting were the three most common responses (*Have you had any problems with your health since your last visit?*)

[c] Asked at study exit

[d] Collected only at study exit (Response option = side effects to *What concerns/problems did you have with taking the pill?*)

[e] Data presented are for responses at 6 months

[f] Collected every 6 months (*TDF/FTC does not always protect you from getting HIV even if you take it every day*)

Table 2

Univariable analysis of adherence measured by pill count and 3-day self-report, BotswanaTDF2 PrEP trial, 2007–2010

		Monthly pill count			3-day self report		
		Relative risk (95 % CI)	**Risk difference (%)**	***p***	**Relative risk (95 % CI)**	**Risk difference (%)**	***p***
Gender	Female	1.00 (0.99–.01)	0.22	0.56	1.00 (0.99–1.01)	0.17	0.73
	Male	Ref.			Ref.		
Age group (years)	18–20	1.01 (0.98–1.03)	1.69	0.59	1.00 (0.97–1.03)	0.90	0.87
	21–29	0.99 (0.98–1.00)	0.59	0.07	0.99 (0.98–1.01)	0.23	0.4
	30–39	Ref.			Ref.		
Education	Primary or less	1.00 (0.97–1.02)	0.41	0.69	1.01 (0.99–1.04)	1.31	0.26
	Secondary	Ref.			Ref.	2.22	
	Postsecondary	0.99 (0.98–1.00)	0.91	0.06	0.99 (0.98–1.00)		0.16
Marital status	Married	1.00 (0.98–1.02)	0.31	0.74	1.02 (1.00–1.04)	1.98	0.01
	Single	Ref.			Ref.		
Employment status	Employed	1.00 (0.99–1.00)	0.43	0.27	1.01 (0.99–1.02)	0.59	0.25
	Unemployed	Ref.			Ref.		
City of residence	Gaborone	0.99 (0.98–1.00)	0.85	0.02	0.97 (0.96–0.98)	2.48	< .0001
	Francistown	Ref.			Ref.		
Perceived TDF/FTC randomization	Yes	1.00 (0.99–1.01)	0.10	0.84	1.01 (1.00–1.02)	0.80	0.14
	No	Ref.			Ref.		
Casual partner[a]	Yes	1.01 (1.00–1.02)	0.95	0.02	1.00 (0.99–1.01)	0.21	0.72
	No	Ref.			Ref.		
Main partner[a]	Yes	1.03 (1.02–1.04)	2.67	< .0001	1.03 (1.02–1.05)	3.12	< .0001
	No	Ref.			Ref.		
HIV-positive partner[b]	Yes	1.02 (1.00–1.03)	1.64	0.02	1.02 (1.01–1.04)	2.32	0.01
	No	Ref.			Ref.		
Adverse events (nausea, dizziness, vomiting)[c]	Yes	0.99 (0.97–1.00)	1.25	0.10	0.98 (0.95–1.01)	1.83	0.17
	No	Ref.			Ref.		
Total sex acts in past 30 days	0	1.00 (0.99–1.02)	0.48	0.78	1.00 (0.98–1.02)	0.62	0.67
	1–2	1.00 (0.98–1.02)	0.22	0.80	1.00 (0.98–1.02)	0.42	0.85
	3+	Ref.			Ref.		

		Monthly pill count			3-day self report		
		Relative risk (95 % CI)	**Risk difference (%)**	***p***	**Relative risk (95 % CI)**	**Risk difference (%)**	***p***
Number of sex partners in past 30 days	0	1.00 (0.98–1.02)	0.06	0.98	1.01 (0.98–1.04)	1.07	0.50
	1	1.00 (0.98–1.02)	0.03	0.97	1.01 (0.99–1.03)	0.18	0.22
	2+	Ref.			Ref.		
Alcohol use	Yes	0.99 (0.98–1.00)	0.95	0.01	0.99 (0.98–1.00)	1.18	0.02
	No	Ref.			Ref.		
Side effect concerns[b,d]	Yes	0.98 (0.97–0.99)	1.77	0.01	0.99 (0.97–1.01)	1.25	0.20
	No	Ref					
Recreational drug use[e]	Yes	0.98 (0.97–0.997)	1.54	0.02	0.98 (0.96–1.00)	2.14	0.03
	No	Ref.			Ref.		
TDF everyday protect[f]	Agree	1.00 (0.99–1.02)	0.44	0.47	0.99 (0.98–1.00)	0.94	0.12
	Disagree	Ref.			Ref.		
HIV meds too strong	Agree	1.01 (1.00–1.01)	0.51	0.17	1.00 (0.99–1.01)	0.19	0.70
	Disagree	Ref.					
Pregnancy occurrence (women only)	Yes	0.98 (0.94–1.02)	1.71	0.28	0.95 (0.88–1.03)	4.55	0.2
	No	Ref.			Ref.		
Pregnancy intention (women only)	Yes	0.94 (0.93–0.94)	1.08	< .0001	0.95 (0.94–0.96)	0.80	< .0001
	No	Ref.			Ref.		

[a] Data presented are for responses at any point during the study

[b] Asked at study exit

[c] Collected monthly; Presence of nausea, dizziness, and vomiting only included here. Dizziness, nausea, and vomiting were the three most common responses (*Have you had any problems with your health since your last visit?*)

[d] Collected only at study exit (*What concerns/problems did you have with taking the pill?*)

[f] Collected every 6 months (*TDF/FTC does not always protect you from getting HIV even if you take it every day*)

[e] Data presented are for responses at 6 months

Table 3

Multivariable analysis of adherence measured by pill count and 3-day self-report, BotswanaTDF2 PrEP trial, 2007–2010

		Monthly pill count			3- day self report		
		Relative Risk (95 % CI)	**Risk difference (%)**	***p***	**Relative Risk (95 % CI)**	**Risk difference (%)**	***p***
Gender	Female	0.99 (0.98–1.00)	0.64	0.22	1.00 (0.99–1.01)	0.03	0.96
	Male	Ref.			Ref.		
Age group (years)	18–20 years	1.00 (0.98–1.03)	−0.44	0.68	1.00 (0.97–1.03)	0.08	0.96
	21–29 years	0.99 (0.98–1.00)	1.09	0.07	1.00 (0.98–1.02)	0.27	0.77
	30–39 years	Ref.			Ref.		
Education	Primary or less	0.99 (0.98–1.00)	0.22	0.11	1.00 (0.98–1.01)	−0.50	0.77
	Secondary	Ref.			Ref.		
	Postsecondary	1.00 (0.98–1.02)	1.00	0.83	1.00 (0.96–1.05)	0.22	0.81
Marital status	Married	0.98 (0.95–1.00)	1.86	0.12	1.00 (0.98–1.02)	0.09	0.93
	Single	Ref.			Ref.		
City of residence	Gaborone	0.99 (0.98–1.00)	0.81	0.16	0.98 (0.96–0.99)	2.40	0.0001
	Francistown	Ref.			Ref.		
Casual partner[a]	Yes	1.00 (0.99–1.01)	0.30	0.59	0.99 (0.97–1.01)	1.13	0.27
	No	Ref.			Ref.		
Main partner[a]	Yes	1.01 (0.99–1.02)	−0.82	0.23	1.00 (0.98–1.03)	−0.41	0.72
	No	Ref.			Ref.		
HIV-positive partner[a]	Yes	1.01 (1.00–1.03)	−1.25	0.07	1.02 (1.00–1.04)	−1.92	0.02
	No	Ref.			Ref.		
Adverse events[a,b], (nausea, dizziness, vomiting)	Yes	0.98 (0.96–1.00)	1.93	0.03	0.97 (0.94–1.01)	2.67	0.11
	No	Ref.			Ref.		
Alcohol use	Yes	0.99 (0.98–1.00)	0.66	0.21	0.99 (0.98–1.01)	0.59	0.34
	No	Ref.			Ref.		
Side effect concerns[c,d]	Yes	0.98 (0.96–0.99)	2.05	0.01	0.98 (0.96–1.00)	1.80	0.08
	No	Ref.			Ref.		
Recreational drug use[e]	Yes	0.98 (0.97–1.00)	1.71	0.07	0.99 (0.96–1.01)	1.09	0.36
	No	Ref.			Ref.		

[a]Data presented are for responses at any point during the study

[b] Collected monthly; Presence of dizziness, nausea, and vomiting only captured. Dizziness, nausea, and vomiting were the three most common responses (*Have you had any problems with your health since your last visit?*)

[c] Asked at study exit

[d] Collected only at study exit (*What concerns/problems did you have with taking the pill?*)

[e] Data presented are for responses at 6 months