Published in final edited form as:

AIDS Behav. 2014 September ; 18(9): 1701–1711. doi:10.1007/s10461-014-0804-1.

Preferences for daily or intermittent pre-exposure prophylaxis regimens and ability to anticipate sex among HIV uninfected members of Kenyan HIV serodiscordant couples

Sarah T. Roberts^{1,2}, Renee Heffron², Kenneth Ngunjiri^{2,3}, Connie Celum^{1,2,4}, Ann Kurth⁵, Kathryn Curran^{1,2}, Nelly Mugo^{2,6}, and Jared M. Baeten^{1,2,4}

¹Department of Epidemiology, University of Washington, Seattle, WA, USA

²Department of Global Health, University of Washington, Seattle, WA, USA

³Jomo Kenyatta University of Agriculture and Technology, Nairobi, Kenya

⁴Department of Medicine, University of Washington, Seattle, WA, USA

⁵College of Nursing, New York University, New York, NY, USA

⁶Kenya Medical Research Institute, Nairobi, Kenya

Abstract

Intermittent dosing for pre-exposure prophylaxis (PrEP) has been proposed as an alternative to daily PrEP to reduce cost and patient drug exposure and to improve adherence. One possible dosing regimen is pre-intercourse PrEP, which requires anticipating sex in advance. We examined preferences for daily versus pre-intercourse PrEP and ability to anticipate sex among 310 HIV uninfected members of HIV serodiscordant heterosexual couples in Thika, Kenya, with high HIV knowledge and experience with daily PrEP use in a clinical trial setting. Preferences were evenly split between daily PrEP (47.4%) and pre-intercourse PrEP (50.7%). Participants were more likely to prefer daily PrEP if they reported unprotected sex during the prior month (adjusted prevalence ratio [aPR]: 1.48, 95% CI: 1.20–1.81) or <80% adherence to study drug (aPR: 1.50, 95% CI: 1.25–1.79), and were less likely to prefer daily PrEP if sex was usually planned, versus spontaneous (aPR: 0.76, 95% CI: 0.61–0.96). A minority (24.2%) reported anticipating sex >3 hours in advance, with younger participants being less likely to do so (aPR: 0.43, 95% CI: 0.23–0.83 for ages 18–29 versus 40). Findings suggest that intermittent PrEP could be a popular option in this population, but that optimal adherence and sufficient drug levels might be challenging with a pre-intercourse regimen.

Keywords

Pre-exposure prophylaxis (PrEP); intermittent pre-exposure prophylaxis (iPrEP); Kenya; HIV serodiscordant couples; sexual behavior

INTRODUCTION

Pre-exposure prophylaxis (PrEP) is a promising new strategy for the prevention of HIV infection. Clinical trials have demonstrated that oral tenofovir (TDF) and combination emtricitabine/tenofovir (FTC/TDF), when taken daily, are effective for HIV prevention in several populations, including heterosexual men and women [1,2], men who have sex with men (MSM) [3], and injection drug users [4]. However, the effectiveness of PrEP depends strongly on participant adherence. In two clinical trials that did not demonstrate PrEP efficacy [5,6], low adherence is the leading hypothesis to explain the lack of HIV protection [7].

Intermittent PrEP (iPrEP) has been proposed as an alternative to daily PrEP to reduce cost, toxicity, and patient burden and to improve adherence among those who find daily pill-taking challenging or unacceptable [8,9]. Optimal iPrEP dosing approaches are under investigation for both adherence and pharmacologic characteristics; proposed regimens include a fixed dose several days per week, event-dependent dosing (e.g. before and/or after sexual intercourse), or some combination thereof. Oral iPrEP has been efficacious in animal models [9,10] and is currently being evaluated in studies among MSM and heterosexual men and women comparing FTC/TDF infix and event-dependent dosing strategies [11–14]. Topical iPrEP, using 1% tenofovir gel, was found effective in reducing HIV risk in women, using a strategy of one pre-intercourse dose within 12 hours before sex and one post-intercourse dose within 12 hours after sex [15].

Acceptability studies, conducted largely in MSM, have found that preferences for daily versus intermittent oral PrEP varied across settings [13,16,17]. One study in African HIV serodiscordant couples found that both daily and intermittent PrEP were highly acceptable to participants [14], but studies have not evaluated preferences for dosing regimens in heterosexual couples [18]. Adherence to pre-intercourse dosing will require the ability to anticipate sex far enough in advance to achieve active antiretroviral metabolites in genital tissues at levels adequate for protection. Only a few studies have evaluated sex planning, primarily among MSM, and results indicated that a high proportion of sex acts are not planned in advance [19–22].

Data about the ability to anticipate sex and the feasibility of oral iPrEP are needed to define iPrEP research priorities and to guide oral PrEP implementation, especially among HIV serodiscordant couples, who are a priority population for PrEP [18]. In sub-Saharan Africa, the region with the highest burden of HIV, up to 50% of all HIV-infected individuals are engaged in a stable HIV serodiscordant relationship [23]. Universal access to antiretroviral therapy (ART) is recommended by the World Health Organization (WHO) for HIV-infected members of HIV serodiscordant couples to prevent transmission to their uninfected partners [24]. However, not all countries have adopted these guidelines, and some HIV-infected individuals may be unwilling to initiate ART before they need it for their own health [25,26]. In this context, PrEP could be used by HIV-uninfected members of HIV serodiscordant couples when their HIV-infected partners delay, decline or are not yet eligible for ART, from the time of initiation until viral suppression is reached, and in couples with ongoing additional risk even in the context of suppressive therapy (e.g.,

conception attempts, outside partners)[7]. We examined preferences for daily versus pre-intercourse PrEP dosing regimens and feasibility of pre-intercourse PrEP in a cohort of HIV serodiscordant couples participating in a daily oral PrEP efficacy trial in Kenya.

METHODS

Study design

Data for this cross-sectional study were collected between March and July 2011 from a convenience sample of HIV uninfected participants attending the Thika, Kenya site for the Partners PrEP Study, a randomized, double-blind, placebo-controlled clinical trial of daily oral TDF and FTC/TDF PrEP to prevent HIV acquisition by uninfected members of heterosexual HIV serodiscordant couples. Detailed procedures for the clinical trial have been described elsewhere [1,27]. Participants were aware of the primary results of the iPrEx study [3] on the efficacy of PrEP for HIV prevention. They were not aware of the secondary results on how the number of doses per week correlated with efficacy, which were published after the survey was completed [29].

Participants

All participants at the Thika, Kenya study site who were currently enrolled and HIV uninfected at the time of the sub-study were eligible to participate; 405 out of 491 were enrolled in the sub-study (82%). Of the 86 who did not participate, 50 were invited and declined, while 36 did not attend a study visit while the survey was being conducted. At an interim review in July 2011, the Partners PrEP Study independent Data and Safety Monitoring Board recommended that the placebo arm of the trial be discontinued early due to clear demonstration of PrEP efficacy for HIV prevention [1]. Participants were excluded from this analysis if they completed the survey after the announcement of PrEP efficacy in this population (n=38) or if they were no longer in a couple with their study partner at the time of the survey (n=57).

Study Procedures

For this sub-study, during a routine clinical trial visit, HIV uninfected participants were invited to answer a staff-administered survey about HIV prevention preferences, including PrEP and ART use by their HIV infected partner [25]. The survey consisted of 35 questions and was administered in Kiswahili, Kikuyu, or English, according to the participant's choice. To assess PrEP dosing preferences, participants were informed that pre-intercourse use would require knowing when they were going to have sex "a few hours" in advance, with no specific timeframe given. Participants were then asked: "If PrEP works, would you rather take PrEP every day, or only before you have sex?" and were also asked to provide reasons for their preference. Participants could cite multiple reasons, and interviewers coded each reason into pre-determined response categories. As a preliminary assessment of the feasibility of pre-intercourse PrEP in this population, participants were also asked how many hours in advance they were "usually" able to anticipate sex. Answer choices were categorical, with options of less than 1 hour, 1–3, 3–6, 6–12, and more than 12 hours. A cut-off of at least 3 hours in advance was chosen for this analysis based on evidence that tenofovir reaches detectable levels in the male and female genital tracts 2–4 hours after

ingestion [30,31]. Potential correlates of dosing preferences and anticipation of sex were assessed either at the study visit in which the interview was administered, or at study screening (for demographic variables). These correlates included age, sex, relationship duration, number of children, desire for more children, contraceptive use (women only), number of sex acts with the study partner in the prior month, report of any unprotected sex in the prior month, number of sexual partners besides the study partner in the prior month, whether sex was usually planned or spontaneous, willingness to pay for PrEP, and adherence to study drug (TDF, FTC/TDF, or placebo) in the prior month, as measured by pill count. CD4 counts were measured for the HIV infected partners at enrollment and every 6 months, and WHO stage and ART status were assessed quarterly. If the cross-sectional survey was completed at a visit that did not correspond with these measurements, we carried forward the values from the most recent visit at which they were measured.

Participants were interviewed individually and written informed consent was obtained separately for the clinical trial and for this site-specific sub-study. The study protocols were approved by the institutional review boards of the University of Washington and Kenyatta National Hospital.

Data Analysis

We calculated descriptive statistics for PrEP dosing preference, anticipation of sex, and other participant characteristics, stratified by gender. Univariate and multivariate log binomial regression methods with robust standard errors were used to examine correlates of preferring a daily PrEP dosing regimen (versus pre-intercourse PrEP) and correlates of anticipating sex at least 3 hours in advance (versus less than 3 hours). The log binomial model directly estimates prevalence ratios, which are preferable to odds ratios when the prevalence of the outcome measure is not rare (i.e. greater than 10%) [32]. Each multivariate model included all factors significantly associated with the outcome at a level of $p < 0.10$ in the univariate analysis. To obtain convergence of the multivariate model for PrEP regimen preference, we used Wacholder's method of truncating estimates to values slightly less than 1.0 [33]. All analyses were conducted using Stata/MP version 12.1 (StataCorp LP, College Station, TX, USA).

RESULTS

Population characteristics

Data from 310 HIV uninfected participants were included in this analysis. The sample was predominantly male (78.4%, Table I), consistent with the proportion of couples with an HIV uninfected male partner enrolled in the parent study overall (62%) [27] and at the Thika site (77.2%) [25]. At the time of enrollment into the Partners PrEP Study, participants had a median age of 34.1 years (interquartile range [IQR]: 29.1–40.8) and the median partnership duration was 5.1 and 10.9 years for couples with HIV uninfected males and females, respectively. At the time of the survey, participants had been followed in the Partners PrEP Study for a median of 21 months (IQR: 15–27), the participants' HIV infected partners had a median CD4 count of 503 cells/mm³ (IQR: 378–704), and 62.9% were not yet eligible for ART according to the 2011 Kenyan guidelines of CD4 count < 350 cells/ μ L or World Health

Organization (WHO) HIV disease stage 3 or 4. Participants reported a median of 4 sex acts with their study partner in the prior month (IQR: 3–8), and very few participants (2.6%) reported sexual partners in addition to their study partner in the prior month. About 85% of participants stated that they would be willing to pay for PrEP if it were effective. Among those willing to pay, participants reported that they could afford a median of 200 Kenyan Shillings (KSh) per month for PrEP (IQR 100–500), or about 2.20 USD. Over 87% of participants had study drug adherence 80%.

Preferences for daily versus intermittent PrEP

Overall, 147 participants (47.4%) preferred a daily PrEP regimen, 157 (50.7%) preferred pre-intercourse PrEP, and 5 (1.6%) did not have a preference (Table I). Among those who preferred daily PrEP, the most common reasons were that they believed it was more effective (74.2%), that they were already used to taking PrEP daily (26.5%), and that sex was not usually planned (15.7%). Among those who preferred pre-intercourse PrEP, the most common reasons were lower pill burden (51.0%), not having to take pills when sex was not anticipated (33.8%), fewer side effects (26.1%) and lower cost (14.7%).

Correlates of PrEP regimen preferences

Participants were more likely to prefer a daily regimen if they reported unprotected sex with their study partner in the prior month (65.7% versus 45.9%, adjusted prevalence ratio [aPR]: 1.48, 95% confidence interval [CI]: 1.20–1.81, Table II), and were less likely to prefer a daily regimen if they reported that sex was usually planned rather than spontaneous (40.5% versus 56.8%, aPR: 0.76, 95% CI: 0.61–0.96). Participants who reported that they could predict sex at least 3 hours in advance tended to be less likely to prefer a daily regimen than those who could not predict sex at least 3 hours in advance, though this association was not significant in the multivariate model, when spontaneity of sex was also included ($p=0.3$). Participants with study drug adherence <80% were significantly more likely to prefer a daily regimen than participants with adherence 80% (69.6% versus 45.3%, aPR: 1.50, 95% CI: 1.25–1.79). Demographic and clinical factors were not significantly associated with PrEP regimen preferences. Similar proportions of men (48.1%) and women (49.2%) preferred a daily regimen. Among participants age 18–29, 56.2% preferred a daily regimen, compared to 46.3% of participants aged 30–39 and 43.0% of participants aged 40 and above, though the trend did not reach statistical significance ($p=0.2$). Regimen preference was not associated with willingness to pay for daily PrEP or participant reports of what they could afford to pay for PrEP.

Correlates of anticipating sex at least 3 hours in advance

Approximately one-quarter of participants (24.2%) reported that they usually anticipated sex at least 3 hours in advance. In multivariate analysis, younger participants were less likely to anticipate sex at least 3 hours in advance (aPR: 0.43, 95% CI: 0.23–0.83 for ages 18–29 versus ages 40, Table III). Although not statistically significant, women were less likely than men to anticipate sex in advance (aPR: 0.60, 95% CI: 0.33–1.10, 15% vs. 27%, respectively) and participants who reported more sex acts in the prior month were less likely to anticipate sex (aPR: 0.57, 95% CI: 0.28–1.18 for >8 versus 1–3 sex acts). Other factors, such as relationship duration, fertility desire, condom use, and the ART status of the

participant's HIV infected partner, were not associated with anticipating sex at least 3 hours in advance.

DISCUSSION

In this population of HIV-uninfected individuals in an HIV serodiscordant partnership who were already accustomed to daily pill taking and well-informed about HIV prevention, preferences were split between daily and intermittent PrEP dosing regimens. Participants were more likely to prefer a daily regimen if they reported unprotected sex in the prior month or that sex is usually spontaneous, or if they had low adherence to study drug. Although half of participants preferred pre-intercourse PrEP, only a quarter reported anticipating sex at least 3 hours in advance, with younger participants being less likely to anticipate sex.

Our findings on both regimen preferences and sex planning differ from studies of MSM, as might be expected based on differences in population, demographics, geography, and sexual behavior. In a study of substance-using MSM in the U.S., 90% preferred daily PrEP because it could be easily incorporated with other daily medication regimens and there would be lower risk of missing doses while intoxicated [17]. In contrast, Kenyan MSM study participants generally preferred iPrEP, due to the lower pill burden, though participants also cited multiple adherence challenges, particularly to post-coital dosing [16]. In studies of MSM in the U.S. and Thailand, 42% and 65% of participants, respectively, reported that sex was usually planned in advance [19,20]. In another study conducted in the same population as our survey, participants correctly anticipated 61% of sexual activity one day in advance [22].

Our results suggest that participants' HIV risk behavior, adherence behavior, and ability to anticipate sex all inform regimen preference. Although the Partners PrEP Study findings were unknown at the time of the survey, and no data are available on the effectiveness of oral iPrEP, a large proportion of participants believed that daily PrEP would be more effective in preventing HIV, and participants with higher risk behaviors in the prior month (i.e. unprotected sex) tended to prefer daily PrEP. In the entire Partners PrEP Study cohort, risk behavior was also associated with adherence to daily PrEP, with not having sex being the strongest single predictor of poor adherence [34]. Known risk, due to couple's mutually-disclosed HIV serodiscordant status, has been hypothesized as one reason for the high adherence to PrEP among HIV-uninfected members of HIV serodiscordant couples [35,36]. Our finding that participants with low adherence to the daily study drug regimen were more likely to prefer a daily regimen is unexpected. However, because we excluded participants no longer in a couple with their study partner, we may have excluded most participants who had low adherence due to sexual inactivity. Participants with low adherence in our sample may have preferred a daily regimen because they felt it would be easier to adhere to than an intermittent regimen, similar to the American substance-using MSM described above [17].

Many participants in our study saw the ability to abstain from PrEP use when not sexually active as an advantage of intermittent dosing, and valued the potential opportunity to reduce their overall pill burden. Given that most study participants reported sex about 4 times per

month (or approximately once per week), an intermittent regimen could reduce dosing requirements substantially. However, many participants also reported that sex is not usually planned, and those who did not plan sex were more likely to prefer a daily regimen. The low proportion of couples reporting planned sex implies that adherence to pre-intercourse dosing within a window to achieve adequate tissue concentrations of activated metabolites may be difficult. Small feasibility studies among MSM and HIV serodiscordant couples have found that adherence to oral fixed and post-intercourse intermittent regimens is lower than to daily regimens [13,14], suggesting that challenges may arise with any iPrEP regimen. If multiple PrEP regimens, including daily, fixed intermittent, pre-intercourse and/or post-intercourse PrEP, were rolled out for public use, counseling would need to help users periodically assess their level of HIV risk and their ability to adhere to various regimens, to select the most appropriate method for them at that time. This counseling could provide an opportunity to emphasize the costs, side effects, and efficacy of different dosing regimens, to tailor regimens to users' preferences and priorities. Current and planned PrEP trials and demonstration projects offer one opportunity to further explore messaging around PrEP delivery.

Our findings that younger people are less likely to anticipate sex are consistent with studies suggesting relationship differences among older versus younger couples, such as communication and control within relationships [37,38], among others, that could impact feasibility of iPrEP. While this suggests that younger people may have trouble adhering to pre-intercourse dosing strategies, these same underlying issues may also complicate adherence to daily PrEP, for example due to difficulty discussing HIV risk or concerns about stigma with PrEP use. Indeed, younger age was associated with poorer daily adherence in PrEP studies [6,34]. Young adults are also at high risk of non-compliance for many other medication regimens, including contraception, ART and several chronic disease medications [39–42]. Interventions found to improve adherence for these medications in youth may therefore be applicable to PrEP [39]. Although not statistically significant in multivariate analysis, we also found that women in our sample were less likely than men to anticipate sex. Many studies have illustrated that men have greater power within sexual relationships in this region [43,44], and may decide when sex will occur without communicating or negotiating with their partners. In this context, women may have greater trouble adhering to a pre-intercourse PrEP regimen than men.

There are several limitations to this study. While our sample is representative of the larger population of Partners PrEP Study participants [25,27], those who participated in the clinical trial and this survey may not be fully representative of HIV serodiscordant couples who would be targeted for PrEP use. Because the study participants had extensive experience with daily PrEP use, as well as extensive counseling on HIV prevention as part of the parent clinical trial, their opinions on daily use were well informed, and they were better able to consider scenarios about iPrEP. However, opinions on iPrEP are hypothetical, and preferences could change with actual use of iPrEP. In addition, the question on preferences did not specify whether iPrEP efficacy would be comparable to daily PrEP, and relative efficacy may also inform preferences. Due to the cross-sectional design, we were unable to assess how PrEP regimen preferences change over time or with changing sexual risk behaviors. Some potential correlates were self-reported, such as condom use and additional

partnerships, and may be biased due to poor recall or social desirability. In an earlier study conducted among HIV serodiscordant couples, self-reported sexual risk behavior was strongly correlated with pregnancy incidence and risk of HIV infection, from both within and outside the partnership[45–48], suggesting that such reports have reasonable validity in this population.

The decision to use 3 hours as a cut-off for considering sex as “anticipated in advance” in this analysis was based on pharmacokinetic (PK) data about tenofovir and emtricitabine metabolites in the genital tract after a single dose of oral FTC/TDF[30,31]. However, this evidence comes from a small number of studies in HIV infected men and women, and the concentrations found in these genital tract samples may not have been high enough to actually prevent HIV infection should an exposure occur. Although the minimum effective intracellular concentration of tenofovir is unknown, a PBMC tenofovir diphosphate (TFV-DP) concentration of 16 fmol/million was estimated to provide 90% protection for MSM in the iPrEx study[29]. Recent PK studies suggest that concentrations of this level may only be attained 12-24 hours after ingestion[49,50]. Only 7% of study participants reported that they could usually anticipate sex at least 12 hours in advance, suggesting that intermittent dosing of PrEP 12-24 hours before sex would be difficult in this population. However, there is limited data to establish the necessary genital concentrations of activated intracellular metabolites of TFV-DP and FTC triphosphate required for effective protection from HIV, and the threshold may differ by site of sexual exposure[50,51]. More pharmacokinetic data are needed to estimate how far in advance PrEP must be taken to provide sufficient levels of protection and to guide the feasibility of pre-intercourse dosing in various populations.

To our knowledge, this study provides the first results on PrEP regimen preferences in HIV serodiscordant couples with high HIV knowledge and experience with daily PrEP use. Preferences for daily versus intermittent PrEP were evenly split, and preferences were strongly correlated with an individual's assessment of their risk behavior and their ability to use iPrEP appropriately, as well as with adherence to study drug. Sexual activity in this population was infrequent enough that iPrEP would significantly reduce drug exposure and pill burden. However, relatively few participants were able to anticipate sex in advance, indicating that pre-intercourse dosing might be challenging, especially among younger persons. In all oral PrEP studies, adherence to the daily regimen has proven challenging for a proportion of the population. A choice of PrEP dosing options might be available in the future, including daily PrEP as well as intermittent fixed dose, pre-intercourse, and/or post-intercourse regimens, depending on the results of ongoing and future studies. Such options would permit individuals to choose between different regimens to suit their personal preferences and changing sexual behavior patterns, similar to the way women choose a contraceptive method to suit their particular circumstances [52]. A variety of options for PrEP dosing, if efficacious for HIV prevention, might increase adherence and maximize the public health impact that this strategy can have on the HIV epidemic.

Acknowledgments

The authors thank the couples who participated in this study and the teams at the Thika, Kenya study site and at the University of Washington for work on data collection and management. This research is supported by grants from

the National Institutes of Health (R21 NR012663), the Bill and Melinda Gates Foundation (grant OOP47674), and by the University of Washington Graduate School and the ARCS® Foundation Seattle Chapter Endowment Fund.

REFERENCES

1. Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N. Engl. J. Med.* 2012; 367(5):399–410. [PubMed: 22784037]
2. Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N. Engl. J. Med.* 2012; 367(5):423–34. [PubMed: 22784038]
3. Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N. Engl. J. Med.* 2010; 363(27):2587–99. [PubMed: 21091279]
4. Choopanya K, Martin M, Suntharasamai P, 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. Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. *N. Engl. J. Med.* 2012; 367(5):411–22. [PubMed: 22784040]
6. Marrazzo, J.; Ramjee, G.; Nair, G., et al. Pre-exposure prophylaxis for HIV in women: daily oral tenofovir, oral tenofovir/emtricitabine, or vaginal tenofovir gel in the VOICE study (MTN 003).. Paper presented at: 20th Conference on Retroviruses and Opportunistic Infections; Atlanta, GA. 2013; Paper #26LB
7. Baeten J, Celum C. Systemic and topical drugs for the prevention of HIV infection: antiretroviral pre-exposure prophylaxis. *Annu. Rev. Med.* 2013; 64:219–32. [PubMed: 23020883]
8. Molina J-M, Pintado C, Gatey C, et al. Challenges and opportunities for oral pre-exposure prophylaxis in the prevention of HIV infection: where are we in Europe? *BMC Med.* 2013; 11(1): 186. [PubMed: 23972284]
9. García-Lerma JG, Cong M, Mitchell J, et al. Intermittent prophylaxis with oral Truvada protects macaques from rectal SHIV infection. *Sci. Transl. Med.* 2010; 2(14):14ra4.
10. García-Lerma JG, Otten RA, Qari SH, et al. Prevention of rectal SHIV transmission in macaques by daily or intermittent prophylaxis with emtricitabine and tenofovir. *PLoS Med.* 2008; 5(2):e28. [PubMed: 18254653]
11. ANRS. The IPERGAY study. <http://www.ipergay.fr/>. Accessed 2013 Jun 11
12. HPTN 067. The ADAPT study: a phase II, randomized, open-label, pharmacokinetic and behavioral study of the use of intermittent oral Emtricitabine/Tenofovir Disoproxil Fumarate pre-exposure prophylaxis (PrEP). http://www.hptn.org/research_studies/hptn067.asp. Accessed 2013 Jun 11
13. Mutua G, Sanders E, Mugo P, et al. Safety and adherence to intermittent pre-exposure prophylaxis (PrEP) for HIV-1 in African men who have sex with men and female sex workers. *PLoS One.* 2012; 7(4):e33103. [PubMed: 22511916]
14. Kibengo FM, Ruzagira E, Katende D, et al. Safety, adherence and acceptability of intermittent tenofovir/emtricitabine as HIV pre-exposure prophylaxis (PrEP) among HIV-uninfected Ugandan volunteers living in HIV-serodiscordant relationships: a randomized, clinical trial. *PLoS One.* 2013; 8(9):e74314. [PubMed: 24086333]
15. Abdool Karim Q, Abdool Karim SS, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science.* 2010; 329(5996):1168–74. [PubMed: 20643915]
16. Van der Elst EM, Mbogua J, Operario D, 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.* 2013; 17(6):2162–72. [PubMed: 23080358]
17. Mitty, JA.; Closson, EF.; Rowley, B.; Mayer, KH.; Mimiaga, MJ. Preference for daily versus intermittent PrEP dosing among substance using high-risk MSM.. Paper presented at: 7th International Conference on HIV Treatment and Prevention Adherence; Miami, FL, USA. 2012; Abstract 80048

18. World Health Organization. Guidance on pre-exposure oral prophylaxis (PrEP) for serodiscordant couples, men, and transgender women who have sex with men at high risk of HIV: recommendations for use in the context of demonstration projects. Geneva, Switzerland: 2012.
19. Van Griensven F, Thienkrue W, Sukwicha W, et al. Sex frequency and sex planning among men who have sex with men in Bangkok, Thailand: implications for pre- and post-exposure prophylaxis against HIV infection. *J. Int. AIDS Soc.* 2010; 13:13. [PubMed: 20398261]
20. Volk JE, Liu A, Vittinghoff E, et al. Sexual frequency and planning among at-risk men who have sex with men in the United States: implications for event-based intermittent pre-exposure prophylaxis. *J. Acquir. Immune Defic. Syndr.* 2012; 61(1):112–5. [PubMed: 22592590]
21. Rendina, HJ.; Ventuneac, A.; Grov, C.; Mustanski, B.; Parsons, JT. Accuracy in predicting daily anal intercourse with casual partners and its relevance for intermittent PrEP: an online diary analysis of highly sexually active gay and bisexual men.. Paper presented at: 8th International Conference on HIV Treatment and Prevention Adherence; Miami, FL, USA. 2013; Abstract 136
22. Curran K, Mugo NR, Kurth A, et al. Daily Short Message Service surveys to measure sexual behavior and pre-exposure prophylaxis use among Kenyan men and women. *AIDS Behav.* 2013; 17(9):2977–85. [PubMed: 23695519]
23. Chemaitelly H, Cremin I, Shelton J, Hallett TB, Abu-Raddad LJ. Distinct HIV discordancy patterns by epidemic size in stable sexual partnerships in sub-Saharan Africa. *Sex. Transm. Infect.* 2012; 88(1):51–7. [PubMed: 22250180]
24. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva, Switzerland: 2013.
25. Heffron R, Ngure K, Mugo N, et al. Willingness of Kenyan HIV-1 serodiscordant couples to use antiretroviral-based HIV-1 prevention strategies. *J. Acquir. Immune Defic. Syndr.* 2012; 61(1): 116–9. [PubMed: 22595872]
26. Curran K, Ngure K, Shell-Duncan B, et al. “If I am given antiretrovirals I will think I am nearing the grave”: Kenyan HIV serodiscordant couples’ attitudes regarding early initiation of antiretroviral therapy. *AIDS.* 2014; 28(2):227–33. [PubMed: 24413310]
27. Mujugira A, Baeten JM, Donnell D, et al. Characteristics of HIV-1 serodiscordant couples enrolled in a clinical trial of antiretroviral pre-exposure prophylaxis for HIV-1 prevention. *PLoS One.* 2011; 6(10):e25828. [PubMed: 21998703]
28. Cohen M, Chen Y, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N. Engl. J. Med.* 2011; 365(6):493–505. [PubMed: 21767103]
29. Anderson PL, Glidden D V, Liu A, et al. Emtricitabine-tenofovir concentrations and pre-exposure prophylaxis efficacy in men who have sex with men. *Sci. Transl. Med.* 2012; 4(151):151ra125.
30. Dumond J, Yeh R, Patterson K, et al. Antiretroviral drug exposure in the female genital tract: implications for oral pre-and post-exposure prophylaxis. *AIDS.* 2007; 21(14):1899–907. [PubMed: 17721097]
31. Vourvahis M, Tappouni H, Patterson K, et al. The pharmacokinetics and viral activity of tenofovir in the male genital tract. *J. Acquir. Immune Defic. Syndr.* 2008; 47(3):329–33. [PubMed: 18197124]
32. Deddens JA, Petersen MR. Approaches for estimating prevalence ratios. *Occup. Environ. Med.* 2008; 65(7):501–6.
33. Wacholder S. Binomial regression in GLIM: estimating risk ratios and risk differences. *Am. J. Epidemiol.* 1986; 123(1):174–84. [PubMed: 3509965]
34. Haberer JE, Baeten JM, Campbell J, et al. Adherence to antiretroviral prophylaxis for HIV prevention: a substudy cohort within a clinical trial of serodiscordant couples in East Africa. *PLoS Med.* 2013; 10(9):e1001511. [PubMed: 24058300]
35. 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 Suppl 2):S91–8. [PubMed: 23253769]
36. Ware NC, Wyatt MA, Haberer JE, 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(5):463–8. [PubMed: 22267018]

37. Katz IT, Ybarra ML, Wyatt MA, et al. Socio-cultural and economic antecedents of adolescent sexual decision-making and HIV-risk in rural Uganda. *AIDS Care*. 2013; 25(2):258–64. [PubMed: 22835224]
38. Maticka-Tyndale E, Gallant M, Brouillard-Coyle C, et al. The sexual scripts of Kenyan young people and HIV prevention. *Cult. Health Sex*. 2005; 7(1):27–41. [PubMed: 16864186]
39. Friedman IM, Litt IF. Adolescents' compliance with therapeutic regimens: psychological and social aspects and intervention. *J. Adolesc. Heal. Care*. 1987; 8(1):52–67.
40. Nachega JB, Hislop M, Nguyen H, et al. Antiretroviral therapy adherence, virologic and immunologic outcomes in adolescents compared with adults in southern Africa. *J. Acquir. Immune Defic. Syndr*. 2009; 51(1):65–71. [PubMed: 19282780]
41. Murphy DA, Wilson CM, Durako SJ, Muenz LR, Belzer M. Antiretroviral medication adherence among the REACH HIV-infected adolescent cohort in the USA. *AIDS Care*. 2001; 13(1):27–40. [PubMed: 11177463]
42. Woods JL, Shew ML, Tu W, et al. Patterns of oral contraceptive pill-taking and condom use among adolescent contraceptive pill users. *J. Adolesc. Heal*. 2006; 39(3):381–7.
43. Jewkes R, Morrell R. Gender and sexuality: emerging perspectives from the heterosexual epidemic in South Africa and implications for HIV risk and prevention. *J. Int. AIDS Soc*. 2010; 13:6. [PubMed: 20181124]
44. Nguni K, Mugo N, Celum C, et al. A qualitative study of barriers to consistent condom use among HIV-1 serodiscordant couples in Kenya. *AIDS Care*. 2012; 24(4):509–16. [PubMed: 22085306]
45. Heffron R, Rees H, Mugo N, Baeten JM. Use of hormonal contraceptives and risk of HIV-1 transmission – Authors' reply. *Lancet Infect. Dis*. 2012; 12(7):510–1. [PubMed: 22742633]
46. Ndase P, Celum C, Thomas K, et al. Outside sexual partnerships and risk of HIV acquisition for HIV uninfected partners in African HIV serodiscordant partnerships. *J. Acquir. Immune Defic. Syndr*. 2012; 59(1):65–71. [PubMed: 21963939]
47. Nguni K, Heffron R, Mugo NR, et al. Contraceptive method and pregnancy incidence among women in HIV-1-serodiscordant partnerships. *AIDS*. 2012; 26(4):513–8. [PubMed: 22156966]
48. Hughes JP, Baeten JM, Lingappa JR, et al. Determinants of per-coital-act HIV-1 infectivity among African HIV-1-serodiscordant couples. *J. Infect. Dis*. 2012; 205(3):358–65. [PubMed: 22241800]
49. Chen J, Flexner C, Liberman RG, et al. Biphasic elimination of tenofovir diphosphate and nonlinear pharmacokinetics of zidovudine triphosphate in a microdosing study. *J. Acquir. Immune Defic. Syndr*. 2012; 61(5):593–9. [PubMed: 23187888]
50. Louissaint N, Cao Y, Skipper P, et al. Single dose pharmacokinetics of oral tenofovir in plasma, peripheral blood mononuclear cells, colonic tissue, and vaginal tissue. *AIDS Res. Hum. Retroviruses*. 2013; 29(11):1443–50. [PubMed: 23600365]
51. Hendrix CW, Chen BA, Guddera V, et al. MTN-001: randomized pharmacokinetic cross-over study comparing tenofovir vaginal gel and oral tablets in vaginal tissue and other compartments. *PLoS One*. 2013; 8(1):e55013. [PubMed: 23383037]
52. Myers JE, Sepkowitz KA. A pill for HIV prevention: Déjà vu all over again? *Clin. Infect. Dis*. 2013; 56(11):1604–12. [PubMed: 23408681]

Table ICharacteristics of HIVuninfected participants (N=310^a)

Total participants, N (%)	Men 243 (78.4)	Women 67 (21.6)	Total 310 (100.0)
Demographics			
Age in years, median (IQR)	34.5 (29.4–40.8)	32.8 (27.0–42.7)	34.1 (29.1–40.8)
Months since study enrollment, median (IQR)	21 (15–27)	21 (15–24)	21 (15–27)
Partnership duration in years, median (IQR)	5.1 (1.9–10.3)	10.9 (5.1–21.2)	6.1 (2.5–12.0)
Number of children with study partner, median (IQR)	2 (1–3)	2 (1–3)	2 (1–3)
Fertility desires			
Desires more children, n (%)	132 (54.3)	24 (35.8)	156 (50.3)
Does not desire more children, n (%)	111 (45.7)	43 (64.2)	154 (49.7)
Contraceptive use (Females only) ^b			
Any effective method, n (%)	-	46 (68.7)	-
No method or other methods, n (%)	-	21 (31.3)	-
ART status of HIV infected partner			
On ART, n (%)	51 (21.0)	18 (26.9)	69 (22.3)
Eligible ^c , not on ART, n (%)	36 (14.8)	10 (14.9)	46 (14.8)
Not eligible, not on ART, n (%)	156 (64.2)	39 (58.2)	195 (62.9)
Clinical characteristics of HIV infected partner			
CD4 count (cells/mm ³), median (IQR)	534 (384–726)	474(369–564)	503(378–704)
WHO Stage 1 or 2, n (%)	215 (88.5)	60 (89.6)	275 (88.7)
WHO Stage 3 or 4, n (%)	25 (10.3)	6 (8.9)	31 (10.0)
Payment for PrEP			
Willing to pay for PrEP, n (%)	209 (86.0)	54 (80.6)	263 (84.8)
Not willing to pay for PrEP, n (%)	34 (14.0)	13 (19.4)	47 (15.2)
Amount able to pay per month (KSh), median (IQR) ^d	200 (100–500)	150 (100–500)	200 (100–500)
Sexual behavior, prior month			
Sex acts with study partner, median (IQR)	4 (3–8)	4 (2–10)	4 (3–8)
Any unprotected sex with study partner, n (%)	27 (11.1)	8 (11.9)	35 (11.3)
Had sexual partner(s) in addition to study partner, n (%)	7 (2.9)	1 (1.5)	8(2.6)
Spontaneity of sex			
Planned, n (%)	135 (55.6)	28 (41.8)	163 (52.6)
Spontaneous, n (%)	108 (44.4)	39 (58.2)	147 (47.4)
Hours in advance that sex is usually anticipated			
Less than 1 hour, n (%)	109 (44.9)	42 (62.7)	151 (48.7)
1–3 hours, n (%)	69 (28.4)	15 (22.4)	84 (27.1)
3–6 hours, n (%)	33 (13.6)	4 (6.0)	37 (11.9)
6–12 hours, n (%)	16 (6.6)	1 (1.5)	17 (5.5)
More than 12 hours, n (%)	16 (6.6)	5 (7.5)	21 (6.8)
Adherence to study drug, prior month			
80% (n, %)	213 (87.7)	57 (85.1)	270 (87.1)

	Men	Women	Total
Total participants, N (%)	243 (78.4)	67 (21.6)	310 (100.0)
< 80% (n, %)	22 (9.0)	1 (1.5)	23 (7.4)
Not on study drug ^e	8 (3.3)	9 (13.4)	17 (5.5)
Preferred PrEP regimen			
Daily, n (%)	115 (47.3)	32 (47.8)	147 (47.4)
Pre-Intercourse, n (%)	124 (51.0)	33 (49.3)	157 (50.7)
Don't know, n (%)	3 (1.2)	2 (3.0)	5 (1.6)

IQR: Interquartile range; ART: Antiretroviral therapy; WHO: World Health Organization; KSh: Kenyan Shillings

^aThe following data were missing: Partnership duration in years (n=6); HIV infected partner WHO stage (n=4); Sex acts with study partner (n=1); Any unprotected sex with study partner (n=1); Had sexual partner(s) in addition to study partner (n=1); Preferred PrEP regimen (n=1).

^bEffective methods include oral contraceptives, injections, implants, IUDs, or surgical sterilization.

^cEligibility for ART was defined according to Kenyan national guidelines at the time of survey implementation: CD4<350 cells/mm³ or WHO stage 3 or 4

^dAmong those willing to pay for PrEP (n=263). 1 KSh equaled approximately 0.011 USD at the time of the survey

^eRefers to participants not currently taking study drug due to product hold, or missing the previous study visit.

Table IICorrelates of preferring a daily PrEP regimen (N = 304^a)

	<i>Frequency</i>		<i>Univariate Analysis</i>			<i>Multivariate Analysis</i>		
	n/N	%	PR	95% CI	p	aPR ^b	95% CI	p
Gender								
Male	115/239	48.1	1	(referent)	0.9			
Female	32/65	49.2	1.02	0.77—1.35				
Age, years								
18—29 years	50/89	56.2	1.31	0.95—1.79	0.2			
30—39 years	63/136	46.3	1.07	0.79—1.47				
40 years	34/79	43.0	1	(referent)				
Months since study enrollment								
<18 months	54/105	51.4	1.25	0.91—1.71	0.3			
18—24 months	58/114	50.9	1.24	0.90—1.69				
>24 months	35/85	41.2	1	(referent)				
Partnership duration, years								
<5 years	66/131	50.4	1.08	0.85—1.36	0.5			
5 years	78/167	46.7	1	(referent)				
Number of children with study partner								
0 children	27/53	50.9	1	(referent)	0.6			
1 child	40/77	51.9	1.02	0.73—1.43				
2 children	80/174	46.0	0.90	0.66 - 1.23				
Desires more children								
No	68/150	45.3	1	(referent)	0.3			
Yes	79/154	51.3	1.13	0.90—1.43				
Contraceptive use (Females only)								
None/Other	12/21	57.1	1.26	0.77—2.06	0.4			
Any effective	20/44	45.5	1	(referent)				
ART status of HIV infected partner								
On ART	38/68	55.9	1.15	0.89—1.48	0.1			
Eligible, not on ART	16/45	35.6	0.73	0.48—1.11				
Ineligible, not on ART	93/191	48.7	1	(referent)				
CD4 count of HIV infected partner (cells/mm³)								
<350 cells/mm ³	21/53	39.6	1	(referent)	0.2			
350 cells/mm ³	126/251	50.2	1.27	0.89—1.81				
WHO stage of HIV infected partner								
Stage 1 or 2	129/270	47.8	1	(referent)	0.8			
Stage 3 or 4	15/30	50.0	1.05	0.72—1.53				
Willing to pay for PrEP								
No	25/45	55.6	1	(referent)	0.3			
Yes	122/259	47.1	0.85	0.63—1.14				

	<i>Frequency</i>		<i>Univariate Analysis</i>			<i>Multivariate Analysis</i>		
	n/N	%	PR	95% CI	p	aPR ^b	95% CI	p
<i>Amount able to pay for PrEP, per month (among those willing to pay only)</i>								
100 KSh	44/100	44.0	1	(referent)	0.6			
101-300 KSh	36/77	46.8	1.06	0.77—1.47				
>300 KSh	42/82	51.2	1.16	0.86—1.58				
<i>Adherence to study drug, prior month</i>								
80%	120/265	45.3	1	(referent)	0.004	1	(referent)	
< 80%	16/23	69.6	1.54	1.14—2.08		1.50	1.25—1.79	<0.001
Not on study drug	11/16	68.8	1.52	1.06—2.17		1.35	0.85—2.14	
<i>Sex acts with study partner, prior month</i>								
0 acts	10/27	37.0	0.75	0.44—1.28	0.5			
1—3 acts	41/83	49.4	1	(referent)				
4—8 acts	55/119	46.2	0.94	0.70—1.25				
>8 acts	40/74	54.1	1.09	0.81—1.48				
<i>Any unprotected sex with study partner, prior month</i>								
No	123/268	45.9	1	(referent)	0.01	1	(referent)	< 0.001
Yes	23/35	65.7	1.43	1.09—1.88		1.48	1.20—1.81	
<i>Had sexual partner(s) in addition to study partner, prior month</i>								
No	143/295	48.5	1.29	0.52—3.19	0.6			
Yes	3/8	37.5	1	(referent)				
<i>Spontaneity of Sex</i>								
Planned	64/158	40.5	0.71	0.56—0.90	0.005	0.76	0.61—0.96	0.02
Spontaneous	83/146	56.8	1	(referent)		1	(referent)	
<i>Hours in Advance Sex is Anticipated</i>								
>3 hours	29/74	39.2	0.76	0.56-1.04	0.09	0.86	0.62—1.18	0.3
3 hours	118/230	51.3	1	(referent)		1	(referent)	

PR: Prevalence Ratio; aPR: Adjusted Prevalence Ratio; CI: Confidence Interval; ART: Antiretroviral therapy; WHO: World Health Organization; KSh: Kenyan Shillings

^aExcludes 5 “Don't know”, 1 missing response for PrEP regimen preference and 1 missing response for any unprotected sex

^bAdjusted model includes unprotected sex, spontaneity of sex, and hours in advance sex is anticipated.

Table IIICorrelates of Reporting that Sex is Usually Anticipated >3 Hours in Advance (N=309^a)

	<i>Frequency</i>		<i>Univariate Analysis</i>			<i>Multivariate Analysis</i>		
	n/N	%	PR	95% CI	P	aPR ^b	95% CI	P
Gender								
Male	65/243	26.7	1	(referent)	0.06	1	(referent)	0.1
Female	10/67	14.9	0.56	0.30—1.03		0.6	0.33—1.10	
Age, years								
18—29 years	11/89	12.4	0.38	0.20-0.71	0.01	0.43	0.23—0.83	0.04
30—39 years	37/139	26.6	0.81	0.53—1.22		0.86	0.57—1.29	
>40 years	27/82	32.9	1	(referent)		1	(referent)	
Months since study enrollment								
<18 months	26/108	24.1	0.85	0.53—1.37	0.5			
18-24 months	25/117	21.4	0.76	0.47—1.23				
>24 months	24/85	28.2	1	(referent)				
Partnership duration, years								
<5 years	34/131	26.0	1.12	0.75—1.67	0.6			
5 years	40/173	23.1	1	(referent)				
Number of children with study partner								
0 children	14/54	25.9	1	(referent)	0.5			
1 child	22/77	28.6	1.10	0.62—1.96				
2 children	39/179	21.8	0.84	0.49—1.43				
Desires more children								
No	41/154	26.6	1	(referent)	0.3			
Yes	34/156	21.8	0.82	0.55—1.22				
Contraceptive use (Females only)								
None/Other	3/21	14.3	0.94	0.27—3.31	0.9			
Any Effective	7/46	15.2	1	(referent)				
ART status of HIV infected partner								
On ART	14/69	20.3	0.86	0.51—1.46	0.3			
Eligible, not on ART	15/46	32.6	1.38	0.85—2.25				
Ineligible, not on ART	46/195	23.6	1	(referent)				
Sex acts with study partner, prior month								
0 acts	8/27	29.6	1.14	0.58—2.27	0.07	1.27	0.65—2.47	0.2
1—3 acts	22/85	25.9	1	(referent)		1	(referent)	
4—8 acts	36/123	29.3	1.13	0.72—1.78		1.17	0.75—1.82	
>8 acts	9/74	12.2	0.47	0.23—0.96		0.57	0.28—1.18	
Any unprotected sex with study partner, prior month								
No	64/274	23.4	1	(referent)	0.3			
Yes	11/35	31.4	1.35	0.79—2.30				
Had sexual partner(s) in addition to study partner, prior month								
No	72/301	23.9	0.64	0.25—1.60	0.3			

	<i>Frequency</i>		<i>Univariate Analysis</i>		<i>Multivariate Analysis</i>			
	n/N	%	PR	95% CI	P	aPR^b	95% CI	P
Yes	3/8	37.5	1	(referent)				

PR: Prevalence Ratio; aPR: Adjusted Prevalence Ratio; CI: Confidence Interval; ART: Antiretroviral therapy; WHO: World Health Organization

^aExcludes 1 missing response for sex acts with study partner in last month

^bAdjusted model includes sex, age, and sex acts with study partner