Sexual behaviour of heterosexual men and women receiving antiretroviral pre-exposure prophylaxis for HIV prevention: a longitudinal analysis

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Summary

Background Scarce data are available to assess sexual behaviour of individuals using antiretroviral pre-exposure prophylaxis for HIV prevention. Increased sexual risk taking by individuals using effective HIV prevention strategies, like pre-exposure prophylaxis, could offset the benefits of HIV prevention. We studied whether the use of pre-exposure prophylaxis in HIV-uninfected men and women in HIV-serodiscordant couples was associated with increased sexual risk behaviour.

Methods We undertook a longitudinal analysis of data from the Partners PrEP Study, a double-blind, randomised, placebo-controlled trial of daily oral pre-exposure prophylaxis among HIV-uninfected partners of heterosexual HIV-serodiscordant couples (n=3163, ≥18 years of age). Efficacy for HIV prevention was publicly reported in July 2011, and participants continued monthly follow-up thereafter. We used regression analyses to compare the frequency of sex—unprotected by a condom—during the 12 months after compared with the 12 months before July 2011, to assess whether knowledge of pre-exposure prophylaxis efficacy for HIV prevention caused increased sexual risk behaviour.

Findings We analysed 56 132 person-months from 3024 HIV-uninfected individuals (64% male). The average frequency of unprotected sex with the HIV-infected study partner was 59 per 100 person-months before unmasking versus 53 after unmasking; we recorded no immediate change (p=0·66) or change over time (p=0·25) after July, 2011. We identified a significant increase in unprotected sex with outside partners after July, 2011, but the effect was small (average of 6·8 unprotected sex acts per year *vs* 6·2 acts in a predicted counterfactual scenario had patients remained masked, p=0·04). Compared with before July, 2011, we noted no significant increase in incident sexually transmitted infections or pregnancy after July, 2011.

Interpretation Pre-exposure prophylaxis, provided as part of a comprehensive prevention package, might not result in substantial changes in risk-taking sexual behaviour by heterosexual couples.

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Introduction

Findings from four randomised trials have shown that oral antiretroviral pre-exposure prophylaxis is effective in protecting against HIV acquisition in diverse geographical and at-risk populations.[1–4] Evidence of the effectiveness of daily oral tenofovir-based pre-exposure prophylaxis in HIV prevention, and of coitally dependent tenofovir gel[5] and antiretroviral treatment as prevention,[6] has spurred optimism that the global HIV epidemic might be reversed. One important question for implementation of these prevention strategies after proof of effectiveness in trials is will they increase behavioural risk compensation, defined as individuals using known effective HIV prevention interventions engaging in increased sexual risk taking. A substantial increase in risky sexual behaviours by people using pre-exposure prophylaxis, and other HIV prevention strategies, could offset the HIV protective benefits[7] and increase the risk of sexually transmitted infections (STIs). In clinical trials of pre-exposure prophylaxis, no significant differences in sexual behaviour between experimental and placebo groups were reported.[1–4,8–10] However, because the comparison groups had equivalent uncertainty of treatment assignment and benefits of the study drug during the double-blind trial period, absence of risk compensation might not fully show sexual behaviour in the context of known pre-exposure prophylaxis efficacy.

In July, 2011, findings from the Partners PrEP Study,[1] a randomised, double-blind, placebo-controlled trial of pre-exposure prophylaxis with daily oral tenofovir with or without emtricitabine among African heterosexual HIV uninfected members of serodiscordant couples, showed efficacy of pre-exposure prophylaxis for HIV prevention. Participants who had been assigned to the active pre-exposure prophylaxis groups continued in the study and were informed that they were receiving active pre-exposure prophylaxis and that this prevention strategy had been shown to reduce risk of HIV acquisition. HIV incidence in the placebo group during the study was 2% per year overall and 3% or more among subgroups with increased risk characteristics; assignment to pre-exposure prophylaxis resulted in a 67% (daily oral

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tenofovir) and 75% (emtricitabine and daily oral tenofovir) reduction in transmission risk, with a roughly 90% reduction in risk estimated for those adherent to pre-exposure prophylaxis. We examined sexual behaviours of individuals before and after July, 2011, to assess the potential risk compensation after they learnt about the effectiveness of pre-exposure prophylaxis for HIV prevention. We hypothesised that individuals using pre-exposure prophylaxis who were aware of its proven efficacy against HIV acquisition might increase sexual behavioural risks.

Methods

Partners PrEP Study

We undertook a longitudinal analysis of data from the Partners PrEP Study, which has been described previously (NCT00557245).[1,11] Briefly, between July, 2008, and November, 2010, 4747 HIV serodiscordant heterosexual couples were enrolled and followed up at nine research sites in Kenya and Uganda. Eligible HIV-uninfected participants were 18 years or older, sexually active, and had normal hepatic and renal function.

HIV-uninfected partners were randomly assigned (1:1:1) to daily oral tenofovir, emtricitabine and daily oral tenofovir, or placebo, and followed up every month for up to 36 months, with sexual behavioural assessment (appendix), HIV serological testing, pregnancy testing (for women), safety monitoring, risk-reduction counselling, and provision of study drug. Laboratory testing for STIs (*Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Trichomonas vaginalis*) was done for all participants annually and when clinically shown by the presence of symptoms.

See Online for appendix

All participants received a comprehensive package of HIV prevention services, which included HIV risk-reduction counselling (individually and as a couple), HIV testing, free condoms, testing and treatment for STIs, counselling, and referral for male circumcision. HIV-infected partners received HIV primary care and referral for initiation of antiretroviral therapy according to national guidelines. The study protocol was approved by the University of Washington Human Subjects Review Committee and ethics review committees at each of the study sites. All participants provided written informed consent in English or their local language.

An independent data and safety monitoring board met every 6 months to review the placebo-controlled trial. At the July 10, 2011, meeting, the board recommended that the placebo group of the study be discontinued and the trial results be made public because of definitive evidence that pre-exposure prophylaxis protected against HIV acquisition. The primary results of the trial, using data up to July 10, 2011 have subsequently been published.[1] Additionally, the board recommended that the active pre-exposure prophylaxis groups be continued, to gain additional information about the relative efficacy, safety, and tolerability of pre-exposure prophylaxis with daily oral tenofovir versus emtricitabine and daily oral tenofovir, and those receiving placebo to receive pre-exposure prophylaxis. On July 13, 2011, the study results were made public and research sites actively disseminated trial findings to study participants, through phone calls, group meetings, and at counselling sessions during their next scheduled monthly visits (appendix). Thus, continued follow-up of study participants initially assigned to the active pre-exposure prophylaxis groups provided an opportunity to assess risk behaviour of individuals on open-label tenofovir-based pre-exposure prophylaxis after efficacy was announced. For patients initially assigned to the active pre-exposure prophylaxis groups, study procedures were unchanged after July 13, 2011, with the exception of continued counselling about the efficacy of pre-exposure prophylaxis for HIV prevention.

Longitudinal analysis

For the present analysis, we used data against a reference date of July 13, 2011 (figure 1). Because the research sites needed time to disseminate the trial results to all study participants, we defined a dissemination window starting on July 13, 2011, and included each participant's first subsequent study visit. A maximum of 12 monthly visits before and 12 visits after the dissemination window were included to study the effect of learning about the effectiveness of pre-exposure prophylaxis and being on active pre-exposure prophylaxis while minimising temporal shifts in sexual behaviour after 1 year. All HIV-uninfected participants who were initially randomly assigned to receive active pre-exposure prophylaxis remained in study follow-up, and those who had not seroconverted to HIV were eligible for inclusion in the present analysis. For participants initially assigned to the placebo group, discontinuation and provision of active pre-exposure prophylaxis was done over several months; because of this staggered gap during which no study procedures were done, participants on the placebo group were not included in this analysis.

We studied four measures of sexual activity: frequency of sex (vaginal or anal) without a condom (unprotected sex acts); frequency of sex with or without a condom (total sex acts), with both their HIV-infected primary study partner (ie, the partner with whom each patient enrolled in the study), and outside partners (ie, any additional partner other than the primary study partner, including concurrent partners and partners acquired if the study partnership dissolved during follow-up).

The predictor of main interest was the participants' knowledge that they were receiving active pre-exposure prophylaxis and that pre-exposure prophylaxis had proven efficacy against HIV acquisition. We compared the double blind period (ie, visits made in the 12 months before July 13, 2011) to the unmasked period (ie, visits made in the 12 months after the results dissemination window from July 13, 2011). Months in which

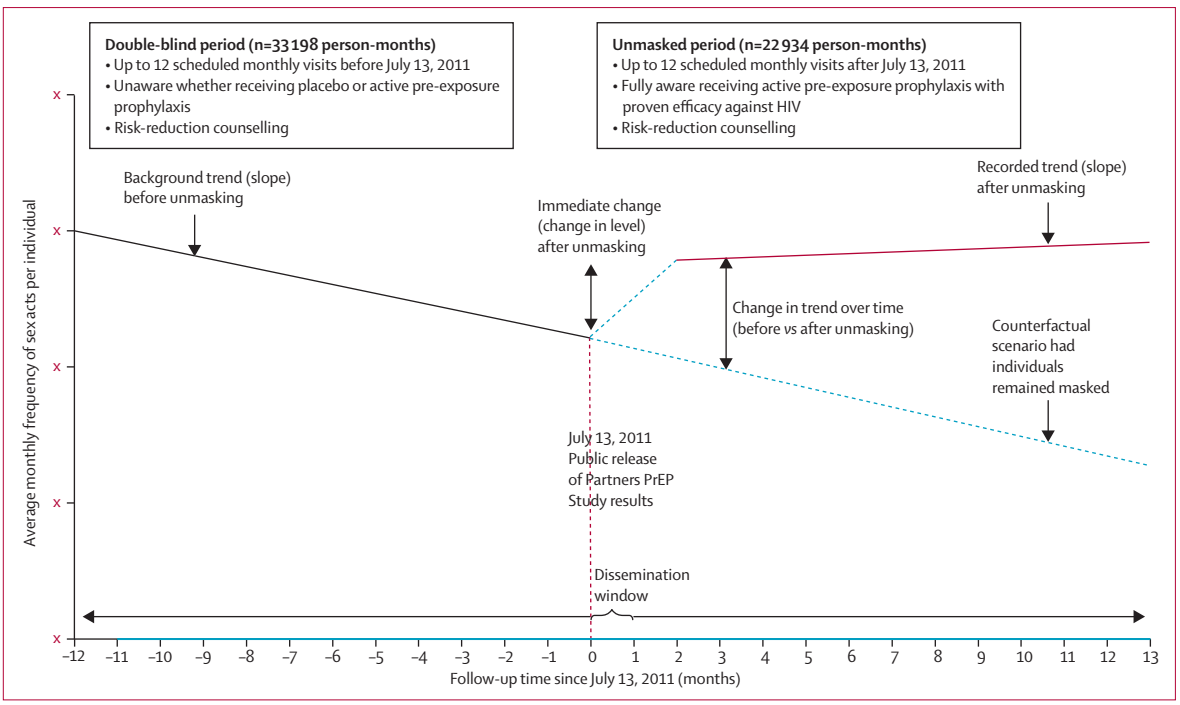

***Figure 1*: Study design**

Hypothetical segmented regression analytic flow. The study population provided data for up to 12 scheduled monthly visits both before and after July 13, 2011 when the Partners PrEP Study results were made public. The y-axis depicts the average frequency of sex acts per patient per month. Segmented regression analysis allowed estimation of the background trend of frequency of sex acts before July 13, 2011, change in level of the frequency of sex acts immediately after unmasking, and then the trend of the frequency of sex acts over time after unmasking. Interpretation of the results was based on change in the levels (immediate effect), changes in trend (trend after versus background trend), and predicted counterfactual frequency that would have been expected had unmasking not occurred.

pre-exposure prophylaxis was not given, either because of a protocol-specified study drug interuption (eg, due to pregnancy or clinical adverse events) or a missed visit, were excluded to measure the direct effect of actual drug use on sexual behaviour.

Statistical analysis

We computed crude frequencies treating each visit as an independent finding. We used a segmented regression model fit[12–14] for each count outcome variable with a zero-inflated negative binomial distribution.[15] The segmented model allowed for change in both the level (intercept, suggesting an immediate change in behaviour) and trend (slope, suggesting a change over time) of the monthly frequency of sex acts before and after unmasking and controlled for potential secular changes (figure 1). The zero-inflated negative binomial distribution allowed flexibility to account for unreported heterogeneity and overdispersion due to high occurrence of zeros common in sexual behaviour data generated either as structural zeros (eg, caused by partnership breakup) or true sampling zeros. In our study, unprotected sex with HIV-infected partner was reported from only 13% of the scheduled study visits. The count and zero-model components of the zero-inflated negative binomial distribution were fit with identical covariates. Robust standard errors were used in all models to control for within-person correlation.

Each model was specified with the following covariates: time, as a linear continuous variable in months since enrolment into the randomised trial to estimate the study background trend before July 13, 2011; unmasking, coded zero before and one after July 13, 2011, the predictor of main interest; and time after unmasking, as a linear continuous variable, coded zero before unmasking and 1–12 months after July 13, 2011, to estimate the change in trend after unmasking versus the study background trend. All models were adjusted for baseline sexual behaviour, age, and sex. The marginal means predicted by the model were used to compute annualised total frequency of sex acts estimated after unmasking and the counterfactual scenario that would have been expected had individuals remained masked. The presented model estimates are interpreted conditional on the participant reporting being sexually active (ie, not an always structural zero process).

In subgroup analysis, we assessed the frequency of unprotected sex within the study HIV-serodiscordant partnership by sex and in subpopulations with potentially high desire to have children (individuals ≤30 years of age or who had no child with study partner) because these

populations might be more likely to have unprotected sex after learning about pre-exposure prophylaxis efficacy for HIV prevention. For sensitivity analysis, we repeated our primary analysis using shorter time periods: 3, 6, and 9 months before and after unmasking.

Finally, as a cross-validation of self-reported sexual behaviour, we compared the proportion of visits at which an STI (for all participants) and pregnancy (for female participants) were diagnosed during the two periods. Reported p values are two-sided for 5% type I error rate and were not adjusted for multiple comparisons. Analyses were done with SAS (version 9.2) and Stata statistical software (version 12).

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of 4747 HIV-uninfected participants enrolled and followed in the Partners PrEP Study, 3163 were initially randomly assigned to the clinical trial's active pre-exposure prophylaxis groups. Of these, 3024 were included in the present analysis; 139 were not included: 38 because they had seroconverted to HIV before July 13, 2011, and 101 because their final study visit (ie, completing the 36 months of follow-up or early withdrawal specified by the protocol) happened on or before July 13, 2011. At enrolment, 64% of individuals were male, the median age was 34 years (IQR 29–40), the median number of sex acts with the HIV-infected study partner in the previous month was four (IQR 2–8), and 827 (27%) participants reported having at least one act of unprotected sex with their study partner in the previous month (table 1). Before unmasking, participants had been studied for a median of 23 months (IQR 16–28).

	Median (IQR) or n (%)
Male	1943 (64%)
Age ≤30 years	1120 (37%)
No child with study partner	683 (23%)
Number of sex acts with HIV-infected study partner, previous month before enrolment	4 (2–8%)
Any unprotected sex with HIV-infected study partner, previous month before enrolment	827 (27%)
Any sex with partners other than the HIV-infected study partner, previous month before enrolment	273 (9%)
Any unprotected sex with partners other than the HIV-infected study partner, previous month before enrolment	175 (6%)

Table 1: **Baseline characteristics of the study population (n=3024)**

60 406 person-months were accrued during the period for this analysis. After exclusion of months at which pre-exposure prophylaxis was not dispensed because of clinical safety hold or missed visits (n=4274 months), the final analysis dataset included 56 132 person-months of observation: 33 198 before unmasking and 22 934 after unmasking. Retention was similar during the two periods: 58 996 of 60 406 (98%) expected visits were completed.

The average crude frequency of unprotected sex with the HIV-infected study partner was 59 per 100 person-months before unmasking versus 53 after unmasking (table 2). We noted a tendency toward a gradually decreasing trend in the frequency of unprotected sex during the study before unmasking (figure 2A). After unmasking, we noted no significant changes in the immediate level (p=0·66) or trend (p=0·25) of unprotected sex (table 2). The annual average total frequency of unprotected sex acts after unmasking was 5·1 versus 4·9, the estimated counterfactual value had individuals remained masked.

Overall, the average frequency of total sex acts (ie, both with and without condoms) with the HIV-infected study partner per 100 person-months was 414 before unmasking versus 361 after unmasking (table 2). We

	Crude average frequency of sex acts per 100 (person-months* [95% CI])		Segmented model regression coefficients (β)†‡ (95% CI), p value		Average cumulative number of sex acts in 12 months†	
	Before unblinding	After unblinding	Immediate effect (change in level)	Effect over time (change in trend)	Counterfactual frequency§	Estimated frequency after unmasking
Within the study primary partnership						
Unprotected sex acts	59 (58–59)	53 (52–54)	−0·0304 (−0·1660 to 0·1050), p=0·66	0·0142 (−0·0099 to 0·0383), p=0·25	4·9	5·1
Total sex acts	414 (411–416)	361 (359–363)	−0·0155 (−0·0511 to 0·0200), p=0·39	0·0026 (−0·0034 to 0·0088), p=0·4	44·3	42·4
Outside the primary partnership						
Unprotected sex acts	49 (48–49)	66 (65–67)	0·0138 (−0·1172 to 0·1450), p=0·84	0·0204 (0·0006 to 0·0400), p=0·04	6·2	6·8
Total sex acts	67 (66–68)	84 (83–85)	−0·0211 (−0·1362 to 0·0939), p=0·72	0·0247 (0·0071 to 0·0424), p=0·006	8·8	9·0

*Crude counts computed from independent monthly observations during each period from 3024 HIV seronegative partners. †Adjusted for within-patient association, secular changes, age, sex, and baseline sexual behaviour in month before enrolment in the trial. ‡The β coefficients represent differences in the month-to-month changes in the frequency of sex acts. §Predicted frequency of sex acts that would have been expected in a counterfactual scenario had patients remained masked.

Table 2: **Sexual frequency before and after unmasking, within and outside the primary study partnership**

recorded a tendency toward a decreasing trend in the frequency of total sex acts before unmasking (figure 2B). After unmasking, no significant changes were recorded in the immediate level or trend in frequency of total sex acts (p=0·39 and 0·40, respectively). The estimated yearly average total frequency of sex after unmasking and the average counterfactual value were not qualitatively different (42·4 *vs* 44·3, respectively).

Overall, before unmasking, 12·4% of visits (4124 of 33 198, representing 794 individuals) had sex outside the primary partnership recorded compared with 15·2% (3480 of 22 934, representing 721 individuals) after unmasking. On average, the crude frequency of unprotected sex acts with outside partners per 100 person-months was 49 before unmasking versus 66 after unmasking (table 2). Before unmasking, we recorded a tendency toward an increasing trend in the frequency of unprotected sex with outside partners (figure 3A). After unmasking, we noted no immediate change in the level of unprotected sex (p=0·84). However, a significant increase in the frequency of unprotected sex over time was evident (p=0·04). The consequence of this change in trend was a small difference in the estimated versus counterfactual annual average total frequency of unprotected sex acts (6·8 *vs* 6·2, respectively; table 2). Findings from total sex act models with outside partners showed qualitatively similar results (table 2 and figure 3B).

Findings from the sensitivity analyses of shorter duration of months before and after unmasking were consistent with those reported in the primary analyses (data not shown). In subgroup analyses, the level, trend, and the annualised estimated and counterfactual cumulative frequency of unprotected sex with HIV-infected partner were not substantially different during the two periods, except among the subgroup of men (table 3). Among men, no immediate change in level for the frequency of unprotected sex acts was reported (p=0·61), but the frequency was slightly increased after unmasking (p value for change in trend=0·04), with an estimated and counterfactual annual average total frequencies of unprotected sex of five versus 4·9, respectively.

Finally, in cross-validation analyses, the proportions of visits (2467 visits before and 2768 after unmasking with testing done) with diagnoses of STIs were similar before unmasking and after unmasking (p values are for changes in immediate level and trend over time after unmasking): *N gonorrhoeae* (1·0% of visits before *vs* 1·2% of visits after unmasking, p=0·23 and p=0·62), *C trachomatis* (1·1% *vs* 1·5%, p=0·11 and p=0·25), *T vaginalis* (3·3% *vs* 2·9%, p=0·93 and p=0·56). Similarly, during 19 369 months of observation for women, we reported incident pregnancy at 125 of 11 611 (1·1%) months before unmasking versus 73 of 7758 (0·9%) months after unmasking (p=0·21 and p=0·32 for changes in level and trend, respectively).

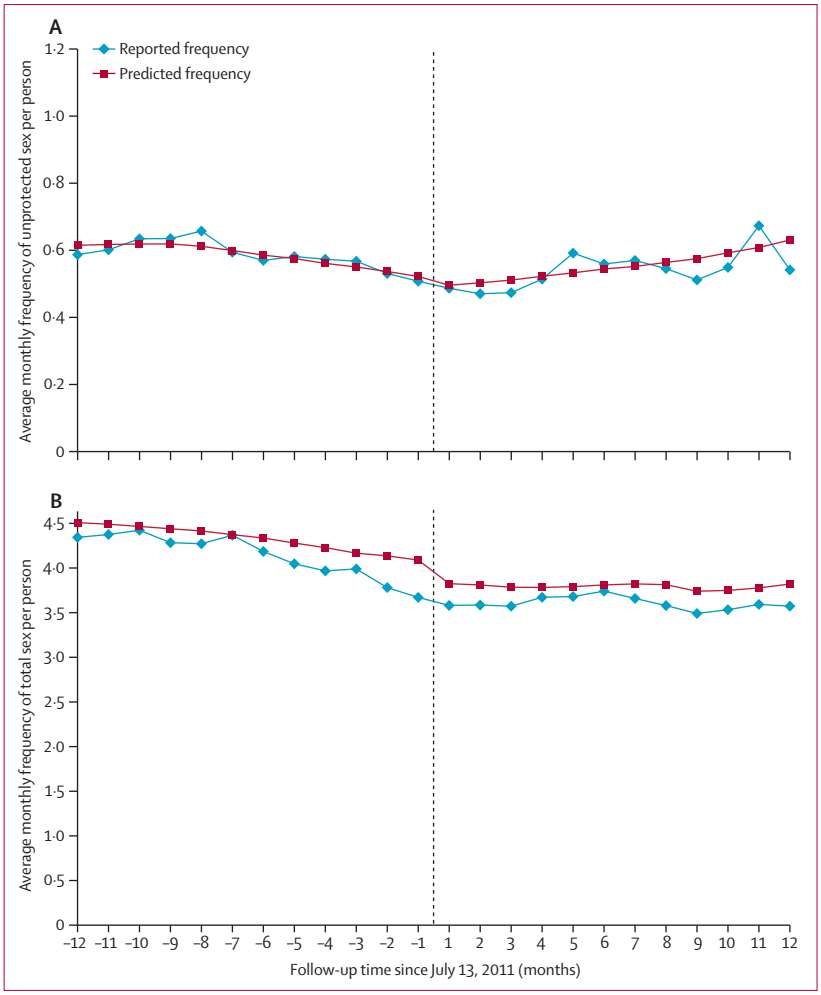

Figure 2: **Trend of monthly frequency of sex acts with known HIV-infected study partner**
(A) Frequency of unprotected sex with HIV-infected study partner. Trend of mean monthly frequency of unprotected sex acts with HIV-infected study partner per person before and after July 13, 2011. A tendency towards decreasing frequency with a significant trend before unmasking was reported (p=0·03). No significant changes in the level (p=0·66) and trend (p=0·25) of frequency of unprotected sex acts were reported after unmasking. Number of patients at each visit (applies also to figures 2B, 3A, and 3B): N=2507 at month –12, N=2594 at month –11, N=2680 at month –10, N=2787 at month –9, N=2839 at month –8, N=2824 at month –7, N=2818 at month –6, N=2832 at month –5, N=2838 at month –4, N=2818 at month –3, N=2818 at month –2, N=2843 at month –1, N=2638 at month +1, N=2557 at month +2, N=2470 at month +3, N=2350 at month +4, N=2209 at month +5, N=1976 at month +6, N=1785 at month +7, N=1725 at month +8, N=1581 at month +9, N=1397 at month +10, N=1249 at month +11, and N=997 at month +12. (B) Frequency of total sex with HIV-infected study partner. Trend of mean monthly frequency of total sex acts with HIV-infected study partner per person before and after July 13, 2011. The pattern was that of decreasing trend (p=0·001) before unmasking, with no significant changes in the level (p=0·39) and trend (p=0·4) of frequency of total sex acts after unmasking.

Discussion

The transition from a double-blinded, placebo-controlled phase to one in which all participants were aware that they were receiving active, effective pre-exposure prophylaxis in the Partners PrEP Study provided a natural experiment to assess behavioural risk compensation in individuals receiving open-label pre-exposure prophylaxis for HIV prevention. Our data suggest that provision of pre-exposure prophylaxis as part of a comprehensive prevention package was not

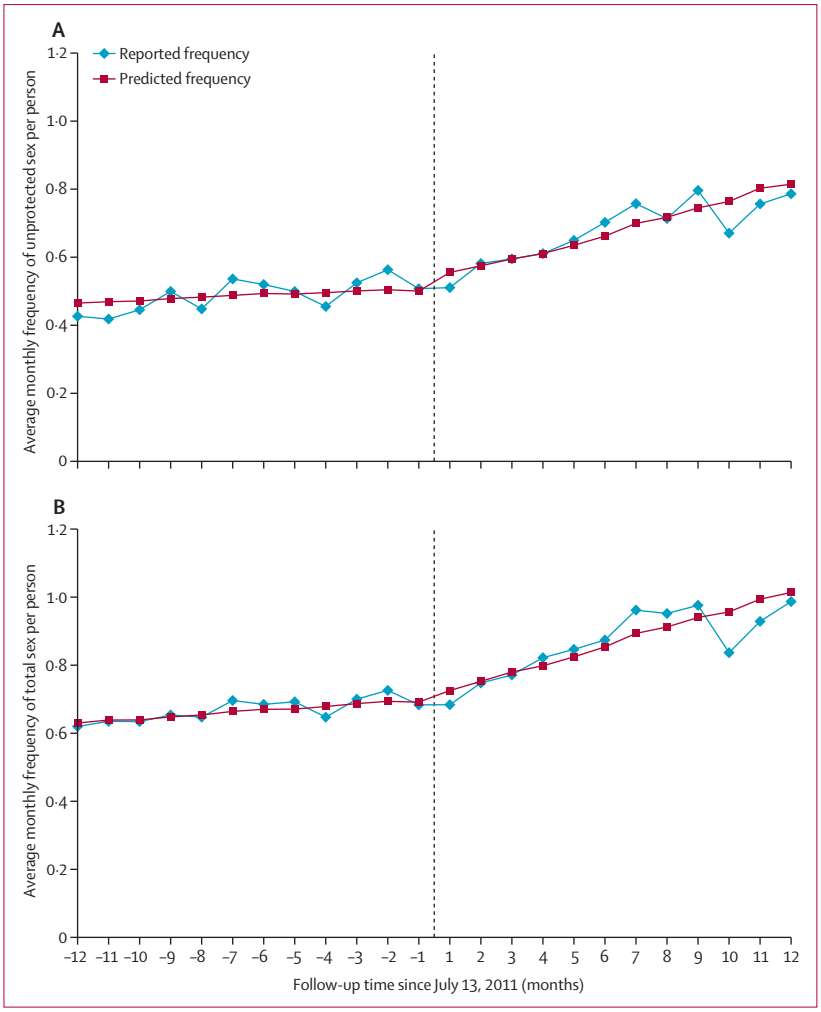

***Figure 3*: Trend of monthly frequency of sex acts with outside partners**

(A) Frequency of unprotected sex acts outside the primary study partnership. Trend of mean monthly frequency of unprotected sex acts per person outside the primary study partnership before and after July 13, 2011. Plots represent recorded and predicted frequency of unprotected sex acts outside the primary study partnership with increasing trend before July 13, 2011. After unmasking, the pattern remained that of an increasing trend but at a slightly faster rate compared with the background trend (p value for change in trend=0·04). (B) Frequency of total sex acts outside the primary study partnership. Trend of mean monthly frequency of total sex acts per person outside the primary study partnership before and after July 13, 2011. Plots represent reported and predicted frequency of total sex acts outside the primary study partnership with increasing trend before July 13, 2011. After unmasking, the pattern remained that of an increasing trend, but at a slightly faster rate than the background trend (p value for change in trend=0·006).

associated with substantial changes in risk-taking sexual behaviour, especially within a known HIV serodiscordant partnership, over 12 months of study (panel). Unmasking was associated with a small increase in the frequency of unprotected sex outside of the primary study partnership; however, this increase was not supported by clinical outcomes because neither STIs nor pregnancy were diagnosed more frequently after unmasking than before unmasking. The potential for risk compensation to undermine the protective benefits of present biomedical prevention technologies has been extensively discussed in the scientific and public literature;[16–20] however, the discussion related to pre-exposure prophylaxis has been largely hypothetical in view of the recent evidence of pre-exposure prophylaxis efficacy. To our knowledge, this study provides the first empirical data on sexual behaviour in heterosexual people receiving open-label oral pre-exposure prophylaxis for HIV prevention.

Findings from previous studies have not shown substantial behavioural risk compensation for other novel HIV prevention interventions, like medical male circumcision.[21,22] In the randomised, placebo-controlled trials of daily oral pre-exposure prophylaxis for HIV prevention, unprotected sex and STIs decreased after enrolment, in both the pre-exposure prophylaxis and placebo groups, suggesting that pre-exposure prophylaxis could be synergistic for risk reduction when given with a package of other HIV prevention services. Data from mathematical modelling suggest little attenuation in population-level effectiveness of pre-exposure prophylaxis with doubling of risk behaviour[23] if pre-exposure prophylaxis has high efficacy and is taken with sufficient adherence to achieve efficacy. Thus, our data provide encouraging evidence that behavioural changes as a result of pre-exposure prophylaxis might not undermine the public health benefits of pre-exposure prophylaxis.

Data from recent studies[21,24,25] suggest that about a quarter of HIV infections in serodiscordant partnerships arise from non-primary partners. In a previous study[26] of HIV-uninfected members of serodiscordant couples, we found that sex with partners other than the HIV-infected study partner increased over time; this was generally indicative of relationship dissolution with the original

	Segmented model regression coefficients (β)*† (95% CI), p value		Average cumulative number of sex acts in 12 months after unmasking*	
	Immediate effect (change in level)	Effect over time (change in trend)	Counterfactual frequency ‡	Estimated frequency after unmasking
≤30 years age	–0·0182 (–0·2416 to 0·2051), p=0·87	0·0230 (–0·0193 to 0·0654), p=0·29	5·5	5·5
No child with study partner	–0·0558 (–0·3613 to 0·2497), p=0·72	–0·0140 (–0·0665 to 0·0385), p=0·60	5·2	5·2
Women	0·0037 (–0·2120 to 0·2195), p=0·97	–0·0214 (–0·0645 to 0·0216), p=0·33	4·9	5·2
Males	–0·0450 (–0·2197 to 0·1296, p=0·61	0·0297 (0·0019 to 0·0574), p=0·04	4·9	5·0

*Adjusted for within patient association, secular changes, age, sex, and baseline sexual behaviour in the month before enrolment in the trial. †The β coefficients represent differences in the month-to-month changes in the frequency of sex acts. ‡Predicted frequency of sex acts that would have been expected in a counterfactual scenario had patients remained masked.

***Table 3*: Subgroup comparisons of frequency of unprotected sex with the HIV-infected study partner before and after unmasking**

HIV serodiscordant partnership and new relationship formation rather than formal concurrency.[26] Similarly, in this study, average sexual frequency decreased over time with primary partners and increased with outside partners, and unprotected sex with outside partners was high among the few participants who reported sex outside the primary partnership. After unmasking, a small but significant increased frequency of unprotected sex with outside partners was reported; however, this finding did not translate into a substantial difference in the average annual total frequency of unprotected sex acts estimated after unmasking compared with the counterfactual value that would have been expected had individuals remain masked. For HIV-serodiscordant couples, some partnerships dissolve, sometimes temporarily, and new partnerships are sometimes established, often with partners of unknown HIV serostatus with whom condoms might be used less than would be with known HIV seropositive partners. Effective messages regarding risk reduction for concurrent and subsequent partners are needed to enhance counselling for HIV-serodiscordant couples.

The ability to support a counterfactual inference in data collected over time is often threatened by alternative hypotheses: regression to the mean, maturation effects, and confounding. Without a nonequivalent control, the use of many datapoints before the intervention can be useful.[27] In our study, we used up to 12 measurements before unmasking and separately modelled the trends before and after unmasking to minimise the likelihood of potential maturation effects and secular changes that might have arisen even in the absence of unmasking.

The results of this study must be viewed in light of its restrictions. First, participants were couples experienced in research who received regular reinforcement of risk-reduction messages and had completed a median of 23 months of follow-up before unmasking. However, HIV-serodiscordant couples are generally a priority group for HIV prevention and regular risk-reduction and adherence counselling will be part of a pre-exposure prophylaxis implementation package. Moreover, for this population, the background trend before unmasking was of decreasing risk behaviour in the context of risk-reduction counselling. Second, the outcome measure, self-reported sexual behaviour, is prone to reporting bias, but sensitivity analyses and cross-validation with incident STI and pregnancy data lend confidence to our findings. Third, we assumed a constant frequency and linear trend of sex acts in each segment, which was in general agreement with graphical presentations of the data. Despite these restrictions, our study provides important new empirical evidence of the association between open-label use of pre-exposure prophylaxis and sexual behaviour in heterosexual men and women. In view of the large number of visits in our cohort and statistical efficiency gained from within-patient comparisons, our study was well powered to detect small differences in risky sexual behaviour.

Panel: Research in context

Systematic review

We searched PubMed for published studies assessing sexual behaviours of heterosexual people using pre-exposure prophylaxis for HIV prevention, with the search terms "sexual", "risk compensation", "dishinhibition", "pre-exposure prophylaxis", "PrEP", "HIV", "prevention", and "heterosexual" in different combinations. We restricted our search to studies published in English from inception to May 31, 2013.

Interpretation

To our knowledge, this study provides the first empirical data for sexual behaviour in heterosexual people receiving open-label oral pre-exposure prophylaxis, once the efficacy of pre-exposure prophylaxis for HIV prevention had been established in clinical trials. Our findings suggest that provision of pre-exposure prophylaxis as part of a comprehensive prevention package might not be associated with substantial changes in risk-taking sexual behaviour that would undermine the public health benefits of pre-exposure prophylaxis. HIV prevention programmes that include pre-exposure prophylaxis should incorporate messages regarding risk reduction, including for HIV serodiscordant couples, within and outside of the partnership.

In conclusion, after unmasking of study participants, oral tenofovir-based pre-exposure prophylaxis was not associated with substantial risk-taking sexual behaviour among heterosexual HIV-uninfected African men and women who continued pre-exposure prophylaxis. A modest increase in sexual risk taking with outside partners was recorded, but no increase within known HIV-serodiscordant relationships was reported; importantly, we noted no increase in clinical endpoints indicative of unprotected sexual activity. Continued counselling, including addressing HIV risks from concurrent and subsequent partners who might have an unknown HIV serostatus, could help sustain risk reduction for HIV-uninfected members of HIV-serodiscordant couples using pre-exposure prophylaxis. Our data support the use of pre-exposure prophylaxis as part of a comprehensive combination HIV prevention package.

Contributors

KKM, DD, CC, and JB conceived the design of the study. KKM and JB wrote the first draft of the report. All authors contributed to the analysis, interpretation, and writing of the final report. All authors have read and approved the final report.

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Conflicts of interest

We declare that we have no conflicts of interest.

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