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Sexual Behavior of Heterosexual Men and Women Receiving Antiretroviral Pre-Exposure Prophylaxis for HIV Prevention: A Longitudinal Analysis

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Abstract

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Author contribution

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

Conflict of interest. None.

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Background—Limited data are available to assess sexual behavior by persons using antiretroviral pre-exposure prophylaxis (PrEP) for HIV prevention. Increased sexual risk taking by persons using effective HIV prevention strategies, like PrEP, could offset HIV prevention benefits.

Methods—The Partners PrEP Study, a randomized, placebo-controlled trial of daily oral PrEP among heterosexual HIV-uninfected members of HIV serodiscordant couples, publicly reported efficacy for HIV prevention 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 to before July 2011 to assess whether knowledge of PrEP efficacy for HIV prevention resulted in increased sexual risk behavior.

Results—We analyzed 56,132 person-months from 3024 HIV-uninfected subjects (64% male). The average frequency of unprotected sex with the HIV-infected study partner was 59 per 100 person-months pre- versus 53 post-unblinding, reflecting no immediate change or change over time after July 2011 ($p=0.66$ and 0.25 , respectively). There was a statistically significant increase in unprotected sex with outside partners over time after July 2011 but the effect was modest (average of 6.8 unprotected sex acts per year versus 6.2 acts in a predicted counterfactual scenario had unblinding not occurred, $p=0.04$). Compared to pre-July 2011, there was no significant increase in incident sexually transmitted infections or pregnancy after July 2011.

Interpretation—The transition from a blinded, placebo-controlled efficacy trial to all participants aware they were receiving active, efficacious PrEP in the Partners PrEP Study provided a “natural experiment” to evaluate sexual risk compensation. PrEP, provided as part of a comprehensive prevention package, may not result in substantial changes in risk-taking sexual behavior for heterosexual couples.

Introduction

Three randomized trials have demonstrated that oral antiretroviral pre-exposure prophylaxis (PrEP) is efficacious in protecting against HIV acquisition in diverse geographic and at-risk populations¹⁻⁴. Evidence of HIV prevention effectiveness for daily oral tenofovir-based PrEP, as well as for coitally-dependent tenofovir gel⁵ 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 following demonstration of effectiveness in trials is the potential for behavioral risk compensation, defined as persons using known effective HIV prevention interventions engaging in increased sexual risk-taking. A substantial increase in risky sexual behaviors by persons using PrEP, and other HIV prevention strategies, could offset the HIV protective benefits,⁷ as well as increase the risk for sexually transmitted infections (STIs). In clinical trials of PrEP, there were no significant differences in sexual behavior between experimental and placebo groups;^{1-4, 8-10} however, because the comparison groups had equivalent uncertainty of treatment assignment and benefits of the study medication during the blinded trial period, absence of risk compensation may not fully reflect sexual behavior in the context of known PrEP efficacy.

In July 2011, the Partners PrEP Study, a randomized, double-blind, placebo-controlled trial of daily oral tenofovir (TDF) and emtricitabine(FTC)/TDF PrEP among HIV-uninfected members of African heterosexual HIV serodiscordant couples, demonstrated efficacy of PrEP for HIV prevention.¹ Participants who had been assigned to the active PrEP arms continued in the study and were informed they were receiving active PrEP and that PrEP had been demonstrated to reduce HIV acquisition risk. Placebo arm HIV incidence during the study was 2% per year overall and 3% among subgroups with higher-risk characteristics; assignment to PrEP resulted in a 67% (TDF) and 75% (FTC/TDF) reduction in transmission risk, with an approximately 90% reduction in risk estimated for those adherent to PrEP. We

examined sexual behaviors before versus after July 2011 to assess the potential risk compensation after learning of the effectiveness of PrEP for HIV prevention. We hypothesized that individuals using PrEP who were aware of its proven efficacy against HIV acquisition might increase sexual behavioral risks.

Methods

Partners PrEP Study

The Partners PrEP Study has been described previously (Clinicaltrials.gov number NCT00557245).^{1, 11} Briefly, between July 2008 and November 2010, 4747 HIV serodiscordant heterosexual couples were enrolled and followed at nine research sites in Kenya and Uganda. Eligible HIV-uninfected participants were 18 years of age, sexually active, and had normal hepatic and renal function.

HIV-uninfected partners were randomized in a 1:1:1 fashion to daily oral TDF, FTC/TDF, or placebo and followed monthly for up to 36 months with sexual behavioral assessment (questionnaire provided as online Appendix A), HIV serologic testing, pregnancy testing (for women), safety monitoring, risk-reduction counseling, and study drug provision. Laboratory testing for STIs (*Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Trichomonas vaginalis*) was done for all participants annually and when clinically indicated due to the presence of symptoms.

HIV prevention package and ethical review

All participants received a comprehensive package of HIV prevention services, which included HIV risk-reduction counseling (individually and as a couple), HIV testing, free condoms, testing and treatment for STIs, counseling and referral for male circumcision, and, for HIV-infected partners, 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.

Data and Safety Monitoring Board (DSMB) review

An independent DSMB met every six months to review the conduct of the placebo-controlled trial. At the July 10, 2011 meeting, the DSMB recommended that the placebo arm of the study be discontinued and the trial results be made public, due to definitive demonstration of PrEP protection against HIV acquisition. The primary results of the trial, using data through July 10, 2011, have subsequently been published.¹ Additionally, the DSMB recommended the active PrEP arms to be continued, to gain additional information on the relative efficacy, safety, and tolerability of PrEP using TDF versus FTC/TDF, and those receiving placebo to receive PrEP. Beginning 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 counseling sessions during their next scheduled monthly visits (information provided in Appendix B). Thus, continued follow-up of study participants initially assigned to the active PrEP arms provided an opportunity to evaluate risk behavior on open-label tenofovir-based PrEP after efficacy was announced. For subjects initially assigned to the active PrEP arms, study procedures were unchanged after July 13, 2011, with the exception of ongoing counseling about the efficacy of PrEP for HIV prevention.

Population for the present analysis

For the present analysis, we considered data against a reference date of July 13, 2011 (Figure 1). Given that research sites required time to disseminate the trial results to all the study participants, we defined a “dissemination window” starting July 13, 2011 and including each participant's first subsequent study visit. A maximum of 12 monthly visits before and 12 visits after the dissemination window were included to provide an assessment of the effect of learning about the effectiveness of PrEP and being on active PrEP while minimizing temporal shifts in sexual behavior over periods of time greater than a year. All HIV-uninfected participants who were initially randomized to active PrEP, remained in study follow-up, and had not seroconverted to HIV were eligible for inclusion in the present analysis. For participants initially assigned to the placebo arm, discontinuation and provision of active PrEP was done over a period of several months; because of this staggered gap during which no study procedures were conducted, participants on the placebo arm were not included in this analysis.

Outcome measurement

Four measures of sexual activity were explored: frequency of sex (vaginal or anal) without a condom (unprotected sex acts) and frequency of sex with or without a condom (total sex acts), with both their HIV-infected primary study partner (i.e., the partner with whom each subject enrolled into the study) and outside partners (i.e., any additional partner other than the primary study partner, including concurrent partners and partners acquired if the study partnership dissolved during follow-up).

Exposure measurement

The main predictor of interest was the participants' knowledge that they were receiving active PrEP and that PrEP had proven efficacy against HIV acquisition. We compared the blinded period (i.e., visits occurring before July 13, 2011) to the unblinded period (i.e., visits occurring after results dissemination window following July 13, 2011). Months at which PrEP was not dispensed, either due to a protocol-specified study drug hold (e.g., due to pregnancy or clinical adverse events) or a missed visit, were excluded to capture the direct effect of actual drug possession on sexual behavior.

Statistical Analysis

Crude frequencies were computed treating each visit as an independent observation. We used a segmented regression model,¹²⁻¹⁴ fit for each count outcome variable using a zero-inflated negative binomial distribution.¹⁵ The segmented model allowed for change in both the level (intercept, indicating an immediate change in behavior) and trend (slope, indicating a change over time) of the monthly frequency of sex acts before and following unblinding while controlling for potential secular changes (Figure 1). The zero-inflated negative binomial distribution allowed flexibility to account for unobserved heterogeneity and over-dispersion due to high occurrence of zeros common in sexual behavior data generated either as structural zeros (e.g. due to partnership break-up) 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 enrollment into the randomized trial to estimate the study background trend before July 13, 2011; *unblinding*, coded zero before and one after July 13, 2011, the main predictor of interest; and *time after unblinding*, as a linear continuous

variable, coded zero before unblinding and 1-12 months after July 13, 2011, to estimate the change in trend after unblinding versus the study background trend. All models were adjusted for baseline sexual behavior, age, and gender. The model-predicted marginal means were used to compute annualized total frequency of sex acts estimated after unblinding and the counterfactual scenario that would have been expected had unblinding not occurred. The presented model estimates are interpreted conditional on the participant reporting being sexually active (i.e. not an always structural zero process).

In subgroup analysis, we evaluated the frequency of unprotected sex within the study HIV serodiscordant partnership by gender and in subpopulations with potentially high propensity for reproductive desires – those < 30 years of age or who had no child with study partner – as these populations might be more likely to practice unprotected sex after receiving knowledge of PrEP efficacy for HIV prevention. As a sensitivity analysis, we repeated our primary analysis using shorter time periods: 3, 6, and 9 months pre- and post-unblinding.

Finally, as a cross-validation of self-reported sexual behavior, 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 five percent type one error rate and were not adjusted for multiple comparisons. Analyses were conducted using SAS (version 9.2, SAS Institute) and Stata statistical software (version 12).

Role of the funding source

The authors designed and executed the study, had full access to the raw data, performed all analyses, wrote the manuscript, and had final responsibility for the decision to submit for publication. The funders had no role in design, data collection, analysis, interpretation, or writing of the manuscript.

Results

Study population

Of 4747 HIV-uninfected participants enrolled and followed in the Partners PrEP Study, 3163 were initially randomized to the clinical trial's active PrEP arms. Of these, 3024 were included in the present analysis; 139 were not included: 38 because they had seroconverted to HIV prior to July 13, 2011 and 101 because their final study visit (i.e., completing the protocol-specified 36 months of follow-up or early withdrawal) occurred on or prior to July 13, 2011. At enrollment, 64% were male, the median age was 34 years (interquartile range [IQR] 29 to 40), the median number of sex acts with the HIV-infected study partner in the prior month was 4 (IQR 2 to 8), and 827 (27%) participants reported having at least one act of unprotected sex with their study partner in the prior month (Table 1). Before unblinding, participants had been followed for a median of 23 months (IQR 16 to 28).

A total of 60,406 person-months were accrued during the period for this analysis. After exclusion of months at which PrEP was not dispensed due to product holds or missed visits (n=4,274 months), the final analysis dataset included 56,132 person-months of observation: 33,198 pre-unblinding and 22,934 post-unblinding. Retention was similar during the two periods: 98% of expected visits were completed.

Frequency of sex with the HIV-infected study partner

The average crude frequency of unprotected sex with the HIV-infected study partner was 59 per 100 person-months pre-unblinding versus 53 post-unblinding (Table 2). There was a

tendency toward a gradually decreasing trend in the frequency of unprotected sex during the study prior to unblinding (Figure 2A). After unblinding, there were no statistically 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 post-unblinding was 5.1 versus 4.9 that would have been expected in the counterfactual situation had unblinding not occurred.

Overall, the average frequency of total sex acts (i.e., both with and without condoms) with the HIV-infected study partner per 100 person-months was 414 pre- versus 361 post-unblinding (Table 2). There was a tendency toward a decreasing trend in the frequency of total sex acts pre-unblinding (Figure 2B). After unblinding, there were no statistically significant changes in the immediate level or trend in frequency of total sex acts ($p=0.39$ and 0.4 , respectively). The estimated post-unblinding and counterfactual (i.e., predicted had unblinding not occurred) annual average total frequency of sex was not qualitatively different (42.4 versus 44.3, respectively).

Frequency of sex outside the primary study partnership

Overall, sex outside the primary partnership was reported at 12.4% (4,124/33,198, representing 794 individuals) of visits pre- versus 15.2% (3,480/22,934, representing 721 individuals) of visits post-unblinding. On average, the crude frequency of unprotected sex acts with outside partners per 100 person-months was 49 pre-unblinding versus 66 post-unblinding (Table 2). Before unblinding, there was a tendency toward an increasing trend in the frequency of unprotected sex with outside partners (Figure 3A). After unblinding, there was no immediate change in the level of unprotected sex ($p=0.84$). However, a modest but statistically significant increase in the frequency of unprotected sex over time was observed ($p=0.04$). The consequence of this change in trend was a small difference in the estimated versus counterfactual annual average total frequency of unprotected sex (6.8 vs. 6.2, respectively). Total sex act models with outside partners demonstrated qualitatively similar results (Table 2 and Figure 3B).

Sensitivity and subgroup analyses

Findings from the sensitivity analyses of shorter duration of months pre- and post-unblinding were consistent with that observed in the primary analyses (data not shown). In subgroup analyses, the level, trend, and the annualized estimated and counterfactual cumulative frequency of unprotected sex with the HIV-infected partner were not substantially different during the two periods, except among the subgroup of men (Table 3). Among men, there was no immediate change in level for the frequency of unprotected sex acts ($p=0.61$), but the frequency was modestly higher following unblinding (p -value for change in trend= 0.04), with an estimated and counterfactual annual average total frequencies of unprotected sex of 5 vs. 4.9, respectively.

Finally, in cross-validation analyses, the proportions of visits (2467 visits pre- and 2768 post-unblinding with testing done) with diagnoses of STIs were similar before versus after unblinding (p -values are for changes in immediate level and trend over time after unblinding): *N. gonorrhoeae* (1.0% of visits pre-versus 1.2% of visits post-unblinding, $p=0.23$ and $p=0.62$), *Chlamydia trachomatis* (1.1% versus 1.5%, $p=0.11$ and $p=0.25$), *Trichomonas vaginalis* (3.3% versus 2.9%, $p=0.93$ and $p=0.56$). Similarly, during 19,369 months of observation for women, incident pregnancy was detected at 125 of 11,611 (1.1%) months pre-unblinding versus 73 of 7758 (0.9%) months post-unblinding ($p=0.21$ and $p=0.32$ for changes in level and trend, respectively).

Discussion

The transition from a blinded, placebo-controlled phase to all participants aware they were receiving active, efficacious PrEP in the Partners PrEP Study provided a “natural experiment” to evaluate behavioral risk compensation in persons receiving open-label PrEP for HIV prevention. Our data suggest that providing PrEP as part of a comprehensive prevention package was not associated with substantial changes in risk-taking sexual behavior, particularly within a known HIV serodiscordant partnership, over a period of up to 12 months of observation. Unblinding 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 as neither STIs nor pregnancy were diagnosed more frequently after unblinding compared to before. The potential for risk compensation to undermine the protective benefits of current biomedical prevention technologies has been extensively discussed in the scientific and public domains,¹⁶⁻²⁰ although, the discussion related to PrEP has been largely hypothetical given the recent demonstration of PrEP efficacy. To our knowledge, this study provides the first empirical data on sexual behavior in heterosexual persons receiving open-label oral PrEP for HIV prevention.

Prior studies have not demonstrated substantial behavioral risk compensation for other novel HIV prevention interventions, like medical male circumcision.^{21, 22} In the randomized, placebo-controlled trials of daily oral PrEP for HIV prevention, unprotected sex and STIs decreased after enrollment, in both the PrEP and placebo arms, suggesting that PrEP could be synergistic for risk-reduction when delivered along with a package of other HIV prevention services. Mathematical modeling suggests relatively little attenuation in population-level effectiveness of PrEP with doubling of risk behavior,²³ if PrEP has high efficacy and is taken with sufficient adherence to achieve efficacy. Thus, our data provide encouraging evidence that behavior changes as a result of PrEP may not undermine the public health benefits of PrEP.

Recent studies suggest that about a quarter of HIV infections in serodiscordant partnership occur from non-primary partners.²⁴⁻²⁶ In a previous study of HIV-uninfected members of serodiscordant couples, we found that sex with partners other than the HIV-infected study partner increased over time;²⁷ importantly, this generally reflected relationship dissolution with the original HIV serodiscordant partnership and new relationship formation rather than formal concurrency.²⁷ 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 minority of participants who reported sex outside the primary partnership. After unblinding, there was a small but statistically significant higher frequency of unprotected sex with outside partners; however, this did not translate into a substantial difference in the average annual total frequency of unprotected sex acts estimated after unblinding compared to the counterfactual that would have been expected without unblinding. 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 may be used less than with known HIV seropositive partners. Effective messages regarding risk-reduction for concurrent and subsequent partners are needed to enhance counseling for HIV serodiscordant couples.

The ability to support a counterfactual inference in data collected over time is often threatened by alternative hypotheses including regression to the mean, maturation effects, and confounding. In absence of a nonequivalent control, use of multiple data points prior to the intervention can be useful.²⁸ In our study, we used up to 12 measurements prior to unblinding and separately modeled the trends pre- and post-unblinding to minimize the

likelihood of potential maturation effects and secular changes that may have occurred even in the absence of the unblinding.

The results of this study must be viewed in light of its limitations. 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 prior to unblinding. However, HIV serodiscordant couples in general are a priority group for HIV prevention and regular risk-reduction and adherence counseling will be part of a PrEP implementation package. Moreover, for this population, the background trend prior to unblinding was of decreasing risk behavior in the context of risk-reduction counseling. Second, the outcome measure, self-reported sexual behavior, 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 limitations, our study provides important new empirical evidence of the relationship between open-label use of PrEP and sexual behavior in heterosexual men and women. Given the large number of visits in our cohort and statistical efficiency gained from within-subject comparisons, our study was well powered to detect small differences in risky sexual behavior.

In conclusion, after unblinding of study participants, oral tenofovir-based PrEP was not associated with substantial risk-taking sexual behavior among heterosexual HIV-uninfected African men and women who continued PrEP. There was a modest increase in sexual risk-taking with outside partners, but no increase within known HIV serodiscordant relationships; importantly, there was no increase in clinical endpoints indicative of unprotected sexual activity. Ongoing counseling, including addressing HIV risks from concurrent and subsequent partners who may be of unknown HIV serostatus, may help sustain risk-reduction for HIV-uninfected members of HIV serodiscordant couples using PrEP. Our data are supportive of PrEP delivered as comprehensive combination HIV prevention package.

Panel: Research in context

Systematic review

We searched PubMed for published studies through May 2013 assessing sexual behaviors of heterosexual persons using pre-exposure prophylaxis for HIV prevention.

Interpretation

To our knowledge, this study provides the first empirical data on sexual behavior in heterosexual persons 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 providing pre-exposure prophylaxis as part of a comprehensive prevention package may be not associated with substantial changes in risk-taking sexual behavior that would undermine the public health benefits of pre-exposure prophylaxis. HIV prevention programs that include pre-exposure prophylaxis should incorporate messages regarding risk-reduction, including for HIV serodiscordant couples, within and outside of the partnership.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Schematic flow of the study design

The figure presents a 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 subject 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 following unblinding, and then the trend of the frequency of sex acts over time after unblinding. Interpretation of the results is 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 unblinding not occurred.

Figure 2. Frequency of unprotected sex with HIV-infected study partner

A. Trend of mean monthly frequency of unprotected sex acts with HIV-infected study partner per person before and after July 13, 2011. There was a tendency towards decreasing frequency with a significant trend before unblinding ($p=0.03$). No statistically significant changes in the level ($p=0.66$) and trend ($p=0.25$) of frequency of unprotected sex acts occurred following unblinding. Number of subjects 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.

Figure 2B. 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 unblinding, with no statistically significant changes in the level ($p=0.39$) and trend ($p=0.4$) of frequency of total sex acts following unblinding.

Figure 3. Frequency of unprotected sex acts outside the primary study partnership

A. Trend of mean monthly frequency of unprotected sex acts per person outside the primary study partnership before and after July 13, 2011. Plots represent observed and predicted frequency of unprotected sex acts outside the primary study partnership with increasing trend before July 13, 2011. Following unblinding, the pattern remained that of an increasing trend but at a modestly faster rate compared to the background trend (p-value for change in trend=0.04).

Figure 3B. 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 observed and predicted frequency of total sex acts outside the primary study partnership with increasing trend before July 13, 2011. Following unblinding, the pattern remained that of an increasing trend but at a modestly faster rate compared to the background trend (p-value for change in trend=0.006).

Table 1

Baseline characteristics of the study population (n=3024)

Characteristics	Median (interquartile range) 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, prior month	4 (2-8)
Any unprotected sex with HIV-infected study partner, prior month	827 (27)
Any sex with partners other than the HIV-infected study partner, prior month	273 (9)
Any unprotected sex with partners other than the HIV-infected study partner, prior month	175 (6)

Table 2
Sexual frequency pre- and post-unblinding within and outside the primary study partnership

Characteristics	Crude average frequency of sex acts per 100 person-months* (95%CI)		Segmented model regression coefficients (β) (95%CI)		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 unblinding
<u>Within the study primary partnership</u>						
Unprotected sex acts	59 (58, 59)	53 (52, 54)	−0.0304 (−0.1660, 0.1050)	0.0142 (−0.0099, 0.0383)	4.9	5.1
			P=0.66	P=0.25		
Total sex acts	414 (411, 416)	361 (359, 363)	−0.0155 (−0.0511, 0.0200)	0.0026 (−0.0034, 0.0088)	44.3	42.4
			P=0.39	P=0.4		
<u>Outside the primary partnership</u>						
Unprotected sex acts	49 (48, 49)	66 (65, 67)	0.0138 (−0.1172, 0.1450)	0.0204 (0.0006, 0.0400)	6.2	6.8
			P=0.84	P=0.04		
Total sex acts	67 (66, 68)	84 (83, 85)	−0.0211 (−0.1362, 0.0939)	0.0247 (0.0071, 0.0424)	8.8	9.0
			P=0.72	P=0.006		

* Crude counts computed from independent monthly observations during each period from 3024 HIV seronegative partners.

[‡] Adjusted for within subject correlation, secular changes, age, gender, and baseline sexual behavior in month prior to enrollment in the trial.

‡ The beta 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 if unblinding had not occurred.

Table 3

Subgroup comparisons of frequency of unprotected sex with the HIV infected study partner pre- and post-unblinding

Characteristics	Segmented model regression coefficients (β) ^{‡*} (95%CI)		Average cumulative number of sex acts in 12 months after unblinding [*]	
	Immediate effect (Change in level)	Effect over time (Change in trend)	Counterfactual frequency [¶]	Estimated frequency after unblinding
30 years	−0.0182 (−0.2416, 0.2051) P=0.87	0.0230 (−0.0193, 0.0654) P=0.29	5.5	5.5
No child with study partner	−0.0558 (−0.3613, 0.2497) P=0.72	−0.0140 (−0.0665, 0.0385) P=0.60	5.2	5.2
Females	0.0037 (−0.2120, 0.2195) P=0.97	−0.0214 (−0.0645, 0.0216) P=0.33	4.9	5.2
Males	−0.0450 (−0.2197, 0.1296) P=0.61	0.0297 (0.0019, 0.0574) P=0.04	4.9	5.0

* Adjusted for within subject correlation, secular changes, age, gender, and baseline sexual behavior in the month prior to enrollment in the trial.

[‡] The beta 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 if unblinding had not occurred.