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Hormonal contraceptive use and risk of HIV-1 transmission: a prospective cohort analysis

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Author contributions
RH, DD, JMB designed the study and RH and DD did the analysis. All authors contributed to data collection and writing of the report and all approved the final draft. RH and JMB wrote the initial draft and vouch for the data, analysis, interpretation, and manuscript submission.

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Summary

Background—Hormonal contraceptives are used widely but their effects on HIV-1 risk are unclear.

Methods—We followed 3790 heterosexual HIV-1 serodiscordant couples from seven African countries participating in two longitudinal HIV-1 incidence studies. Among hormonal contraceptive users (including injectable and oral contraceptive users) and nonusers, we compared rates of HIV-1 acquisition in women and HIV-1 transmission from women to men.

Findings—Among 1314 couples in which the HIV-1 seronegative partner was female, HIV-1 acquisition rates were 6.61 and 3.78 per 100 person-years among hormonal contraceptive users and nonusers (adjusted hazard ratio [AHR]=1.98, 95% confidence interval [CI] 1.06–3.68, p=0.03). Among 2476 couples in which the HIV-1 seronegative partner was male, HIV-1 transmission rates from women to men were 2.61 and 1.51 per 100 person-years in those whose partners currently used versus did not use hormonal contraception (AHR=1.97, 95% CI 1.12–3.45, p=0.02). In subgroup analysis, injectable contraceptive users had increased risk for acquiring and transmitting HIV-1 to their partner and HIV-1 seropositive women using injectable contraception had higher genital HIV-1 RNA concentrations, suggesting a mechanism for increased transmission risk. Oral contraceptives were used too infrequently to draw definitive conclusions about HIV-1 risk.

Interpretation—Women should be counseled about potentially increased risk of HIV-1 acquisition and transmission with hormonal contraception, particularly injectable methods, and about the importance of dual protection with condoms to decrease HIV-1 risk. Non-hormonal or lower-dose hormonal contraceptive methods should be considered for women with or at-risk for HIV-1.

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Keywords

HIV-1; serodiscordant couples; Africa; hormonal contraception

Introduction

Safe and effective family planning services are central to initiatives to reduce unintended pregnancies, promote economic development, and improve the health of women and children worldwide. Among women with and at-risk for HIV-1, the prevention of unintended pregnancy is a key component of strategies to reduce vertical HIV-1 transmission.[1,2]

Hormonal contraceptive methods, including daily oral pills and long-acting injectables, are used by >140 million women worldwide.[3] During the past two decades, epidemiologic and laboratory studies have suggested that hormonal contraception may alter HIV-1 acquisition risk in women.[4–8] However, results have been inconsistent.[9] Only one study to date has addressed the effect of hormonal contraception and HIV-1 transmission risk from women to men.[10] Increased HIV-1 risk related to hormonal contraceptive use would be of global public health importance, given the large number of women using such methods. The World Health Organization has called for high-quality studies to assess the potential role of

hormonal contraception to increase HIV-1 risk.[11,12] In a prospective cohort analysis of data from 3790 African HIV-1 serodiscordant couples (where one partner was HIV-1 infected and the other HIV-1 uninfected), we examined the relationship between hormonal contraceptive use and risk of HIV-1 acquisition by women and HIV-1 transmission from HIV-1 infected women to their male partners.

Methods

Population and procedures

From 2004–2010, we conducted two prospective HIV-1 incidence studies among African HIV-1 serodiscordant couples. The Partners in Prevention HSV/HIV Transmission Study was a randomized, placebo-controlled, clinical trial of daily acyclovir herpes simplex virus type 2 (HSV-2) suppressive therapy provided to 3408 HIV-1/HSV-2 dually-infected persons as an intervention to reduce HIV-1 transmission to their heterosexual HIV-1 seronegative partners (Clinicaltrials.gov #NCT00194519); acyclovir did not significantly reduce HIV-1 transmission.[13] Couples were from seven countries in East and southern Africa and followed for up to 24 months. In a parallel study at two of the clinical trial sites (Kampala, Uganda and Soweto, South Africa), we enrolled an additional 485 HIV-1 serodiscordant couples into an observational study of immune correlates of HIV-1 protection and followed them for up to 12 months. For both studies, participants were ≥18 years of age and sexually active. HIV-1 seropositive partners had no history of AIDS-defining conditions and were not using antiretroviral therapy (ART). In addition, HIV-1 seropositive partners in the clinical trial had a CD4 count ≥250 cells/mm^3, were seropositive for HSV-2, had no known history of adverse reactions to acyclovir, and were not pregnant. Couples were recruited through study-initiated community outreach activities and referrals from HIV-1 testing and care centers, antenatal clinics, and non-governmental organizations.[14] The principal reasons couples who were screened for study participation did not enroll were that they did not meet the CD4 count, HSV-2, pregnancy, or sexual activity eligibility criteria.[15]

HIV-1 uninfected partners were seen quarterly for HIV-1 serologic testing. For HIV-1 infected partners, CD4 counts were measured every six months, and participants eligible for ART initiation during follow-up were referred to local HIV-1 care clinics. All participants received comprehensive HIV-1 prevention services, including individual and couples counseling, free condoms, and treatment of sexually transmitted infections (STI). Contraceptives were offered by referral or on-site, and there were differences across sites in contraceptive use.[16,17] The protocols were approved by institutional review boards at the University of Washington and collaborating institutions at each study site. Participants provided written informed consent.

Twenty-seven couples enrolled in the clinical trial were subsequently found to not have HSV-2 or HIV-1 infection and were excluded from the analysis[13] as were 76 couples in which the HIV-1 uninfected participant did not complete any follow-up visits for assessment of HIV-1 seroconversion. For couples in which the HIV-1 infected partner initiated ART, subsequent visits were censored, since ART essentially eliminated HIV-1 risk in the study population.[18]

Laboratory testing

Rapid HIV-1 antibody tests were used for HIV-1 serologic testing and positive results were confirmed by ELISA.[13] For HIV-1 seroconverters, analysis of HIV-1 *env* and *gag* gene sequences from both members of the couple was used to determine whether transmission was linked within the partnership.[19] Nucleic acid amplification testing for bacterial STI was performed on samples collected from both partners at study enrollment.[15] All participants

were tested for HSV-2 using HerpeSelect-2 EIA (Focus Technologies, Cypress CA) or by HSV-specific Western blot.[20] CD4 quantification was performed using standard flow cytometry. Plasma HIV-1 RNA levels were quantified from a sample collected at study enrollment and six months later using the COBAS TaqMan real-time HIV-1 RNA assay, version 1.0 (Roche Diagnostics, Indianapolis, IN). Endocervical HIV-1 concentrations were quantified using the COBAS assay from a swab sample collected six months after enrollment from HIV-1 infected women in the clinical trial cohort, as previously detailed.[21] The lower quantification limit for HIV-1 RNA testing was 240 copies.

Measurement of hormonal contraceptive exposure

At each quarterly study visit, women were asked about their current contraceptive method using a standard questionnaire. Women were assessed as exposed to hormonal contraception for each quarterly time period if they reported hormonal use at the quarterly visit; contraceptive use was analyzed as a time-dependent exposure, with women assumed to have used the same method during the 3 months that elapsed between study visits. Analyses were conducted for exposure to any hormonal contraception and then separately for injectable and oral contraception; the comparison group was women not using hormonal contraception, which included women who had had a hysterectomy or tubal ligation, used condoms only, or used no contraceptive method. Due to small numbers, visits at which women reported use of implantable hormonal methods or an intrauterine device (IUD) were excluded (<2% of visits). Many women reported condom use, either with or without another method for pregnancy prevention; condom use was thus included in analyses as a potential confounder. HIV-1 uninfected men were considered exposed to hormonal contraception if their HIV-1 infected female partner reported using an injectable or oral method at her corresponding study visit. For 4% of male follow-up time, missing contraceptive data from their female partners were imputed to be the method consistently reported at adjacent study visits; data were not imputed if methods during adjacent periods were inconsistent.

Statistical analysis

The primary outcome measure was HIV-1 seroconversion. We conducted separate analyses of the association of hormonal contraception and 1) HIV-1 acquisition by women (male-to-female transmission) and 2) HIV-1 transmission from women to men (female-to-male transmission). For female-to-male transmission, only genetically-linked seroconversions were included as outcomes to minimize misclassification of HIV-1 transmissions from outside partners with unknown hormonal contraceptive use, and follow-up time was censored for those men at the time they acquired HIV-1 from a partner other than the HIV-1 infected partner with whom they enrolled.

We compared participant characteristics during periods of hormonal contraceptive use and non-use using generalized estimating equations. To assess the effect of contraceptive method on HIV-1 risk, we used time-dependent Cox proportional hazards regression with robust standard errors to account for within subject correlation with repeated measurements.[22] Models were adjusted for variables that have confounded the contraception-HIV-1 risk relationship in prior analyses[7,8] – age and time-dependent pregnancy and any sex without condoms – as well as plasma HIV-1 levels in the HIV-1 infected partner, a strong predictor of HIV-1 transmission.[23] We also assessed a number of additional variables for potential confounding: region (East versus southern Africa), the couple's marital status and number of children together, HSV-2 status of the HIV-1 uninfected partner, circumcision status of the male partner, and STI in either partner, all measured at study enrollment, as well as time-dependent measures of sexual frequency (with and without condoms), sex with additional partners, CD4 count of the HIV-1 infected partner, and genital ulcer disease in either partner. None of these additional variables

substantially (>10%) changed the effect estimates and thus they were not included in the final multivariate models. For analysis of HIV-1 acquisition in women, we tested for effect modification by baseline HSV-2 status and age using a likelihood ratio test, given results reported by others that the hormonal contraception-HIV-1 risk relationship was stronger for women who were HSV-2 seronegative or who were <25 years old.[24]

We repeated our analyses using marginal structural modeling, a technique to adjust for time-dependent confounding.[25,26] We computed stabilized inverse probability weights using logistic regression to predict the probability of hormonal contraceptive use at each visit (by plasma HIV-1 levels, age, region, and number of children) as described by Cole et al.;[27] the weights adjusted for time-dependent measures of pregnancy and unprotected sex. Weights for the effect of any hormonal contraception on HIV-1 risk (mean 1.00, range 0.82–1.34) were computed separately from the weights to assess the separate effects of injectable and oral contraception on HIV-1 risk (mean 1.07, range 0.19–4.56). These weights were then used in a pooled logistic regression model of hormonal contraception versus HIV-1 risk.

Finally, we assessed the prevalence and quantity of genital HIV-1 RNA in women using versus not using hormonal contraception by logistic and linear regression. All analyses were performed using SAS 9.2 (Cary, NC).

Role of the funding source

The authors designed and undertook the study, had full access to the raw data, did all analyses, wrote the report, and had final responsibility for the decision to submit for publication. The funder had no role in design, data collection, analysis, interpretation, or writing of the report. No authors received payment from a pharmaceutical company or other agency to write this report. JMB had full access to all the study data and had final responsibility for the decision to submit for publication.

Results

Population

For the majority of the 3,790 HIV-1 serodiscordant couples, the HIV-1 infected partner was female (Table 1). Most couples were married with children. The median age was in the mid-30s, and 24.4% of uninfected women were aged <25 years. Among HIV-1 seropositive participants, the median CD4 count was 455 (interquartile range [IQR] 337–626) cells/mm^3 and median plasma HIV-1 RNA concentration was 4.10 (IQR 3.37–4.73) $\log_{10}$ copies/mL. More than a quarter of women experienced a pregnancy during study follow-up.

Hormonal contraceptive use

At enrollment, 14.8% of HIV-1 seronegative and 17.4% of HIV-1 seropositive women used hormonal contraception; injectable contraception was more commonly used than oral pills (used by 12.5% and 3.9% of women, respectively). In total, 21.2% of HIV-1 seronegative and 33.3% of HIV-1 seropositive women used hormonal methods during study follow-up. Most (82.6% [n=1085] of HIV-1 seronegative and 77.1% [n=1909] of HIV-1 seropositive) women did not switch contraceptive methods during follow-up. However, among women who ever used hormonal contraception during the study, 48.0% (47.4% of HIV-1 seropositive and 49.5% of HIV-1 seronegative women) were not using such methods at some point during follow-up.

Follow-up and incident HIV-1 infection

Median follow-up for HIV-1 seronegative women and men was 18.0 (IQR 12.6–24.2) and 18.7 months (IQR 12.8–24.2), respectively. Retention at 12 and 24 months was 93.1% and 87.4% for HIV-1 seronegative women and 90.0% and 83.7% for HIV-1 seronegative men. HIV-1 seronegative partners accrued 5157.9 person-years of follow-up for assessment of HIV-1 seroincidence, during which 167 HIV-1 seroconversions occurred. Of the 73 infections in women, 62 (84.9%) were determined by viral sequencing to be genetically linked within the partnership, and of the 93 infections in men, 59 (63.4%) were determined to be linked.

During follow-up, hormonal contraceptives were used more frequently by couples with younger HIV-1 uninfected partners and couples who did not experience pregnancy (Table 2). Sexual behaviors did not differ for HIV-1 uninfected women during periods when they were using versus not using hormonal contraception. For HIV-1 uninfected men, unprotected sex was more likely and sex with an external partner was less likely during periods when their female partner was using hormonal contraception. Plasma HIV-1 RNA concentrations and CD4 counts were similar for hormonal contraception exposed versus unexposed periods.

Hormonal contraception and HIV-1 acquisition in women

HIV-1 acquisition rates were 6.61 and 3.78 per 100 person-years in women using and not using hormonal contraception (Table 3). In multivariate Cox proportional hazards analysis adjusted for age, pregnancy, unprotected sex and plasma HIV-1 levels in the HIV-1 infected partner, hormonal contraceptive use was associated with a 2-fold increased risk of HIV-1 acquisition (adjusted hazard ratio [AHR] 1.98, 95% confidence interval [CI] 1.06–3.68). Elevated risk was seen for both injectable (AHR=2.05, 95% CI 1.04–4.04) and oral contraceptive use (AHR=1.80, 95% CI 0.55–5.82), although the oral contraceptive use analysis included only 50.5 person-years and did not achieve statistical significance. The results from the marginal structural models were generally in agreement with the Cox regression models. We found no evidence that the effect of hormonal contraception on HIV-1 risk was different for HSV-2 seronegative (15.2% of women) versus seropositive women (AHR=1.56 versus 2.00, interaction p=0.82) or for women <25 (24.4% of women) versus ≥25 years of age (AHR=1.96 versus 2.21, interaction p=0.82).

Hormonal contraception and HIV-1 transmission from women to men

HIV-1 transmission rates from women to their male partners were 2.61 and 1.51 per 100 person-years from hormonal contraceptive users and nonusers, respectively (Table 4). In multivariate analysis adjusted for age, pregnancy, unprotected sex and plasma HIV-1 levels in the HIV-1 infected partner, men's HIV-1 risk was increased 2-fold when their partners were using hormonal contraception (AHR=1.97, 95% CI 1.12–3.45). Both injectable (AHR=1.95, 95% CI 1.06–3.58) and oral contraceptive use by female partners (AHR=2.09, 95% CI 0.75–5.84) were associated with increased HIV-1 risk for men, although the effect was statistically significant only for injectable contraception. The marginal structural model analyses generated similar results to the Cox proportional hazards regression.

Sensitivity analyses

In order to account for the potential persistent biologic effects of hormonal contraception on HIV-1 risk when women switched contraceptive methods, we assessed the effect of extending the exposure window for 3 months after last hormonal contraceptive use (thus, women could be exposed to >1 method during one study visit window). This affected 1.8% of person-years and one seroconversion event for the HIV-1 acquisition analysis and 2.1%

of person-years and one event for the female-to-male transmission analysis. The results of these analyses were not substantially different than those presented in Tables 3 and 4 (data not shown). When we limited the analysis of HIV-1 acquisition by women to those 62 outcomes that were genetically-linked to their male study partners, the effect estimates were not substantially changed (for any hormonal contraceptive use, Cox regression AHR=2.06, 95% CI 1.05–4.03 and marginal structural model odds ratio=2.01, 95% CI 1.02–3.95). In a third sensitivity analysis, we censored observations during pregnancy and adjusted our Cox model for age, unprotected sex and plasma HIV-1 levels in the HIV-1 infected partner. We did not see substantial differences in the effect estimates (Cox regression AHR=1.84, 95% CI 0.97–3.49 for the association of hormonal contraception and HIV-1 acquisition among women and AHR=1.86, 95% CI 1.04–3.32 for the association of hormonal contraception and HIV-1 transmission to men) for this approach compared with our primary study models.

Contraceptive use and genital HIV-1 RNA concentrations in HIV-1 seropositive women

We measured endocervical HIV-1 RNA concentrations from a single time-point in 1691 HIV-1 infected women (Table 5). Women using injectable contraception at the time of endocervical sample collection were more likely to have genital HIV-1 RNA detected than those not using hormonal contraception. Genital HIV-1 RNA concentrations were also higher in those using injectable contraception, by an average of 0.19 $\log_{10}$ copies/swab, after adjusting for plasma HIV-1 levels and CD4 count. There was no association between contraception and plasma HIV-1 RNA levels collected at the same time as the endocervical sample (median 3.91 versus 4.03 $\log_{10}$ copies/mL for injectable users versus non-users, p=0.10), suggesting a localized effect of hormonal contraception on increased levels of HIV-1 in the female genital tract.

Discussion

In this prospective study, we found that hormonal contraceptive use was associated with a twofold increase in the risk of HIV-1 acquisition by women and HIV-1 transmission from women to men. Injectable methods were the predominant form of hormonal contraception used by our study population and subgroup analyses demonstrated statistically significant increased HIV-1 risk associated with injectable use. Few women used oral contraceptives in our study; oral contraceptive use was associated with increased HIV-1 risk but did not achieve statistical significance and our results are insufficient for drawing definitive conclusions about oral contraceptive use and HIV-1 risk. Our results were robust to adjustment for multiple potential confounding factors, to different analytic approaches, and in sensitivity analyses.

Prior studies of HIV-1 acquisition risk related to contraceptive use have had inconsistent results, in part due to variable methodologic quality.[9] As a result, public health policies – targeted risk-reduction counseling and strategies to promote alternative contraceptive methods for women with or at risk of HIV-1 – have not been implemented. Our findings provide new and compelling data that contraception may increase a woman's risk of acquiring HIV-1, and they are consistent with prior longitudinal studies among sex workers in Kenya and family planning attendees from Uganda and Zimbabwe.[7,24] Moreover, to our knowledge, ours is the first prospective study to demonstrate elevated HIV-1 risk in male partners of HIV-1 infected women using hormonal contraception. We observed elevated HIV-1 RNA concentrations in endocervical secretions from HIV-1 infected women using injectable methods, offering a potential mechanism for increased HIV-1 transmission risk. Other studies of HIV-1 transmission from women to men are urgently needed to confirm or refute our findings.

Hormonal contraceptives may have physiologic actions beyond pregnancy prevention, including possible risks of bone density loss, cervical cancer and *Chlamydia trachomatis*.[28–30] Clinical and laboratory studies have suggested possible mechanisms by which hormonal contraception may influence HIV-1 susceptibility and infectiousness including changes to vaginal structure, cytokine regulation, CCR5 expression, and cervicovaginal HIV-1 shedding.[31]

Our analyses controlled for age, pregnancy, condom use, and HIV-1 levels in the infected partner; controlling for additional demographic, clinical, and behavioral factors did not alter our results. Only a clinical trial that randomly assigns women to effective hormonal versus non-hormonal contraception could definitively assess HIV-1 risk from different contraceptive methods with certainty that bias in contraceptive choice and due to unmeasured confounding did not influence the results. Such a study may be difficult to implement due to women's preferences for different contraceptive methods and the likelihood of contraceptive switching that could undermine randomization. Limitations of our study were that contraceptive use was determined by self-report – we did not collect data on adherence to contraception, and we did not record the specific brand of contraception and thus cannot comment on HIV-1 risks from specific exogenous hormones. During the study period, low-dose combination hormonal oral contraceptives and long-acting injectable depot medroxyprogesterone acetate (DMPA) were the most commonly used methods in national family planning programs; few studies have assessed HIV-1 risk from other injectable methods (e.g., Net-En).[12] Most participants in our study were participating in an HIV-1 prevention randomized clinical trial and were recruited broadly from HIV-1 testing and care centers. Nearly all HIV-1 infected partners were co-infected with HSV-2; however, HSV-2 seroprevalence is >80% among HIV-1 infected persons in sub-Saharan Africa.[32] Thus, these factors are unlikely to limit the generality of our findings. We censored follow-up for those couples in which the HIV-1 infected partner initiated ART. Future studies with longer post-ART follow-up should assess whether there is increased risk of HIV-1 acquisition and transmission in the context of ART use.

Multiple observational studies have now demonstrated increased HIV-1 risk for women using hormonal contraceptives; our findings suggest that male partners of HIV-1 infected women using hormonal contraception also face elevated HIV-1 risk. The benefits of effective hormonal contraceptive methods are unequivocal and must be balanced with the risk for HIV-1 infection. Our findings argue for policies to counsel women about the potential for increased HIV-1 risk with hormonal contraceptive use, particularly injectable DMPA use, and the importance of dual protection with condoms to decrease HIV-1 risk. Our data do not provide estimates of HIV-1 risk related to other hormonal contraceptives, such as implants, patches, or combination injectables. Data on HIV-1 risk associated with these methods as well as non-hormonal contraceptive methods, such as IUDs, are urgently needed, and strategies to improve the accessibility and uptake of these lower-dose and non-hormonal methods should be prioritized. Contraceptive counseling should be coupled to HIV-1 counseling and testing, with joint scale-up of both essential for optimizing reproductive health and HIV-1 prevention choices for women and couples. In addition, as national HIV-1 prevention programs begin to incorporate antiretroviral pre-exposure prophylaxis[33–35] this new HIV-1 prevention method could be offered to contracepting women or their partners.

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Panel: Research in Context

Systematic review

A systematic search of the literature in PubMed through July 2011 was done to identify studies relating hormonal contraceptive use to HIV-1 risk, using search terms “hormonal contraception,” “hormonal contraceptive”, “HIV-1,” and “HIV-1 acquisition or transmission” in different combinations. Additionally, systematic reviews and one meta-analysis that have been published on this topic were reviewed.

Interpretation

Multiple studies now demonstrate – with similar magnitude of their effect estimates – the potential for hormonal contraception to increase a woman’s risk for acquiring HIV-1, even after controlling for sexual behavior. The present study is the first with adequate power to assess and demonstrate the potential for hormonal contraceptive use by HIV-1 seropositive women to increase risk of transmitting the virus to their male partners. The findings presented in this paper have important implications for family planning and HIV-1 prevention programs, particularly in settings with high HIV-1 prevalence.

Table 1

Participant characteristics, prospective study of 3790 African heterosexual HIV-1 serodiscordant couples

	Median (interquartile range) or number (%)			
	Analysis of HIV-1 acquisition by women N=1314 couples		Analysis of HIV-1 transmission from women to men N=2476 couples	
	HIV-1 uninfected women	*HIV-1 infected men*	*HIV-1 uninfected men*	*HIV-1 infected women*
Demographic characteristics				
Age, years	30•2 (25•0–37•2)	37•0 (31•8–44•1)	35•0 (29•5–42•0)	29•9 (25•1–34•6)
Education, years	8•0 (6•0–10•0)	8•0 (6•0–11•0)	9•0 (7•0–12•0)	8•0 (6•0–11•0)
Couple characteristics				
Married	1081 (82•3)		1846 (74•6)	
Partnership duration, years	6•5 (2•7–13•4)		4•9 (2•1–9•4)	
Number of children	2•0 (1•0–4•0)	3•0 (2•0–5•0)	2•0 (1•0–4•0)	2•0 (1•0–3•0)
Number of children with study partner	2•0 (0•0–3•0)		1•0 (0•0–2•0)	
Sexual behavior, month prior to enrollment				
Number of sex acts	3•0 (2•0–6•0)		4•0 (2•0–8•0)	
Any unprotected sex	312 (23•7)		727 (29•4)	
Any sex with an outside partner	8 (1•0)	98 (7•5)	119 (9•2)	34 (1•4)
Medical characteristics				
Sexually transmitted infection*	160 (14•5)	85 (6•6)	230 (9•5)	429 (19•2)
HSV-2 seropositive	1088 (84•8)	1249 (97•6)	1441 (60•2)	2440 (99•0)
Circumcised (men)		427 (32•5)	1332 (53•8)	
Ever pregnant during study (women)	390 (29•7)			571 (23•1)
HIV-1 characteristics				
Plasma HIV-1 RNA, (log_{10} copies/mL) at enrollment		4•37 (3•71–4•94)		3•97 (3•24–4•56)
CD4 count (cells/mm^3) at enrollment		417 (323–562)		478 (348–663)
Ever used ART during study		173 (13•3)		235 (9•6)
Contraceptive use (women)				
Any hormonal contraceptive use at enrollment	194 (14•76)			430 (17•37)
Any injectable use at enrollment	142 (10•81)			335 (13•53)
Any oral use at enrollment	52 (3•96)			95 (3•84)
Any hormonal contraceptive use during follow up	275 (21•20)			815 (33•28)
Any injectable contraceptive use during follow up	208 (16•04)			656 (26•79)
Any oral contraceptive use during follow up	87 (6•71)			219 (8•94)

[*] *N. gonorrhoeae, C. trachomatis,* or *T. vaginalis;* 72.3% of participants with a sexually transmitted infections were infected with *T. vaginalis* only, <5% of participants had *N. gonorrhoeae* or *C. trachomatis.*

HSV-2: herpes simplex virus type-2; ART: antiretroviral therapy

Table 2

Participant characteristics during quarterly follow up intervals with and without hormonal contraceptive use

	Follow-up intervals for analysis of HIV-1 acquisition by women (N=1314 HIV-1 seronegative women)			Follow-up intervals for analysis of HIV-1 transmission from women to men (N=2476 HIV-1 seropositive women)		
	n/N (%) or median (IQR)		p-value*	n/N (%) or median (IQR)		p-value*
	Any hormonal contraception	No hormonal contraception		Any hormonal contraception	No hormonal contraception	
Demographic characteristics						
Age of HIV-1 seronegative partner, years	30•0 (26•0–35•4)	30•5 (25•0–37•8)	0•02	34•0 (29•7–39•9)	35•6 (30•0–43•0)	<0•001
Children within the partnership partnership	2•0 (1•0–3•0)	2•0 (0•0–3•0)	0•9	1•0 (1•0–2•0)	1•0 (0•0–2•0)	0•03
Sexual behavior, HIV-1 uninfected partner						
Any unprotected sex with study partner, past month	77/896 (8•6)	460/6125 (7•6)	0•4	389/3006 (12•9)	1011/9998 (10•1)	0•009
Any sex with an outside partner, past month	29/897 (3•2)	160/6024 (2•7)	0•5	294/3006 (9•8)	1221/10000 (12•2)	0•01
Medical characteristics						
CD4 count (cells/mm^3) in the HIV-1 infected partner	402 (286–601)	405 (298–562)	0•7	467 (343–656)	452 (324–631)	0•04
Plasma HIV-1 level (log_{10} copies/mL) in the HIV-1 infected partner	4•3 (3•3–4•9)	4•4 (3•6–5•0)	0•2	3•9 (3•2–4•5)	4•0 (3•2–4•7)	0•1
Pregnant, female partner**	47/898 (5•2)	967/6027 (16•0)	<0•001	146/2876 (5•1)	1288/9675 (13•3)	<0•001

*Comparisons among contraceptive exposure groups are adjusted for correlation by multiple measures from the same woman using generalized estimating equations. The number of data points considered for each cell is total number of visits with each covariate characteristic during study follow-up.

**Contraceptive use during pregnancy intervals was either contraceptive failures documented at the time of pregnancy detection or contraceptive uptake during the early postpartum period.

Table 3

Hormonal contraceptive use and risk of HIV-1 acquisition in women

			Unadjusted Cox proportional hazards regression analysis		Adjusted Cox proportional hazards regression analysis*		Adjusted marginal structural models analysis**	
	# HIV-1 seroconversions/person-years	Incidence per 100 person-years	HR (95% CI)	p-value	HR (95% CI)	p-value	OR (95% CI)	p-value
All women	73/1782•8	4•09						
No hormonal contraception	60/1586•2	3•78	Reference		Reference		Reference	
Any hormonal contraception	13/196•6	6•61	1•73 (0•95–3•15)	0•07	1•98 (1•06–3•68)	0•03	1•84 (0•98–3•47)	0•06
Injectable	10/146•1	6•85	1•80 (0•92–3•52)	0•08	2•05 (1•04–4•04)	0•04	2•19 (1•01–4•74)	0•05
Oral	3/50•5	5•94	1•53 (0•48–4•90)	0•47	1•80 (0•55–5•82)	0•33	1•63 (0•47–5•66)	0•44

*Multivariate Cox proportional hazard regression model, adjusted for age, plasma HIV-1 levels in the HIV-1 infected partner, and time varying unprotected sex and pregnancy. Further adjustment for additional factors did not substantially change the findings.

**Weighted marginal structural model is adjusted for age, region, number of children, plasma HIV-1 RNA concentration in the HIV-1 infected partner, and visit month (5-knot cubic spline with knots at the 5^{th}, 25^{th}, 50^{th}, 75^{th} and 95^{th} percentiles) and contraceptive history; weights are truncated at the 1^{st} and 99^{th} percentiles.

Table 4

Hormonal contraceptive use and risk of HIV-1 transmission from women to men

			Unadjusted Cox proportional hazards regression analysis		Adjusted Cox proportional hazards regression analysis*		Adjusted marginal structural models analysis**	
	# genetically linked HIV-1 seroconversions/ person years	**Incidence per 100 person-years**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
All men	59/3375•1	1•75						
No hormonal contraception	40/2647•9	1•51	Reference		Reference		Reference	
Any hormonal contraception	19/727•2	2•61	1•76 (1•02–3•05)	0•04	1•97 (1•12–3•45)	0•02	2•05 (1•12–3•74)	0•02
Injectable	15/567•3	2•64	1•79 (0•99–3•22)	0•05	1•95 (1•06–3•58)	0•03	3•01 (1•47–6•16)	0•003
Oral	4/159•9	2•50	1•70 (0•60–4•81)	0•31	2•09 (0•75–5•84)	0•16	2•35 (0•79–6•95)	0•12

* Multivariate Cox proportional hazard regression model, adjusted for age, plasma HIV-1 levels in the HIV-1 infected partner, and time varying unprotected sex and pregnancy. Further adjustment for additional factors did not substantially change the findings.

** Weighted marginal structural model is adjusted for age, region, number of children, plasma HIV-1 RNA concentration in the HIV-1 infected partner, and visit month (5-knot cubic spline with knots at the 5^{th}, 25^{th}, 50^{th}, 75^{th} and 95^{th} percentiles) and contraceptive history; weights are truncated at the 1^{st} and 99^{th} percentiles.

Table 5

Endocervical HIV-1 RNA concentrations in HIV-1 seropositive women (n=1691), by contraceptive method

	Detection of any genital HIV-1 RNA			Quantity of genital HIV-1 RNA detected (log_{10} copies/swab)		
	n/N (%)	**Odds Ratio (95% CI)**	**Adjusted Odds Ratio* (95% CI)**	**Median (IQR)**	**Regression coefficient (average difference in HIV-1 RNA concentration) (95% CI)**	**Adjusted regression coefficient* (95% CI)**
All HIV-1 seropositive women	1011/1691 (59•9)			3•18 (2•08–3•85)		
No hormonal contraception	782/1333 (58•7)	Reference	Reference	3•14 (2•08–3•91)	Reference	Reference
Any hormonal contraception	230/358 (64•3)	1•27 (0•99–1•61) *p-value=0•06*	1•51 (1•13–2•01) *p-value < 0•01*	3•29 (2•08–3•91)	+0•10 (−0•01, +0•21) *p-value=0•08*	+0•14 (+0•04, +0•23) *p-value<0•01*
Injectable	180/272 (66•2)	1•77 (1•29–2•43) *p-value=0•01*	1•67 (1•21–2•31) *p-value=0•02*	3•38 (2•08–4•02)	+0•15 (+0•03, +0•28) *p-value=0•02*	+0•19 (+0•08, +0•30) *p-value<0•01*
Oral	50/86 (58•1)	1•13 (0•66–1•91) *p-value=0•54*	1•06 (0•62–1•84) *p-value=0•49*	2•96 (2•08–3•65)	−0•07 (−0•28, +0•14) *p-value=0•53*	−0•05 (−0•24, +0•14) *p-value=0•60*

*Adjusted for plasma HIV-1 RNA concentration and CD4 count