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Oral and injectable contraceptive use and HIV acquisition risk among women in 4 African countries: a secondary analysis of data from a microbicide trial

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Abstract

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POTENTIAL CONFLICTS OF INTEREST

All authors declare no commercial or other associations that might pose a conflict of interest relevant to the submitted work.

Objective—To assess the effect of oral and injectable contraceptive use compared to non-hormonal contraceptive use on HIV acquisition among Southern African women enrolled in a microbicide trial.

Study Design—Prospective cohort study using data from women enrolled in HIV Prevention Trials Network (HPTN) protocol 035. At each quarterly visit, participants were interviewed about self-reported contraceptive use and sexual behaviors and underwent HIV testing. Cox proportional hazards regression was used to assess the effect of injectable and oral hormonal contraceptive use on HIV acquisition.

Results—The analysis included 2,830 participants, of whom 106 became HIV infected (4.07 per 100 person-years.) At baseline, 1,546 (51%) participants reported using injectable contraceptives and 595 (21%) reported using oral contraceptives. HIV incidence among injectable, oral and non-hormonal contraceptive method users was: 4.72, 2.68 and 3.83 per 100 person-years, respectively. Injectable contraceptive use was associated with a non-statistically significant increased risk of HIV acquisition (adjusted hazard ratio [aHR] = 1.17; 95% confidence interval [CI] 0.70, 1.96), while oral contraceptive use was associated with a non-statistically significant decreased risk of HIV acquisition (aHR=0.76; 95% CI 0.37,1.55).

Conclusion—In this secondary analysis of randomized trial data, a marginal, but non-statistically significant, increase in HIV risk among women using injectable hormonal contraceptives was observed. No increased HIV risk was observed among women using oral contraceptives. Our findings support the World Health Organization's recommendation that women at high risk for acquiring HIV, including those using progestogen-only injectable contraception, should be strongly advised to always use condoms and other HIV prevention measures.

Keywords

hormonal contraception; HIV infection; injectables; oral contraceptive pills; Southern Africa; women

INTRODUCTION

Access to safe and effective contraceptive methods is one of the cornerstones of reproductive health. Use of these methods has contributed to reductions in unintended pregnancies and improvements in maternal and child health outcomes throughout the world.[1] Approximately 140 million women use hormonal contraception (HC) globally, with 100 million using oral contraceptive pills (OCPs) and 40 million using injectable contraceptives.[2] After two decades of investigation, the relationship between injectable and oral HC and HIV acquisition remains unclear.[3-8] A prospective study of heterosexual HIV-serodiscordant couples from seven African countries enrolled in an HIV prevention trial, which reported that women using injectable contraceptives had a 2.05-fold increased risk of HIV acquisition (95% CI 1.04, 4.04), has re-focused attention to this question.[9] Despite these findings and findings from several other studies that reported an increased risk of HIV acquisition among injectable HC users,[10-15] the overall body of evidence assessing this relationship is still inconclusive,[5-8] leading the World Health Organization (WHO) to call for further research on this topic.[4] Continued evaluation of the association between

injectable and oral HC and HIV acquisition through well-designed secondary analyses using data from rigorously conducted, prospective HIV prevention studies has the potential to improve our understanding of this important public health issue.[16] Here we report the findings from a secondary analysis that assessed the effect of injectable and oral contraceptive use on HIV acquisition among women from 4 southern African countries enrolled in the HIV Prevention Trials Network (HPTN) 035 microbicide trial.

METHODS

Study design, population and procedures

The HPTN 035 trial was a phase II/IIB, four-arm, multisite, randomized, controlled trial comparing BufferGel and 0.5% PRO 2000 gel against two comparator arms (hydroxycellulose [HEC] placebo gel and no gel) for HIV prevention (#NCT00074425). Detailed trial methods have been described.[17] Briefly, between 2005-2008, women from five countries (Malawi, South Africa, USA, Zambia, and Zimbabwe) were enrolled and followed for a minimum of 12 months and a maximum of 30 months, depending on enrollment date. Eligible women were at least 18 years of age, HIV-1 seronegative, non-pregnant and sexually active. All institutional review boards approved the trial at each site and all participants provided written informed consent.

Participants received a comprehensive HIV prevention package that included ongoing HIV risk reduction counseling, free male latex condoms, and diagnosis and treatment of sexually transmitted infections (STIs) throughout the trial. Use of contraception was not required for study participation; however, participants at all research sites received contraceptive methods counseling. Participants in Malawi, Zambia and Zimbabwe were offered free contraceptive services at the research sites, while participants in South Africa were provided referrals to the nearest health center offering contraceptive services.

At monthly follow-up visits, a urine pregnancy test was performed. At quarterly visits, data were collected on self-reported condom use, sexual behaviors and contraceptive use (participants were asked “Which family planning method or methods are you currently using?”). Data on brand of injectable or oral contraceptives was not available. If a participant reported a change in method since her last visit, the self-reported date of change was systematically recorded on the medications log form. Blood was collected for HIV serologic testing at the quarterly visits. Herpes simplex virus type 2 (HSV-2) was evaluated at baseline and study exit visits.

Laboratory procedures

HIV-1 infection status was determined using a standardized algorithm, with initial testing conducted using rapid tests and confirmatory testing using Western blot.[17] HSV-2 testing was performed using the HerpesSelect-2 EIA (Focus Technologies; Cypress, California, USA). Vaginal saline microscopy was performed for the presence of motile trichomonads for diagnosis of *Trichomonas vaginalis*. Urine specimens were tested for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* annually using BD ProbeTec ET (Becton Dickinson; Franklin Lakes, New Jersey, USA).

Statistical analysis

Our primary aim was to estimate the association between self-reported injectable (depot medroxyprogesterone acetate [DMPA] or norethisterone oenanthate [NET-EN]) or OCP use and HIV acquisition risk among African women enrolled in HPTN 035. The primary outcome was detection of HIV-1 infection. Participants who reported using contraceptive implants were excluded from the analysis due to small numbers. In addition, we excluded women enrolled at the US site as there were no HIV infections observed at that site. To avoid potential bias from informative censoring this analysis was limited to the first 12 months of follow-up for each participant, which was the minimum planned length of follow-up. Pearson's chi-square test was used to assess categorical variables (unstratified) at enrollment. The Cochran-Mantel-Haenszel test was used to test the association between categorical variables and baseline contraceptive use stratified by site. Cox proportional hazards (PH) regression models stratified by site were used to assess the effect of injectable and OCP use versus non-HC methods (male condoms, surgical sterilization, or no contraceptive method) on HIV acquisition, with contraceptive use included in the models as a time-varying characteristic. Pregnancy incidence was calculated by contraceptive method (excluding those who reported having a tubal ligation) and participants were censored at their first positive pregnancy test or at the 12-month of follow-up visit. Participants were classified as being exposed to a contraceptive method if they reported use of the method at the quarterly follow-up visit. If a participant reported a change in method since her last visit quarterly, the self-reported date of change (recorded on the medications log form) was used to indicate initiation of exposure to the new method. If a participant missed a visit, time-varying covariates were imputed using last value carried forward. Age, marital/co-habiting status, HSV-2 status and unprotected sex were included in the multivariable model based on *a priori* assumptions. Additional potential confounding factors were considered for inclusion in the final model if they were related to both HC use (at baseline or during follow-up) and HIV acquisition (Cochran-Mantel-Haenszel test stratified by site using an alpha level <0.10).

We repeated the above analyses separately stratifying by age category (<25 years versus ≥25) and baseline HSV-2 status.[12,18] A likelihood ratio test was used to test for effect modification. We evaluated the sensitivity of our findings with regard to pregnancy by adjusting for pregnancy rather than censoring follow-up at the time of pregnancy detection. Due to differences in demographic and clinical characteristics by site, including differences in HC use and HIV incidence, we conducted an exploratory analysis restricted to participants enrolled at the South African sites. These sites contributed the majority of HIV seroconversions and participant follow-up and we hypothesized that participants from these sites may be more similar with respect to measured and unmeasured characteristics that affect HIV acquisition risk. Sub-group analyses were not performed for other countries due to low HIV incidence and limited contraceptive variability. All statistical tests were assessed using a 2-sided α of 0.05. Analyses were conducted using Stata version 12.0 (StataCorp, Inc., College Station, Texas, USA).

RESULTS

Among 3,099 participants enrolled in HPTN 035, we excluded 200 participants from the US and 34 participants who did not attend any follow-up visits. An additional 35 participants who reported using contraceptive implants were excluded, leaving 2,830 participants for analysis. Baseline demographic and clinical characteristics are presented in Table 1. Several baseline characteristics varied greatly across sites. Overall, most participants reported living with a partner (70%); however, the proportion varied substantially by site (range: 11-99%). The majority of participants reported having only one sex partner, with only 43 (2%) reporting more than one partner in the 3 months prior to enrollment. Less than half (42%) of participants were HSV-2 seropositive. At enrollment, HC use was high, with 2,051 (72%) participants reporting HC use (injectable or OCP). However, HC methods varied widely across sites (Table 1). Many of the same baseline factors that varied significantly across sites were also associated with baseline contraception method (Table 2).

Demographic, clinical and behavioral characteristics by contraceptive use at each quarterly follow-up visit were similar to those reported at baseline (data not shown). Among participants not using HC at baseline, there were 281 instances of initiation of an injectable method, and 154 instances of OCP initiation. Among participants using HC at baseline, the majority of participants did not change methods during the trial (1,707/2,051 [83%]), with 344 instances of a switching from the initial HC method to another HC method (184 instances of switching from injectable to OCP; and 160 instances of switching from OCP to injectable). The overall pregnancy incidence was 11.34/100 person-years. Participants who reported using injectables had the lowest pregnancy rate (3.56/100 person-years), followed by OCP users (19.64/100 person-years), and participants who reported non-HC (excluding those with tubal ligation) = 31.62/100 person-years.

Over 2,605 person-years of follow-up, there were 106 incident HIV infections (overall HIV incidence of 4.07/100 person-years). HIV incidence varied by country and was highest in South Africa (6.76/100 person-years; 95% confidence interval [CI] 5.30, 8.61), followed by Zambia (3.42/100 person-years; 95% CI 1.84, 6.36), Malawi (2.82/100 person-years; 95% CI 1.49, 3.50) and Zimbabwe (2.32/100 person-years; 95% CI 1.25, 4.32). Compared to non-HC, injectable use was associated with an increased risk of HIV acquisition (adjusted hazard ratio [aHR] = 1.17; 95% CI 0.70, 1.96), however, the association was not statistically significant. In contrast, OCP use was associated with a decreased risk of HIV acquisition that was also not statistically significant (aHR=0.76; 95% CI 0.37,1.55) [Table 3]. Sensitivity analyses adjusting for pregnancy rather than censoring at the first pregnancy showed similar results (data not shown). Additional analyses showed no evidence of effect modification by age category (<25 versus ≥25 years) [$p_{interaction}$=0.51] or baseline HSV-2 status ($p_{interaction}$=0.51) [Table 3]. Among South African participants, there was a trend towards a two-fold increased HIV risk among women using injectables in unadjusted analyses, with a slight attenuation of the association after controlling for potential confounders (Table 3). No association between OCP and HIV acquisition was observed.

DISCUSSION

In this secondary analysis, we did not observe a significant increased risk of HIV acquisition among women using injectable or oral contraceptive methods. Our overall findings are similar to several other secondary analyses using data from women enrolled in HIV prevention trials in Africa that reported modest increases in HIV acquisition risk among women using injectable HC.[7,19,20] No statistically significant interactions between baseline age or HSV-2 status and HC method were observed.[12,18] Our primary results differed from those reported in a prospective analysis of HIV serodiscordant couples participating in the Partners in Prevention HSV/HIV Transmission study, where women who reported using injectables had a significant increased HIV risk compared to women using non-HC.[9,21]

One feature of our study was the high rate of injectable use reported at baseline and throughout the study. Specifically, 51% of participants reported using injectables at enrollment. This level of use was similar to the levels reported in analyses from other microbicide trials,[13,14,20] but substantially higher than what was reported in the Partners study (baseline injectable use=13%).[9,20] OCP use was similar to levels observed by others (range: 4-22%).[9,13-15,20,22,23] Despite frequent contraceptive counseling, pregnancy was also common. We observed high pregnancy rates among women reporting OCP use versus OCP failure rates reported by others,[24] suggesting that adherence to OCP was low. It is possible that we didn't observe an association between OCP use and HIV risk due to lower adherence of oral contraceptives.

Another feature was the high degree of heterogeneity in demographic, behavioral and clinical characteristics between study sites, including HIV incidence. In a multisite trial, it is desirable to have some heterogeneity between sites in order to demonstrate that an intervention is effective in a variety of populations; however, this heterogeneity can be problematic in secondary analyses where the exposure (HC use) is not balanced across sites. Contraceptive method choice was highly dependent on site. At some sites, uptake of OCP was <10%, a rare exposure in a population with a rare outcome, thus limiting our ability to assess the relationship between OCP and HIV acquisition by site. Several potential confounders were highly correlated with site and may have different confounding relationships across sites. In addition, HIV incidence varied across sites and was highest in South Africa at 6.76% compared to 2.51% in all other countries combined. Differential exposure to HIV-infected partners is likely to have varied by site, further contributing to site heterogeneity in HIV acquisition risk. Although our analysis attempted to address heterogeneity by stratifying by site and adjusting for potential confounders, residual confounding may be present. We attempted to address this further by performing an analysis restricted South African sites, where we observed a trend toward an increased risk of HIV acquisition among injectable users in unadjusted analyses, which attenuated slightly after adjustment for potential confounders. Others have reported differences by country in the effect of HC on HIV risk.[18] If a true biologic effect of HC use exists, then effect estimates should be consistent across countries. However, confounding by site or country may contribute to differences across populations. Careful assessment of and adjustment for potential confounders is critical in order to attempt to achieve unbiased estimates of HIV risk.

Several recent studies that assessed the effect of HC on HIV acquisition have used marginal structural models (MSM),[25,26] in addition to Cox models, to attempt to address bias that may be present as a result of time-dependent confounding.[9,12,15,19,20] In these studies, results from MSM models have been similar to those generated by Cox models. The similarities could be due to the absence of strong time-dependent confounding or due to violation of one more of the assumptions required to achieve unbiased estimates with MSM.[27,28] One key assumption is the positivity assumption, which states that there must be both exposed and unexposed individuals at every level of a confounder. For example, in hormonal contraception and HIV acquisition analyses, the positivity assumption may be violated if a participant becomes pregnant, since pregnant women are not exposed to hormonal contraception although they continue to be at risk for HIV.[28] Due to concerns over violation of the positivity assumption with regard to pregnancy in our data, we did not feel it was appropriate to perform MSM.

The findings from this analysis should be interpreted in the context of several limitations. Among South African participants, data were not available on the specific type of injectable method used (DMPA versus NET-EN); therefore, we cannot assess the potential differing effects of these two injectable methods on HIV acquisition. Data on contraceptive use was obtained by self-report and data on partner characteristics, including HIV status, were not collected. Although we adjusted for potential confounders, there was heterogeneity across sites and the potential for residual confounding. In this study, participants underwent quarterly HIV testing and assessment of contraceptive methods and potential confounders, including condom use; future studies will be strengthened by more frequent assessments of HC use, potential confounders and HIV status in order to allow for a more precise evaluation of the HC and HIV acquisition relationship.[16]

In summary, we observed a marginal, but not statistically significant increase in HIV risk among women using injectable HC, which was similar in multiple sensitivity analyses. Among women from South Africa, the magnitude of HIV risk among injectable HC users was greater but did not reach statistical significance. We did not observe an increased risk of HIV acquisition among women using OCP in any of our analyses. Rather, effect estimates indicated a modest decrease in HIV acquisition; although, these associations also did not achieve statistical significance. Continued research on the relationship between widely used contraceptive methods and HIV acquisition is essential. In addition, the uncertainty regarding the impact of injectable contraception on HIV acquisition risk coupled with the high pregnancy rate among OCP users observed in our analysis highlight the urgent need to expand the contraceptive method mix by increasing access to long acting reversible contraceptive (LARC) methods, such as intrauterine devices and hormonal implants, and developing low-dose hormonal methods. The effect of these long-acting contraceptive methods on HIV risk requires evaluation. Despite frequent counseling and access to condoms, the HIV incidence in our study was high, particularly in South Africa. Given this high incidence, our findings support the WHO's recommendation that women at high risk for HIV, including those using progestogen-only injectable HC, should be strongly advised to always use condoms in addition to other HIV prevention measures.[4]

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IMPLICATIONS

Among Southern African women participating in an HIV prevention trial, women using injectable hormonal contraceptives had a modest increased risk of HIV acquisition, however this association was not statistically significant. Continued research on the relationship between widely used hormonal contraceptive methods and HIV acquisition is essential.

Table 1

Demographic and clinical characteristics at enrollment by study site

Baseline characteristic	All Clinics	Malawi		South Africa		Zambia	Zimbabwe		p-value*
	N=2830	Blantyre N=428	Lilongwe N=579	Durban N=700	Hlabisa N=347	Lusaka N=313	Chitungwiza N=245	Harare N=218	
Age group									<0.001
< 25 years	1338 (47)	200 (47)	217 (37)	345 (49)	193 (56)	206 (66)	106 (43)	41 (32)	
25-34 years	1358 (48)	209 (49)	301 (52)	353 (5)	111 (32)	107 (34)	134 (55)	143 (66)	
≥ 35 years	134 (5)	19 (4)	61 (11)	2 (<1)	43 (12)	0 (0)	5 (2)	4 (2)	
Living with partner	1985 (70)	405 (95)	573 (99)	273 (39)	37 (11)	252 (81)	233 (95)	212 (97)	<0.001
Education (> primary school)	1710 (60)	131 (31)	88 (15)	653 (93)	270 (78)	138 (44)	229 (93)	201 (92)	<0.001
Number of live births									<0.001
0	146 (5)	4 (1)	2 (<1)	89 (13)	21 (6)	29 (9)	0 (0)	1 (<1)	
1-2	1695 (60)	209 (49)	206 (36)	500 (71)	225 (65)	193 (62)	200 (82)	162 (74)	
≥ 3	989 (35)	215 (50)	371 (64)	111 (16)	101 (29)	91 (29)	45 (18)	55 (25)	
More than 1 sex partner in the past 3 months	43 (2)	1 (<1)	1 (<1)	27 (4)	3 (1)	9 (3)	1 (<1)	1 (<1)	<0.001
Condom used at last vaginal sex act	1938 (68)	221 (52)	322 (56)	541 (77)	215 (62)	240 (77)	214 (87)	185 (85)	<0.001
Contraceptive use**									
Injectable	1456 (51)	272 (64)	390 (67)	335 (48)	145 (42)	210 (67)	66 (27)	38 (17)	<0.001
Oral	595 (21)	34 (8)	56 (10)	78 (11)	18 (5)	60 (19)	172 (70)	177 (81)	<0.001
Male condoms	548 (19)	30 (7)	36 (6)	312 (45)	90 (26)	38 (12)	33 (13)	9 (4)	<0.001
Tubal ligation	130 (5)	25 (6)	45 (8)	41 (6)	17 (5)	2 (1)	0 (0)	0 (0)	<0.001
No contraception	261 (9)	58 (14)	53 (9)	54 (8)	88 (25)	6 (2)	1 (<1)	1 (<1)	<0.001
HSV-2 seropositive	1188 (42)	186 (43)	232 (40)	324 (46)	163 (47)	138 (44)	68 (28)	77 (35)	<0.001
Chlamydia	104 (4)	3 (1)	2 (<1)	46 (7)	26 (7)	10 (3)	11 (4)	6 (3)	<0.001
Gonorrhea	21 (<1)	6 (1)	2 (<1)	5 (1)	4 (1)	2 (1)	1 (<1)	1 (<1)	0.52
T. vaginalis	218 (8)	27 (6)	67 (12)	36 (5)	51 (15)	21 (7)	14 (6)	2 (1)	<0.001
Any curable STI***	325 (11)	33 (8)	71 (12)	84 (12)	74 (21)	33 (11)	23 (9)	7 (3)	<0.001

Data are presented as N (%).

* Pearson's chi-squared test.

** Participants could choose more than one option; therefore, the total percent is greater than 100%.

*** STI = Sexually transmitted infection at baseline (*Chlamydia trachomatis*, *Neisseria gonorhoeae* or *Trichomonas vaginalis*)

Table 2

Selected characteristics and baseline contraceptive use

	Injectable contraception N=1456	Oral contraception N=595	Non-hormonal methods[1] N=779	p-value[2]
Age group				<0.001
< 25 years	750 (52)	248 (42)	340 (44)	
25-35 years	674 (46)	335 (56)	329 (45)	
≥ 35 years	32 (2)	12 (2)	90 (11)	
Living with partner	1055 (72)	525 (88)	405 (52)	<0.001
Education (> primary school)	783 (54)	459 (77)	468 (60)	<0.001
Number of live births				<0.001
0	23 (2)	16 (3)	107 (14)	
1-2	910 (63)	427 (72)	358 (46)	
≥ 3	523 (36)	152 (25)	314 (40)	
More than 1 sex partner in the past 3 months[3]	19 (1)	2 (<1)	22 (3)	<0.001
Condom used at last vaginal sex act	924 (63)	458 (77)	556 (71)	<0.001
HSV-2 seropositive	614 (42)	210 (35)	364 (47)	<0.001

[1] Use of male condoms, surgical sterilization, or no contraceptive method.

[2] Cochran-Mantel-Haenszel test stratified by site.

[3] Report of sexual activity in the last 3 months was required in order to be eligible for enrollment.

Table 3

Hormonal contraceptive use and risk of HIV-1 seroconversion

	Number of HIV infection/p-yrs	Incidence	Unadjusted HR[1] (95% CI)		p-value	Adjusted HR (95% CI)		p-value
All participants [2]	106/2605	4.07						
No hormonal contraception	29/481	3.95	Ref	--	--	--	--	--
Injectable	72/1543	4.66	1.26	(0.76, 2.10)	0.37	1.17	(0.70, 1.96)	0.56
Oral	15/580	2.58	0.77	(0.38, 1.57)	0.47	0.76	(0.37, 1.55)	0.45
Stratified by age at enrollment [3]								
Age <25 years	58/1218	4.76						
No hormonal contraception	9/172	5.22	Ref	--	--	--	--	--
Injectable	38/788	4.82	1.01	(0.48, 2.11)	0.98	1.01	(0.48, 2.11)	0.99
Oral	11/257	4.29	0.93	(0.37, 2.45)	0.89	0.93	(0.37, 2.35)	0.88
Age ≥ 25 years	48/1388	3.46						
No hormonal contraception	10/309	3.24	Ref	--	--	--	--	--
Injectable	34/755	4.50	1.53	(0.75, 3.12)	0.24	1.42	(0.70, 2.91)	0.34
Oral	4/324	1.23	0.46	(0.13, 1.59)	0.22	0.45	(0.13, 1.59)	0.22
Stratified by HSV-2 status at enrollment [4]								
HSV-2 positive	64/1088	5.88						
No hormonal contraception	14/224	6.26	Ref	--	--	--	--	--
Injectable	41/654	6.27	0.99	(0.54, 1.85)	0.99	0.87	(0.46, 1.63)	0.66
Oral	9/211	4.27	0.80	(0.33, 1.93)	0.62	0.72	(0.29, 1.75)	0.46
HSV-2 negative	42/1517	2.77						
No hormonal contraception	5/257	1.94	Ref	--	--	--	--	--
Injectable	31/890	3.48	2.08	(0.80, 5.38)	0.13	1.96	(0.75, 5.12)	0.17
Oral	6/369	1.62	0.93	(0.27, 3.24)	0.91	0.94	(0.27, 3.30)	0.92
Enrolled at South African sites [2]	65/962	6.76						
No hormonal contraception	10/256	3.91	Ref	--	--	--	--	--
Injectable	47/551	8.53	1.93	(0.97, 3.80)	0.06	1.70	(0.85, 3.39)	0.13
Oral	8/156	5.14	1.24	(0.49, 3.16)	0.65	1.23	(0.48, 3.13)	0.67

P-yrs = person-years. HR= hazard ratio. CI = confidence interval.

[1] Cox proportional hazards models stratified by site.

[2] Adjusted model =Time-varying Cox proportional hazards models stratified by site and adjusted for baseline age (as a continuous variable), living with a partner, HSV-2 status, and time-varying unprotected sex at last vaginal sex act with censoring at the first positive pregnancy test.

[3] Adjusted models =Time-varying Cox proportional hazards models stratified by site and adjusted for living with a partner, HSV-2 status, and time-varying unprotected sex at last vaginal sex act with censoring at first the positive pregnancy test. Likelihood ratio test for age: p=0.51.

[4] Adjusted models =Time-varying Cox proportional hazards models stratified by site and adjusted for baseline age, living with a partner, and time-varying unprotected sex at last vaginal sex act with censoring at first positive pregnancy test. Likelihood ratio test for baseline HSV-2 status: p=0.51.