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Pregnancy, Contraceptive Use, and HIV Acquisition in HPTN 039: Relevance for HIV Prevention Trials Among African Women

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Abstract

Background—Biomedical HIV prevention trials enroll sexually active women at risk of HIV and often discontinue study product during pregnancy. We assessed risk factors for pregnancy and HIV acquisition, and the effect of pregnancy on time off study drug in HPTN 039.

Methods—1358 HIV negative, HSV-2 seropositive women from South Africa, Zambia, and Zimbabwe were enrolled and followed for up to 18 months.

Results—228 pregnancies occurred; time off study drug due to pregnancy accounted for 4% of woman-years of follow-up among women. Being pregnant was not associated with increased HIV risk (hazard ratio [HR] 0.64 95% CI [0.23, 1.80], $p=0.40$). However, younger age was associated with increased risk for both pregnancy and HIV. There was no association between condom use as a sole contraceptive and reduced pregnancy incidence; hormonal contraception was not associated with increased HIV risk. Bacterial vaginosis at study entry was associated with increased HIV risk (HR 2.03, $p=0.02$).

Conclusions—Pregnancy resulted in only a small amount of woman-time off study drug. Young women are at high risk for HIV and are an appropriate population for HIV prevention trials but also have higher risk of pregnancy. Condom use was not associated with reduced incidence of pregnancy.

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Keywords

HIV prevention; prevention trials; pregnancy; contraception; Africa; HSV-2; HIV risk factors

Introduction

In sub-Saharan Africa, women account for most HIV infections among adults and are a priority population for evaluation and delivery of novel HIV prevention interventions. As a result, many HIV prevention trials enroll sexually active women of reproductive age. Despite counseling and provision of contraception, trial participants may become pregnant during the study follow-up period [1,2]. For many prevention trials, particularly those testing biomedical strategies such as oral antiretroviral pre-exposure prophylaxis and topical vaginal microbicides, study protocols frequently require that women who become pregnant be removed from the investigational product to minimize fetal exposure. Although stopping study product during pregnancy may reduce the generalizability of study findings [3], the consensus to date has generally been that safety and efficacy of new interventions should first be demonstrated in non-pregnant women. Thus, because of protocol-required time off study product, high numbers of pregnancies during prevention trials can reduce the statistical power of such trials and potentially their final outcomes.

Understanding the predictors of pregnancy within HIV prevention trials will assist in developing more effective strategies for pregnancy prevention for future studies involving women. Moreover, given evidence from some studies suggesting increased risk of HIV acquisition associated with pregnancy [4], as well as with hormonal contraceptive use [5], it is also important to characterize the effect of both pregnancy and contraception on HIV acquisition risk among women in HIV prevention studies. We analyzed incidence and timing of pregnancy, risk factors for pregnancy, proportion of time off study product due to pregnancy, contraceptive practices, and relationship between pregnancy, contraceptive use, and HIV risk among HIV negative women from three African sites participating in a recently completed HIV prevention trial (HPTN 039).

Methods

HPTN 039 recruited and followed 1358 HIV seronegative, HSV-2 seropositive women from sites in South Africa, Zambia and Zimbabwe, as well as high-risk men who have sex with men from Peru and the United States, between October 2003 and November 2007. The primary aim of the trial was to assess the effect of daily antiviral suppression of herpes simplex virus type 2 (HSV-2) on HIV acquisition risk; the study demonstrated no significant effect of acyclovir in reducing HIV incidence, as published [6].

Women were recruited from family planning, well-baby, and voluntary counseling and testing clinics as well as from community venues. Participants were randomized to acyclovir 400 mg twice daily or matching placebo. Study drug was provided at monthly follow-up visits, and HIV testing was done quarterly. Follow-up was for up to 18 months. All participants received a comprehensive HIV prevention package at each monthly visit consisting of HIV counseling, free condoms, and treatment of curable sexually transmitted infections (STIs), according to local guidelines. Screening for syphilis, *Trichomonas vaginalis*, bacterial vaginosis, *Chlamydia trachomatis*, and *Neisseria gonorrhoeae* was performed at the enrollment visit [6]. At quarterly visits, interviews about risk behavior and STI symptoms were conducted, and a genital examination to evaluate the presence of genital ulcers was performed. Women were offered episodic treatment for symptomatic HSV-2 recurrences with open label acyclovir.

Urine pregnancy testing was performed at screening, enrollment, and at quarterly follow-up visits, as well as at any non-quarterly follow-up visits at which women reported late menses. Pregnant women were excluded from enrollment, and study drug was withheld in cases where enrolled women became pregnant during follow-up. Women were allowed to resume study drug after a pregnancy was completed, and pregnancy testing was confirmed negative. As part of the study enrollment consent, women were counseled to avoid pregnancy during the follow-up period if possible, and informational materials about available safety data related to acyclovir and pregnancy were provided and discussed. The status of infants born to women who became pregnant while enrolled in the trial was obtained by interview of the woman after delivery; if a woman exited the study prior to completion of her pregnancy every effort was made to obtain this information.

Contraceptive use, including self-report of male condoms as a primary method, was recorded at the enrollment visit. During follow-up contraceptive method was captured in site chart notes and abstracted into a database at the end of the study. Early in the study, women requesting contraception (other than condoms) were referred to local family planning providers. Due to a higher-than-anticipated pregnancy incidence during the first year of the study, in March 2005 sites intensified family planning counseling at monthly visits and provided hormonal contraceptives (oral and injectable) and intrauterine devices (IUD) in addition to condoms on-site.

The study protocol was approved by the Division of AIDS Prevention Science Review Committee, Family Health International Regulatory Affairs, University of Washington Human Subjects Research Committee, and the ethics review committees at all local institutions and collaborating organizations. All participants provided written informed consent.

Statistical Analysis

The goals of the analyses were 1) to characterize pregnancy incidence and predictors of pregnancy, 2) to assess the association between pregnancy and incident HIV infection, and 3) to evaluate the effect of contraceptive use on pregnancy and HIV risk. For the analysis of incident pregnancy, women were defined as not at risk for pregnancy during a window beginning on the date of the first positive pregnancy test and ending 6 weeks past the first negative pregnancy test. For the analysis of HIV infection, women were considered “being pregnant” if they were in that window. Predictors of incident pregnancy and HIV were evaluated using univariate and multivariate Cox proportional hazard regressions, stratified by study site and randomization arm since these factors are not of primary interest in this study [7]. Multivariate models included demographic and behavioral measures and STIs to address potential confounding. Variables with univariate p-values <0.1 were selected for the multivariate models. Sexual behavioral variables, contraceptive methods, and reported genital ulcer disease (GUD) on exam, all collected quarterly, were included as time-varying covariates in survival analyses (the covariate “being pregnant” was turned on in the quarter of the first positive pregnancy test and remained on through the quarter of the last positive pregnancy test). Although self-reported condom use as a contraceptive method is clearly associated with frequency of unprotected sex odds ratio (OR) for condom (yes/no) versus any unprotected sex (yes/no) = 0.26, they appear to capture somewhat different information and only minor attenuation of the hazard ratio (HR) is seen when both are included in the multivariate model. Multiple pregnancies were accounted for by a proportional rates model [8] with robust standard errors. To evaluate the effect of the enhanced family planning services, a generalized estimation equation (GEE) method with Poisson modeling and robust variances was used to compare pregnancy incidence before and after the initiation of the enhanced family planning services. Analyses were performed using SAS version 9.1.3 (SAS Institute, Inc).

Results

A total of 1358 HIV seronegative, HSV-2 seropositive women were analyzed: 392 from South Africa, 602 from Zambia, and 364 from Zimbabwe, for a total of 1758 person-years of follow-up. The median age was 31 years (interquartile range [IQR] 24-39), and there were substantial demographic differences across sites (Table 1). Most women (88.1%) reported a single sexual partner during the prior 12 months; the median number of vaginal sex acts in the prior 3 months was 24 (IQR 10-40). Very few women (1.9%) reported a known HIV positive partner, and most (95.1%) did not know the HIV status of their partners. At enrollment, a minority (6.9%) reported always using male condoms during sex; 58% reported never using condoms in the previous 3 months.

At enrollment, 69.7% of participants used some form of hormonal or barrier contraception, with oral contraceptives more frequently used in Zimbabwe (59.6%). Injectables were more commonly used in South Africa (42.3%). Contraception data were missing for 7.6% of participants.

Pregnancy Incidence, Outcomes, and Risk Factors

A total of 228 pregnancies occurred during the study (incidence 13.2 per 100 woman-years); 195 women had one pregnancy and 15 women had more than one pregnancy (Table 2). As previously reported, randomization to acyclovir was not associated with decreased HIV incidence but was associated with a slightly higher pregnancy incidence (15% vs. 11% per year for acyclovir vs. placebo) [6]. The median time to first pregnancy was 7.9 months (IQR 4.9-12.8). A total of 109 live births were reported. The highest proportion of full-term live births occurred in the Zambia site and highest proportion of elective terminations occurred at the South Africa site. Of 228 positive pregnancy tests, 59 (25.9%) were negative on repeat testing at the next monthly visit. Of these, 41 were miscarriages, 14 were elective terminations and 4 had no reported outcome. After implementation of enhanced family planning counseling and availability of on-site family planning methods, pregnancy incidence was modestly reduced (from 15.9 to 12.8 per 100 woman-years, $p=0.23$). The enhanced family planning services appeared to have a greater effect in reducing pregnancy incidence at the South Africa (from 14.9 to 9.6 per 100 woman-years) and Zambia sites (from 21.1 to 17.8 per 100 woman-years) than at the Zimbabwe site (from 6.7 to 8.6 per 100 woman-years), although throughout the study pregnancy incidence was lower at the Zimbabwe site. Pregnancy (and thus missed study drug) accounted for only 4% of study woman-years for female trial participants.

In multivariate analysis (Table 3), there was a decreased pregnancy incidence with increasing age, with higher risk for women <25 years of age. Oral contraceptives, injectable contraceptives, and IUDs were each associated with decreased pregnancy risk; there was some indication, in a separate analysis, that oral contraceptives were slightly less protective against pregnancy than injectable methods (adjusted hazard ratio [HR] for pregnancy, oral vs. injectables 2.21, 95% confidence interval 1.29-3.80, $p=0.004$). Self-reported condom use as the primary contraceptive method was not associated with a statistically significant decrease in pregnancy (HR 0.67, $p=0.09$). However, the number of unprotected vaginal sex acts was significantly associated with pregnancy, while other measures of sexual behavior (number of sexual partners, number of total sex acts), education, and income were not associated with pregnancy risk.

Pregnancy, Contraceptive Use, and HIV Acquisition

Seventy-two women acquired HIV during follow-up (incidence 4.0 per 100 woman-years). There was significant heterogeneity in HIV incidence across the three sites: 4.8, 4.7, and 2.1 per 100 woman-years among South African, Zambian, and Zimbabwean participants,

respectively ($p=0.01$). In multivariate analysis, younger women (<21 years), women who reported new partners in the previous 3 months, and who had bacterial vaginosis (HR 2.03 for Nugent's score ≥ 7 compared with Nugent's score ≤ 3 [9]) were at higher risk of HIV acquisition (Table 4). Other genital tract infections, including GUD observed on examination during clinic visits, were not associated with increased HIV risk. The frequency of self-reported unprotected vaginal sex was also not related to HIV risk. Contraceptive methods, including hormonal methods, were not associated with increased HIV risk, although there was a statistical trend for women who used condoms as their primary contraceptive method to be at reduced risk for HIV (HR 0.31, $p=0.06$). Pregnancy was not associated with HIV risk in univariate analysis or, in a separate analysis, when added into the multivariate model in Table 4 (multivariate HR 0.64, 95% CI 0.23-1.80; $p=0.40$).

Discussion

In this large HIV prevention trial, which included 1358 women followed for up to 18 months from three urban sites in southern Africa, pregnancy and HIV incidence were 13.2 and 4.0 per 100 woman-years, respectively. Contraceptive use reduced the risk of pregnancy, particularly longer-acting contraceptive methods. Neither being pregnant nor use of hormonal methods of contraception was associated with increased risk of HIV acquisition.

The overall pregnancy rate and consequent woman-time off study product observed in this study were similar to the estimates in the pre-trial sample size calculations and thus did not reduce the study's statistical power to measure the efficacy of acyclovir in reducing HIV acquisition. Interestingly, intensified provision of family planning counseling and access to free contraceptive methods on-site only modestly reduced the pregnancy incidence overall, with the effect concentrated at two of the three sites with higher rates of pregnancy. Other recently-completed HIV prevention trials have reported similar or lower overall pregnancy rates: 6.6 per 100 woman-years in the treatment arm and 8.2 per 100 woman-years in the control arm in the Carraguard microbicide trial [10] and 11.3 per 100 woman-years in HPTN 035 [11]. However, a phase II pre-exposure prophylaxis trial among commercial sex workers found a much higher pregnancy incidence (52 per 100 woman-years) [12].

High pregnancy incidence in biomedical HIV prevention trials has the potential to adversely impact study statistical power, as women are often taken off the product during pregnancy. In addition, discontinuation of study products due to pregnancy precludes evaluation of the efficacy and safety of the products among pregnant women and their infants, creating a dilemma for eventual public health promotion of these interventions, if proven efficacious in clinical trials [13]. For our study, women were discontinued from study drug during pregnancy, a conservative approach given long-standing experience with use of acyclovir in pregnant women, including no suggestion of increased congenital abnormalities from registry data from the US and Europe [14]. Finally, pregnancy testing conducted with reported amenorrhea and at scheduled quarterly visits in our study artificially inflated the pregnancy rate by indentifying "chemical" pregnancies that would otherwise be spontaneously lost early. Monthly pregnancy testing, as is being conducted in some HIV prevention trials (e.g., those testing antiretroviral pre-exposure prophylaxis), will likely result in higher numbers of "chemical" pregnancies. This is a challenge for any prevention trial that includes frequent, scheduled pregnancy testing in the protocol to minimize maternal and fetal exposure to candidate oral or topical products. About one-third of pregnancies in this study were reported to be miscarriages, which would be in agreement with this hypothesis; the elective termination rate may have been underestimated, given that these were only legal in South Africa.

Use of modern contraceptive methods (oral contraceptive pills, injectable hormonal methods, and IUDs) was associated with decreased pregnancy incidence in our population. Notably,

longer-acting methods (injectables, IUD) were more effective in preventing pregnancy than oral contraceptive pills, emphasizing the importance of user-independent methods for contraception [15]. Condom use as a primary contraceptive method was relatively uncommon in the cohort, and thus the statistical power to detect a protective effect of condoms for pregnancy or HIV was modest. However, condoms were associated with statistical trends for decreased risk of pregnancy and HIV in multivariate models, although the confidence intervals for these risk estimates were wide.

We found no association between being pregnant or using hormonal contraceptives and increased risk of HIV acquisition in our population. These findings are in contrast to some, but not all, earlier prospective studies that have suggested that pregnancy and contraceptive use may increase women's HIV risk [4,5]. One recent study [16] among women from the general population found marked increased HIV risk for HSV-2 seronegative women who used oral contraceptive pills or the injectable progestin depot medroxyprogesterone acetate (HR 2.48 and 4.96, respectively), with no increased risk for HSV-2 seropositive women. However, another study among sex workers [17] found a modest increase in HIV risk (HR 1.5-1.7) overall with no difference by HSV-2 status. Participants in our study were all HSV-2 seropositive by protocol design, so cannot contribute information about the effects of hormonal contraception among HSV-2 negative women. Effective contraception and safe pregnancies are essential for women at risk for HIV, and continued study of the interaction between contraception, pregnancy, and HIV risk is important for informed counseling of women in areas where HIV is prevalent.

Younger women were at high risk of both HIV acquisition and pregnancy in our study, and those with new partners were at higher risk for HIV. These demographic and behavioral findings suggest areas to target HIV and pregnancy counseling in HIV prevention clinical trials. Bacterial vaginosis was also associated with increased HIV risk; bacterial vaginosis is the most common vaginal infection in African populations, with prevalences that can range from 15 to 70% [18,19]. A meta-analysis of 23 studies which included 30,739 women, showed that bacterial vaginosis increased the risk of HIV acquisition by 60% (RR= 1.6, 95% CI 1.2-2.1), and given its high prevalence, was calculated to explain 15% of HIV infections in that combined population [18]. Other STIs were not associated with HIV risk, although these were measured only at study enrollment. Notably, genital ulcers, identified on quarterly genital exams, were also not associated with increased risk of HIV infection in our cohort of HSV-2 seropositive women.

Biomedical HIV prevention trials must frequently balance a need to enroll a population at high risk for HIV with minimizing time off study product due to pregnancy. Our results demonstrate that some factors, particularly younger age, may be associated with increased risk for both pregnancy and HIV. Some HIV prevention trials have limited recruitment to women using dual contraceptive methods (i.e., an effective method such as hormonal contraception, plus condoms) in order to minimize pregnancy incidence within trials. This approach will not ensure that no pregnancies occur, as women may elect to discontinue contraception after trial enrollment and contraceptive use may not reduce pregnancy risk entirely. Moreover, limiting trial participation to women using contraception may reduce the generalizability of the trial results. Contraception counseling and provision should continue to be a high priority for study sites conducting biomedical HIV prevention trials.

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Table 1

Enrollment Demographic and Behavior Characteristics

	South Africa			Zambia			Zimbabwe			Total	
	N	%		N	%		N	%		N	%
Total enrolled	392	100		602	100		364	100		1358	100
Age Group											
<21	26	6.6		53	8.8		27	7.4		106	7.8
21 - 24	84	21.4		91	15.1		69	19.0		244	18.0
25 - 29	83	21.2		119	19.8		69	19.0		271	20.0
30 - 34	78	19.9		92	15.3		77	21.2		247	18.2
>35	121	30.9		247	41.0		122	33.5		490	36.1
Marital Status											
Married with one wife	87	22.2		493	81.9		324	89.0		904	66.6
Married with more than one wife	19	4.8		46	7.6		27	7.4		92	6.8
Never married	256	65.3		19	3.2		3	0.8		278	20.5
Divorced/widowed	30	7.7		44	7.3		10	2.8		84	6.2
Living											
Alone	25	6.4		19	3.2		9	2.5		53	3.9
With male partner	205	52.3		528	87.7		340	93.4		1073	79.0
Other	162	41.3		55	9.1		15	4.1		232	17.1
Education level											
None	3	0.8		55	9.1		-	-		58	4.3
Some or completed primary school	35	8.9		352	58.5		90	24.7		477	35.1
Some or completed secondary school	312	79.6		189	31.4		270	74.2		771	56.8
Higher than secondary	42	10.7		6	1.0		4	1.1		52	3.8
Any monthly income of own	154	39.3		70	11.6		57	15.7		281	20.7
Partner own income											
Don't know/Missing	171	45.4		61	10.1		10	2.7		249	18.3
Yes	190	48.5		347	57.6		264	72.5		801	59.0
No	24	6.1		194	32.2		90	24.7		308	22.7

	South Africa			Zambia			Zimbabwe			Total		
	N	%		N	%		N	%		N	%	
No. partners – last 12 months, median (IQR)	1	(1,2)		1	(1,1)		1	(1,1)		1	(1,1)	
Known HIV positive partner in past 3 months	2	0.5		19	3.2		5	1.4		26	1.9	
Number of vaginal sex acts in past 3 months, median (IQR)	20	(10/36)		21	(6/36)		36	(24/50)		24	(10/40)	
Condom use with last 3 partners in past 3 months												
Always	27	6.9		53	8.8		14	3.8		94	6.9	
Sometimes *	157	40.1		202	33.6		77	21.2		436	32.1	
Never	203	51.8		322	53.5		262	72.0		787	58.0	
Missing/No acts	5	1.3		25	4.2		11	3.0		41	3.0	
Contraceptive use at Enrollment												
Oral	82	20.9		126	20.9		217	59.6		425	31.3	
Injectable	166	42.3		64	10.6		48	13.2		278	20.5	
IUD	5	1.3		0	0.0		1	0.2		6	0.4	
Condom	48	12.2		52	8.6		13	3.4		113	8.3	
Other **	28	8.5		50	8.3		47	12.9		125	9.2	
None	63	16.1		207	34.4		38	10.4		308	22.7	
Missing	0	0.0		103	17.1		0	0.0		103	7.6	

IQR = interquartile range

* Sometimes = Total number of vaginal sex is greater than total number of condom use

** Other = menopause, hysterectomy, tubal ligation

Table 2

Pregnancy Incidence and Outcomes

	South Africa		Zambia		Zimbabwe		Total	
	N	%	N	%	N	%	N	%
Total number of pregnancies	47	100	139	100	42	100	228	100
Number of women with 1 pregnancy	37		118		40		195	
Number of women with >1 pregnancy	5		9		1		15	
Time from enrollment to first pregnancy in months, median (IQR)	7.0	(3.7/12.1)	7.8	(5.0/12.8)	8.9	(4.9/13.8)	7.9	(4.9/12.8)
Pregnancy incidence throughout follow-up (per 100 woman-years)	9.9		18.3		8.4		13.2	
Pregnancy outcome								
Full term live birth	15	31.9	67	48.2	27	64.3	109	47.8
Premature live birth	-	-	2	1.4	1	2.4	3	1.3
Fetal death/still birth	1	2.1	2	1.4	1	2.4	4	1.8
Miscarriage	15	31.9	42	30.2	12	28.6	69	30.3
Ectopic pregnancy	2	4.3	-	-	-	-	2	0.9
Elective termination	14	29.8	2	1.4	-	-	16	7.0
Missing	-	-	24	17.3	1	2.4	25	11.0

Table 3

Risk Factors for Pregnancy

	Univariate			Multivariate		
	HR	95% CI	p-value	HR	95% CI	p-value
Age						
<21	Ref	Ref	Ref	Ref	Ref	Ref
21-24	0.81	(0.53, 1.24)	0.34	0.77	(0.49, 1.19)	0.23
25-29	0.54	(0.35, 0.84)	0.006	0.59	(0.37, 0.93)	0.02
30-34	0.57	(0.36, 0.90)	0.015	0.57	(0.36, 0.91)	0.02
≥35	0.18	(0.11, 0.29)	<0.0001	0.19	(0.12, 0.31)	<0.0001
Marital status						
Married, husband has one wife	Ref	Ref	Ref	Ref	Ref	Ref
Married, husband has more than one wife	0.60	(0.32, 1.14)	0.121	0.79	(0.41, 1.52)	0.48
Never married/divorced /widowed	1.59	(1.08, 2.33)	0.019	1.57	(0.87, 2.83)	0.14
Living with male partner vs. alone/other	0.90	(0.63, 1.30)	0.58			
Education Level						
None	Ref	Ref	Ref			
Higher than secondary	0.99	(0.33, 2.94)	0.99			
Some or completed secondary school	1.61	(0.85, 3.05)	0.14			
Some or completed primary school	1.07	(0.57, 2.00)	0.84			
Any monthly income of own (Yes vs. No)	1.1	(0.78, 1.56)	0.59			
Partner own income						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.42	(1.01, 1.99)	0.04	1.10	(0.77, 1.55)	0.61
Don't know/missing	1.54	(0.96, 2.46)	0.07	0.75	(0.41, 1.38)	0.36
Number of partners in last 12 months						
1	Ref	Ref	Ref	Ref	Ref	Ref
>1	1.32	(0.84, 2.07)	0.23	1.01	(0.63, 1.59)	0.98
Missing	3.4	(1.05, 11.04)	0.04	3.26	(0.98, 10.8)	0.05
Any GUD on examination in last 3 months	1.15	(0.80, 1.67)	0.45			
Any new partners in last 3 months (Yes vs. No)	1.24	(0.51, 3.06)	0.63			
Any HIV+ partners in last 3 months (Yes vs. No)	1.03	(0.50, 2.09)	0.94			

	Univariate			Multivariate		
	HR	95% CI	p-value	HR	95% CI	p-value
Total vaginal sex acts in last 3 months						
<8	Ref	Ref	Ref			
8-24	1.20	(0.82, 1.75)	0.35	1.16	(0.77, 1.77)	0.48
24-36	1.64	(1.13, 2.40)	0.01	1.45	(0.87, 2.41)	0.16
>36	1.50	(1.01, 2.23)	0.04	1.08	(0.51, 2.27)	0.84
Unprotected vaginal sex acts in last 3 months						
0	Ref	Ref	Ref			
1-12	3.78	(2.33, 6.13)	<0.0001	3.97	(2.43, 6.49)	<0.0001
12-36	3.50	(2.16, 5.69)	<0.0001	3.18	(1.83, 5.54)	<0.0001
>36	4.04	(2.38, 6.87)	<0.0001	4.06	(1.75, 9.40)	0.001
Contraceptive						
None	Ref	Ref	Ref	Ref	Ref	Ref
Oral	0.40	(0.27, 0.59)	<0.0001	0.31	(0.21, 0.46)	<0.0001
Injectable	0.19	(0.11, 0.33)	<0.0001	0.13	(0.07, 0.22)	<0.0001
IUD/other	0.23	(0.07, 0.74)	0.01	0.27	(0.08, 0.87)	0.03
Condom	0.58	(0.37, 0.91)	0.02	0.67	(0.42, 1.07)	0.09
Menopause	0.00	(0.00, 0.00)	0.97	0.00	(0.00, 0.00)	0.97
Missing	4.36	(3.02, 6.29)	<0.0001	3.19	(2.21, 4.62)	<0.0001

Table 4

Risk Factors for HIV Acquisition

	Univariate			Multivariate		
	HR	95% CI	p-value	HR	95% CI	p-value
Age						
<21	Ref	Ref	Ref	Ref	Ref	Ref
21-24	0.40	(0.19, 0.83)	0.01	0.41	(0.19, 0.87)	0.02
25-29	0.41	(0.20, 0.83)	0.01	0.46	(0.22, 0.98)	0.04
30-34	0.31	(0.14, 0.68)	0.004	0.40	(0.18, 0.90)	0.03
≥35	0.18	(0.09, 0.38)	<0.0001	0.30	(0.14, 0.66)	0.003
Marital status						
Married, husband has one wife	Ref	Ref	Ref	Ref	Ref	Ref
Married and husband with > one wife	0.46	(0.11, 1.90)	0.28	0.46	(0.11, 2.00)	0.30
Never married/divorced/widowed	2.28	(1.21, 4.29)	0.01	1.36	(0.49, 3.76)	0.56
Living with male partner vs. alone/other	0.53	(0.31, 0.93)	0.03	1.07	(0.29, 3.94)	0.92
Education Level						
None	Ref	Ref	Ref			
Higher than secondary	2.04	(0.42, 9.87)	0.37			
Some or completed secondary school	1.42	(0.42, 4.84)	0.57			
Some or completed primary school	1.34	(0.41, 4.44)	0.63			
Any monthly income of own	1.16	(0.65, 2.05)	0.62			
Partner own income						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.21	(0.64, 2.30)	0.56	0.87	(0.45, 1.68)	0.67
Don't know/missing	2.39	(1.11, 5.13)	0.03	1.23	(0.30, 5.04)	0.77
Number of partners in last 12 months						
1	Ref	Ref	Ref	Ref	Ref	Ref
>1	2.21	(1.15, 4.25)	0.02	1.47	(0.73, 2.96)	0.28
Missing	0.00	(0.00, -)	0.99	0.00	(0.00, -)	0.99
Any GUD on exam in last 3 months	1.39	(0.73, 2.67)	0.32			
Any new partners in last 3 months	4.68	(1.94, 11.29)	0.0006	3.91	(1.57, 9.73)	0.003
Any HIV+ partners in last 3 months	0.89	(0.21, 3.72)	0.88			

	Univariate			Multivariate		
	HR	95% CI	p-value	HR	95% CI	p-value
Being pregnant	1.20	(0.48, 3.00)	0.70			
Total vaginal sex in last 3 months						
<8	Ref	Ref	Ref			
8-24	1.02	(0.57, 1.83)	0.93			
24-36	0.92	(0.48, 1.78)	0.81			
>36	0.65	(0.31, 1.38)	0.26			
Unprotected vaginal sex in last 3 months						
0	Ref	Ref	Ref	Ref	Ref	Ref
1-12	1.15	(0.59, 2.25)	0.69	1.02	(0.51, 2.04)	0.95
12-36	1.79	(0.96, 3.32)	0.07	1.78	(0.94, 3.40)	0.08
>36	1.11	(0.46, 2.65)	0.82	1.03	(0.42, 2.49)	0.96
Contraceptive						
None	Ref	Ref	Ref	Ref	Ref	Ref
Oral	0.93	(0.48, 1.82)	0.83	0.91	(0.45, 1.83)	0.80
Injectable	1.01	(0.51, 1.98)	0.98	0.94	(0.46, 1.92)	0.86
IUD/other	0.41	(0.05, 3.11)	0.39	0.55	(0.07, 4.31)	0.57
Condom	0.27	(0.08, 0.94)	0.04	0.31	(0.09, 1.07)	0.06
Menopause	0.21	(0.03, 1.61)	0.13	0.38	(0.05, 3.00)	0.35
Missing	2.36	(1.05, 5.27)	0.04	2.10	(0.92, 4.79)	0.08
Trichomonas						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.89	(0.96, 3.71)	0.07	1.25	(0.60, 2.58)	0.55
Not done/missing	6.32	(0.83, 48.05)	0.07	13.55	(1.51, 121.3)	0.02
Chlamydia						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.10	(0.44, 2.75)	0.83			
Not done/missing	0.36	(0.05, 2.69)	0.32			
Gonorrhea						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	2.43	(0.33, 17.73)	0.38			
Not done/missing	0.37	(0.05, 2.72)	0.33			

	Univariate			Multivariate		
	HR	95% CI	p-value	HR	95% CI	p-value
Bacterial vaginosis (by Nugent's criteria)						
0-3	Ref	Ref	Ref	Ref	Ref	Ref
4-6	1.46	(0.72, 2.94)	0.30	1.16	(0.55, 2.41)	0.70
7-10	2.21	(1.27, 3.88)	0.005	2.03	(1.15, 3.58)	0.02
not done/missing	0.00	(0.00, -)	0.99	0.00	(0.00, -)	0.99