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HIV Acquisition During Pregnancy and Postpartum is Associated with Genital Infections and Partnership Characteristics: A Cohort Study

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Abstract

Objective—To determine the risk and cofactors for HIV acquisition during pregnancy and postpartum.

Design—Prospective cohort study

Methods—Pregnant women in western Kenya were enrolled if HIV seronegative at that visit or within 3 months. Serial HIV nucleic acid amplification tests (NAATs) were conducted at 1–3 month intervals to 9 months postpartum. Genital swabs were collected for detection of chlamydia and gonorrhea at baseline, and for trichomonas, bacterial vaginosis (BV), and yeast at baseline and follow-up.

Results—Among 1304 pregnant women, median age was 22 years, 78% were married for a median of 4 years, 66% reported knowing partner HIV status, and 8% reported using condoms. Study retention was 98%. During 1235 person-years of follow-up, HIV incidence was 2.31/100 person-years (95% Confidence Interval [CI]:0.71–4.10). Incident HIV was associated with syphilis (Hazard Ratio [HR] 9.18, 95% CI:2.15–39.3), chlamydia (HR 4.49, 95% CI:1.34–15.0),

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Competing interests

The authors declare that no competing interests exist

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BV (HR 2.91, 95% CI:1.25–6.76), yeast (HR 3.46, 95% CI:1.46–8.19), STI history (HR 3.48, 95% CI:1.31–9.27), lifetime number of sex partners, (HR 1.19, 95% CI:1.03–1.37), partner age discordance (HR 1.07 per year, 95% CI:1.02–1.13) and shorter marriage (HR 1.19 per year, 95% CI:1.03–1.38). No women with incident HIV reported an HIV-infected partner. In multivariate analyses, chlamydia, older partners, and yeast infection remained significant; however, power was limited.

Conclusions—Pregnant and lactating women may not perceive HIV risk and rarely used condoms. Prevention and treatment of genital infections and risk stratification to identify women for pre-exposure prophylaxis (PrEP) could decrease HIV acquisition in pregnant/lactating women.

Keywords

HIV; incidence; mother-to-child transmission; acute; seroconversion

INTRODUCTION

Tremendous progress has been made in identifying HIV-infected women during pregnancy and initiating them on antiretrovirals for prevention of mother-to-child HIV transmission (PMTCT).[1] These efforts have resulted in a dramatic reduction in infant HIV infections, from 400,000 new infections among children in 2009 to 240,000 in 2013.[2, 3] However, PMTCT interventions predominantly target women with chronic HIV infection. Women in the “window period” prior to HIV seroconversion and those who acquire HIV infection after their first antenatal HIV test may go unrecognized and fail to receive PMTCT interventions.

Several, but not all, studies have noted increased HIV incidence during pregnancy and/or the postpartum period.[4–8] Epidemiologic approaches to determine the influence of pregnancy and postpartum period on risk of HIV acquisition are challenged by difficulties in defining an appropriate comparison group. A recent meta-analysis using data from 19 cohorts representing 22,803 total person-years of follow-up reported a pooled HIV incidence rate of 3.8/100 person-years (95% Confidence Interval [CI]:3.0–4.6) during pregnancy or postpartum.[4] Increased susceptibility to HIV during pregnancy/postpartum could result from hormonal changes that alter genital mucosal surfaces or distribution of target cells at these surfaces [9–11]. Behavioral factors may also play a role if male partners seek other partners during pregnancy or postpartum and bring HIV back to the relationship.[12, 13]

Previous studies of HIV acquisition during pregnancy and postpartum have not utilized detailed longitudinal sampling with serial sensitive assays to detect HIV, nor comprehensively evaluated genital infections and sexually transmitted infections (STIs) as risk factors in pregnant or postpartum cohorts. Additionally, women presenting to antenatal care (ANC) clinics have distinct social, demographic, sexual networks, and partnership characteristics that may influence cofactors of HIV acquisition. While women are recognized to be at risk for HIV acquisition during and after pregnancy, it remains important to estimate magnitude and define cofactors of risk - the first step to developing sensible preventive strategies for this large population of women. We determined rates and cofactors of incident HIV among HIV-uninfected women to characterize mechanisms for risk during and after pregnancy.[14]

METHODS

Study design and population

Between May 2011 and June 2013, we recruited HIV-seronegative pregnant women seeking ANC at the Ahero sub-District and Bondo District Hospitals in rural western Kenya into a prospective cohort study. Women were eligible for inclusion if they were pregnant, 14 years of age, had a documented HIV-negative rapid HIV test at enrollment or 3 months prior during routine care, planned to reside in the study area until 9 months postpartum, would provide locator information and have a home visit, and were not participating in other research. Women who were 28–36 weeks gestation, calculated by last menstrual period, were initially eligible; eligibility criteria were expanded to include women 14–28 weeks gestation in June 2011, >36 weeks gestation in November 2011 and <14 weeks gestation in March 2012. Gestational age eligibility criteria were broadened to increase enrollment, and generalize to women throughout the pregnancy/postpartum continuum. Enrollment at <14 weeks gestation required a protocol modification to incorporate urine pregnancy test confirmation. Study retention efforts included calling women by phone three times for missed study visits, followed by calling contacts provided by participants and conducting home visits (if necessary). All study procedures were approved by the Kenyatta National Hospital/University of Nairobi Ethical Research Committee and the University of Washington Institutional Review Board prior to study initiation.

Clinical procedures

Eligible women interested in study participation provided written informed consent. Women were scheduled for follow-up during pregnancy (20, 24, 32, 36 weeks gestation) and postpartum (2, 6, 10, 14 weeks; 6 and 9 months). At study visits, women had blood collected for HIV RNA nucleic acid amplification tests (NAATs), self-collected vaginal swabs, physical exams, and completed questionnaires to assess maternal health, sexual behavior, and vaginal washing and drying practices. At enrollment, women had a vaginal swab collected for chlamydia (CT) and gonorrhea (GC) testing. STIs were treated following microbiologic diagnosis using antimicrobial regimens in Kenyan guidelines.[15] After December 19, 2011 HIV NAAT assays were performed at enrollment; 28 and 36 weeks gestation; and 6, 14, 24, 36 weeks postpartum. All women with incident HIV were offered lifelong antiretroviral therapy (ART), Option B+, which began being implemented in Kenya in 2013 for all pregnant women.

Laboratory procedures

HIV NAATs were performed at the HIV Research Laboratory at Kenya Medical Research Institute (KEMRI)/Centers for Disease Control and Prevention in Kisumu, Kenya using the Roche COBAS Ampliprep and COBAS TaqMan HI2CAP platforms. This method of HIV detection is highly sensitive for detection of acute HIV in the “window period”.[16, 17] Pools of ten samples were tested via NAATs; individual samples were retested if pooled results were positive, followed by HIV viral loads to confirm positive results. Self-collected vaginal swabs were tested at the University of Nairobi/Washington Research Laboratory at Coast Hospital in Mombasa, Kenya for CT and GC using polymerase chain reaction (PCR) technology and Gen-Probe APTIMA Combo2 (GC/CT) kits and for trichomoniasis and

bacterial vaginosis (BV). Detection of *Trichomonas vaginalis* (TV) was by wet microscopy in clinic. Women with a Nugent score >7 were diagnosed with BV. Syphilis serology (rapid plasma reagin tests) were conducted during routine ANC, or by study staff if results were not available.

HIV incidence definitions

All HIV infections detected during the study were considered incident infections, with three distinct types of incident infection. Pregnant women with a documented negative rapid HIV tests 3 months prior to enrollment and positive NAAT and rapid HIV tests were classified as having seroconversion at enrollment, whereas pregnant with HIV rapid negative and NAAT positive results were classified as having acute infection at enrollment. Incidence rates for seroconversions and acute infections at enrollment were calculated according to the Serologic Testing Algorithm for Recent HIV Seroconversion.[18] These incidence rates are calculated as: number with incident infection (Ninc), divided by the window period in days (w), multiplied by 365, and dividing this figure by the number at risk ($[365 \times Ninc/w] / [\text{number at risk} \times 1 \text{ year}]$). HIV-uninfected women and women with a seroconversion or acute infection at enrollment were included. Incidence rates per 100 person-years were based on assay window periods of 48 and 28 days for seroconversions and acute infections at enrollment, respectively.[19] Women with HIV-negative rapid tests and NAAT at enrollment, but NAAT positive at a follow-up visit were classified as having acute infection during follow-up. Incidence rates for acute infection in follow-up were calculated based on number of infections per 100 person-years of follow-up. Overall incidence rates were weighted averages of incidence rates for seroconversion at enrollment, acute infection at enrollment, and acute infection during follow-up.

Statistical analysis

We anticipated enrolling 1730 women, accumulating 60 incident HIV infections assuming an incidence of 3% per year. This sample size would give 80% power to detect a 2.1–2.3-fold difference in HIV risk for an exposure with a prevalence of 25–50%, respectively, assuming a two-sided test ($\alpha=0.05$). Due to slower enrollment, the sample was limited to 1304.

Timing of HIV was recoded as the midpoint between the last negative and first positive NAAT and incident HIV infections detected at enrollment were recoded as being infected at 0.5 days for inclusion in Cox proportional hazards models. Univariate Cox proportional hazards regression models were used to identify cofactors associated with maternal HIV acquisition in a complete case analysis. Multivariate imputation by chained equations, which account for within-cluster correlation for time-varying covariates, were used to create ten datasets to multiply impute missing values for the multivariate model covariates. Missing data were assumed to be missing at random. This approach is flexible in that it does not require the conditional distributions to be normal, and has been shown to perform similarly to a multivariate normal imputation when variously scaled variables are involved.[20] Multivariate Cox proportional hazards regression modeling was performed on each of the ten imputed datasets, and final coefficient estimates were produced by averaging the ten imputed regression coefficients for each covariate. Missing values were imputed for the

following variables: CT, syphilis, yeast infection, BV, partner age difference, and lifetime number of sex partners. Variables identified as *a priori* cofactors (age, STIs, and BV) were included in an initial multivariate model along with any cofactor in univariate analyses with $p < 0.15$; variables not associated with HIV acquisition at the $p < 0.15$ level in the multivariate model were dropped from the final model as a group. Coital frequency was calculated as the number of sexual acts women reported in the month before the study visit (and prior to HIV detection) multiplied by the number of months between visits; total coital frequency was calculated as the sum of monthly coital frequency over the duration of the study for each woman who acquired HIV. Per coital act risk of HIV acquisition was modeled for all women using generalized estimating equations with a Poisson distribution, log link, and exchangeable covariance matrix. Statistical analyses were performed using Stata version 13.1 (College Station, TX).

RESULTS

Study population

At the Ahero and Bondo maternal child health (MCH) clinics, 4245 women sought ANC and 3408 (80%) were HIV-seronegative (Figure 1). Among 2351 HIV-seronegative women eligible for participation, 1304 (55%) were enrolled. Median age was 22 years and median duration of education was 8 years (Table 1). Median gravidity was 2 and age of sexual debut was 16 years. The majority (78%) of women were married, 14% in polygamous relationships, and the median relationship duration was 4 years. Unprotected sex among sexually active women in the month before enrollment was common (92%) and 8 (1%) of 782 women reported having multiple partners. Male partners were older than women (median 5 years older). While 879 of 1203 (73%) women reported that their partner was tested for HIV, only 1% of women knew their partner was HIV-infected and 28% did not know their partner's HIV status. Study retention to 9 months postpartum was high (98%).

HIV incidence

After 1235 person-years of follow-up, 25 women were identified with incident HIV infections: 7 seroconversions and 3 acute infections at enrollment, and 15 acute infections during follow-up (2 during pregnancy, 13 postpartum) (Figure 2). Mean duration of follow-up was 0.95 person-years. The overall incidence rate was 2.31 per 100 person-years (95% CI: 0.71–4.10); the incidence rate of acute infection during follow-up was 1.21 (95% CI: 0.73–2.01). During pregnancy, the incidence rate was 3.44 per 100 person-years (95% CI: 0.60–6.63) compared to 1.40 (95% CI: 0.81–2.42) during the postpartum period ($p = 0.6$). Symptoms of primary infection, including sore throat, swollen glands, headache, malaise, vomiting, diarrhea, fever, or macular papular rash, were reported by 7 (28%) women. None of the women with incident infection reported having an HIV-infected partner at baseline; 12 (48%) reported that their partner was HIV-negative and 13 (52%) had a partner of unknown status. Risk of HIV acquisition was 0.51 per 1000 coital acts during pregnancy, similar to the postpartum period (0.42) ($p = 0.8$).

STIs and genital tract infections

The most common STIs at baseline were TV and CT (both 6%), followed by GC (3%) and syphilis (1%). Co-infection with two STIs was identified in 22 women: 12 with TV and CT, 3 with TV and GC, 5 with CT and GC, 1 with CT and syphilis, and 1 with TV and syphilis. Nearly one-fourth (23%) of women were diagnosed with BV at baseline, and 25% had yeast infections.

Cofactors for HIV incidence

Risk factors for HIV incidence are shown in Table 2. Both prior history and diagnosis of STIs in pregnancy were significantly associated with HIV acquisition. Women who reported a history of STIs were 3 times more likely to acquire HIV than women without a history of STIs (Hazard Ratio [HR] 3.48, 95% CI: 1.31–9.27; $p=0.01$). CT (HR 4.49, 95% CI: 1.34–15.0; $p=0.02$), and syphilis (HR 9.18, 95% CI: 2.15–39.3; $p=0.003$) at enrollment, and BV (HR 2.91, 95% CI: 1.25–6.76; $p=0.01$) and yeast infection (HR 3.46, 95% CI: 1.46–8.19; $p=0.005$) at enrollment or follow-up, were also associated with HIV incidence. Prevalence of other STIs (GC, TV) were similar between HIV-infected and -uninfected women. HIV risk was higher among women in shorter relationships (HR 1.19 for each year), with older male partners (HR 1.07 for each year older), and with higher lifetime number of sexual partners (HR 1.19 for each additional partner). Among married women, shorter duration of marriage was also a significant risk factor. Marital status, partner HIV status, partner circumcision status, maternal age, educational level, age at sexual debut, history of commercial sex, and vaginal washing or drying practices did not differ between HIV-infected and uninfected women. .

We imputed values for independent variables with missing data. The percent missing values were as follows: syphilis (21.1%), BV (18.1%), partner age difference (17.8%), yeast infection (17.4%), TV (17.4%), CT (0.3%), and lifetime number of sex partners (0.2%). In the multivariate model, having an older partner (HR 1.06, 95% CI: 1.00–1.13; $p=0.04$), CT (HR 4.49, 95% CI 1.34–14.2; $p=0.01$), and yeast infection (HR 2.78, 95% CI 1.17–6.63; $p=0.02$) remained significant cofactors for HIV.

DISCUSSION

We found high HIV incidence rates during pregnancy and postpartum; a period when women can transmit the virus to their infants. Our HIV incidence estimate is consistent with other studies in Africa and a recent meta-analysis [5–8], and is comparable to those seen in discordant couples and sex workers, suggesting that pregnancy and postpartum is a period of appreciable susceptibility to HIV.[21, 22] Risk per coital act was also high, ~0.5 per 1000, considering that partner HIV serostatus was not directly measured and this estimate includes women whose partners were HIV-uninfected. Per coital risk among pregnant and lactating women in serodiscordant couples is ~1 per 1000,[23] and estimated at 0.38 per 1000 among women in low income countries.[24] Importantly, our study identified for the first time, key risk factors for acquiring HIV in this population. Syphilis was associated with a 9-fold increased risk and CT with a >4-fold increased risk of HIV in women. In addition, BV and yeast infection were associated with ~3-fold increased risk of acquiring HIV. Women with a

history of STIs had higher risk as did women in age-discordant partnerships and shorter duration of marriage.

Women who acquire HIV in pregnancy and postpartum acquire HIV in one of three scenarios – first, increased mucosal susceptibility in the context of a stable partnership with an HIV-infected partner, second, due to a recent partner HIV infection through external partnerships, and third by having a new HIV-infected partner. Our finding that syphilis and CT were risk factors for HIV suggests that some infections were from an external partner. Our finding of increased HIV risk with BV and yeast infection suggest that for some women, HIV acquisition occurred in an undiagnosed chronic serodiscordant relationship, in which women had increased mucosal susceptibility due to vaginal infections. Age-discordance and short duration of partnership may be proxies for unknown partner HIV status or increased likelihood of external partnerships.

Women with STIs and genital infections were more likely to have incident HIV, with large effect sizes that were highly significant. There is substantial evidence that STIs increase the likelihood of acquiring HIV; however, this has not been studied in context of pregnancy and postpartum.[25, 26] Importantly, routine screening for STIs other than syphilis is not performed in ANC in many regions.[27] Laboratory diagnosis for STIs/genital infections is largely unavailable and health providers rely on syndromic management, which has poor diagnostic performance.[28, 29] Yeast infections are more prevalent during pregnancy and our finding of a 3.4-fold increased for HIV acquisition with yeast infection may reveal one potential mechanism for susceptibility to HIV in pregnancy. Our findings reinforce the need to integrate STI services in MCH clinics, particularly in high HIV prevalence settings, and develop low-cost diagnostics to detect STIs and genital infections, which may contribute to decreased risk of HIV and prevent other adverse MCH outcomes.

Partnership characteristics were associated with HIV acquisition in our study. Women with age-discordant partnerships (young women-older men) had higher HIV risk, as has been seen in other populations.[30–32] Shorter duration of marriage was also associated with HIV risk. Less than 10% of women reported using condoms, which may indicate women and their partners perceive low risk of HIV acquisition. Male partner HIV testing could identify men who need ART to reduce infectiousness; [33] however, uptake remains low and few men accompany women to ANC for testing.[34, 35] In our study, a third of the women did not know their partners' HIV status despite repeated encouragement from study clinicians to have their partners tested. Home-based approaches may increase male HIV testing and treatment.[36] It was notable that *none* of the women in our study who became HIV-infected reported having a seropositive partner. Conversely, none of the women with known HIV-infected partners became infected, likely because of taking precautions to minimize transmission. Thus, in the antenatal/postpartum setting, women in known HIV serodiscordant relationships may be a relatively low risk compared the large number of women with unknown partner status. Prioritizing partner HIV testing and treatment will continue to be important to protect women from HIV during pregnancy and postpartum.

Primary HIV prevention in women is the first of four prongs recommended by the World Health Organization (WHO) for effective PMTCT.[37] However, there are challenges in

implementing strategies to keep HIV-uninfected women from acquiring HIV in pregnancy or postpartum. Pre-exposure prophylaxis (PrEP) could be considered for HIV-uninfected pregnant and breastfeeding women, especially those unable to negotiate mutual monogamy or condom use. Although PrEP is effective in preventing HIV acquisition, data from pregnant and postpartum women are limited.[21] In the Partners PrEP study, the most common reason for not dispensing study medication was pregnancy.[21] Given PrEP efficacy among adherent women, but balancing potential concerns regarding the fetus/infant, identification of “high risk” pregnant/postpartum women may be useful to limit PrEP provision to those who are most likely to acquire HIV, for example, women with STIs and shorter relationships. Studies to explore risk scores that identify subgroups to consider for PrEP in pregnancy/postpartum may be useful.

Our findings of high HIV incidence during pregnancy reinforce need for repeat HIV testing in PMTCT programs. Although WHO guidelines recommend repeat HIV testing, few programs offer repeat HIV testing.[38] Repeat testing is recommended in regions with HIV incidence of >1 per 1000 person-years and is highly acceptable and cost-effective.[6, 39–41] In a recent US study, 97% of women offered retesting in pregnancy accepted.[40] In Kenya, ~95% of >2,000 women accepted HIV retesting at 6 weeks postpartum.[6] However, repeat testing is infrequently performed due to erratic availability of test kits, concerns of increased workload, late ANC initiation and low emphasis by programs.[6, 40] Addressing these challenges would enhance early detection of incident maternal HIV infections and enable prompt ART initiation to decrease vertical HIV transmission. Clinical detection of acute HIV is poor - symptoms are often non-specific or absent.[42] In our study, only 28% of women with incident HIV were symptomatic. HIV RNA testing has higher sensitivity and specificity to detect acute HIV than serologic tests. [43, 44] While widespread use of maternal NAAT assays by PMTCT programs is restricted by cost, this could be lowered by pooling samples (\$2 per specimen).[45–47] However, RNA testing requires sophisticated laboratories and does not have a rapid turn-around time. As early infant diagnosis programs introduce new point-of-care viral testing for infants in the future, these could be expanded for detection of maternal HIV.

Our study had several strengths. The prospective cohort design enabled detection of incident HIV throughout pregnancy and postpartum, with frequent sampling to determine timing of acquisition. Retention was high (98%) and we used a highly sensitive test, which detects infections soon after infection. We prospectively evaluated demographic, clinical, and behavioral characteristics associated with HIV acquisition and included time-varying covariates in our model, using robust imputation methods to account for missing data. However, our study had some limitations. HIV incidence may be underestimated, due to HIV prevention counseling or selection bias among women who elect to participate in a longitudinal study.[48] The number of incident infections detected was also small and may have limited power to detect associations in our adjusted model, particularly those cofactors of lower prevalence. We did not perform longitudinal testing for CT, GC, and syphilis; thus, associations between these STIs and HIV acquisition is based on baseline STI prevalence. TV diagnosis was based on wet mount microscopy, which has poor sensitivity (60%) compared to PCR assays.

In summary, we found high HIV incidence in pregnant and postpartum women without evidence for increased incidence in pregnancy versus postpartum and with strong associations with genital infections and partner characteristics. Our findings are important to inform new strategies for HIV prevention in this vulnerable population.

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Figure 1.

Study Recruitment, Eligibility, and Enrollment.¹ Included 429 women rebooked to come back at a later date, 176 women who consulted their male partner, and 39 women who wanted to think about it.² Includes women who completed the last study visit or acquired HIV at or prior to study exit; 20 women were lost to follow-up and 5 refused to continue study participation.

IR = incidence rates; CI = confidence interval; P36 = 36 weeks gestation

Figure 2.

Timing of detection of HIV infection and incidence rates during pregnancy and postpartum

Figure 3.

Cumulative risk of HIV acquisition during pregnancy and postpartum, by risk factor a) age, b) marriage duration, c) chlamydia d) syphilis, e) bacterial vaginosis, f) history of sexually transmitted infection (STI). Parentheses indicate number of HIV infections between each risk period.

Table 1

Baseline Characteristics (N=1304)

<i>Demographic Characteristics</i>	All Women (n=1304)		HIV-Infected Women (n=25)		HIV-Uninfected Women (n=1279)	
	N	Median (IQR) ¹ or n (%)	N	Median (IQR) ¹ or n (%)	N	Median (IQR) ¹ or n (%)
Age (years)	1304	22 (19–27)	25	21 (19–24)	1279	22 (19–27)
Education (years)	1304	8 (7–10)	25	8 (7–11)	1279	8 (7–10)
Married	1304	1022 (78)	25	19 (76)	1279	1003 (78)
Polygamous relationship	1022	146 (14)	19	6 (32)	1003	140 (14)
Marriage duration (years)	1049	4 (1–8)	19	1 (0–5)	1030	4 (1–8)
Gravidity	1304	2 (1–4)	25	2 (1–2)	1279	2 (1–4)
Gestational age	1304	27 (22–31)	25	26 (23–28)	1279	27 (22–31)
<i>Partner Characteristics</i>						
Has current partner	1303	1202 (92)	25	25 (100)	1278	1177 (92)
Partner age difference (years older)	1060	5 (3–8)	23	9 (5–9)	1037	5 (3–8)
Partner circumcised	1172	364 (31)	22	7 (32)	1150	357 (31)
Partner HIV tested	1203		25		1178	
Yes		879 (73)		14 (56)		865 (73)
No		162 (13)		4 (16)		158 (13)
Unknown		162 (13)		7 (28)		155 (13)
Partner HIV status	1203		25		1178	
Negative		844 (70)		12 (48)		832 (71)
Positive		18 (1)		0 (0)		18 (2)
Unknown		328 (28)		13 (52)		328 (28)
Has more than 1 partner ²	782	8 (1)	13	0 (0)	769	8 (1)
<i>Sexual Behavior and Practices</i>						
Age at menarche (years)	1252	14 (13–16)	24	14 (13–15)	1228	14 (13–16)
Age at sexual debut (years)	1240	16 (15–18)	24	15 (15–18)	1216	16 (15–18)
Sexually active in the last month	1282	770 (60)	25	18 (72)	1257	752 (60)
Any unprotected sex	770	707 (92)	18	13 (72)	752	694 (92)

	All Women (n=1304)	HIV-Infected Women (n=25)	HIV-Uninfected Women (n=1279)
Lifetime number of male sexual partners	1301	2 (1–3)	2 (1–3)
History of trading sex	1303	135 (10)	130 (10)
Any vaginal washing in the past week	1304	781 (60)	767 (60)
Any vaginal drying in the past week	1304	233 (18)	226 (18)
<i>STIs³ and Genital Tract Infections</i>			
History of STIs	1304	87 (7)	82 (6)
Chlamydia	1300	73 (6)	70 (5)
Gonorrhea	1300	33 (3)	32 (3)
Trichomoniasis	1303	83 (6)	81 (6)
Syphilis	1029	13 (1)	11 (1)
Bacterial vaginosis	1296	300 (23)	289 (23)
Yeast infection	1303	325 (25)	316 (25)

¹ IQR, interquartile range;

² only ascertained among a 782 women due to inclusion of this question mid-way through the study;

³ STI, sexually transmitted infections

Table 2

Cofactors for Maternal HIV Acquisition

	Crude HR (95% CI)	P	Adjusted HR* 95% CI	P
Age (years)	0.97 (0.90 – 1.05)	0.49	–	–
Education (years)	0.99 (0.84 – 1.16)	0.88	–	–
Married	0.87 (0.35 – 2.19)	0.77	–	–
Polygamous marriage	2.44 (0.97 – 6.11)	0.06**	–	–
Marriage duration (years shorter)	1.19 (1.03 – 1.38)	0.02[±]	–	–
Partner age difference (years older)	1.07 (1.02 – 1.13)	0.01	1.06 (1.00 – 1.13)	0.04
Partner circumcised	1.03 (0.42 – 2.54)	0.94	–	–
Age at sexual debut (years)	0.98 (0.84 – 1.16)	0.87	–	–
Lifetime number of male sexual partners	1.19 (1.03 – 1.37)	0.02	1.14 (0.99 – 1.33)	0.07
History of trading sex	2.14 (0.80 – 5.71)	0.13	–	–
Vaginal washing at baseline	0.75 (0.33 – 1.75)	0.51	–	–
History of STIs	3.48 (1.31 – 9.27)	0.01	–	–
Chlamydia	4.49 (1.34 – 15.0)	0.02	4.42 (1.37 – 14.2)	0.01
Gonorrhea	3.00 (0.41 – 22.2)	0.28	–	–
Trichomonas	1.14 (0.16 – 8.16)	0.89	–	–
Syphilis	9.18 (2.15 – 39.3)	0.003	4.28 (0.89 – 20.6)	0.07
Bacterial vaginosis	2.91 (1.25 – 6.76)	0.01	2.14 (0.90 – 5.10)	0.09
Yeast infection	3.46 (1.46 – 8.19)	0.005	2.78 (1.17 – 6.63)	0.02

HR=hazard ratio, CI=confidence interval.

* Adjusted model using multivariate imputation by chained equations and accounting for within-cluster correlation for time-varying covariates. Imputations were used for the following variables: Chlamydia, syphilis, yeast infection, bacterial vaginosis, partner age difference, and lifetime number of sex partners. All cofactors statistically significant at the $p < 0.10$ level were included in the multivariate model and cofactors that were no longer significant at $p < 0.10$ were dropped as a group from the model.

** Among married women; excluded from the multivariate model to allow for unmarried women to be included in the multivariate model.

[±] Among married women for univariate model; reparameterized in multivariate model to allow for non-married women to be included in the model.