Published in final edited form as:
J Infect Dis. 2009 August 1; 200(3): 370–378. doi:10.1086/600074.

Adult Male Circumcision Does Not Reduce Risk of Incident *Neisseria gonorrhoeae, Chlamydia trachomatis, and Trichomonas vaginalis*: Results from a Randomized Controlled Trial in Kenya

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Abstract

Objectives—We examined the effect of male circumcision on the acquisition of three non-ulcerative sexually transmitted infections (STIs).

Methods—We evaluated STI incidence among men aged 18–24 enrolled in a randomized trial of circumcision to prevent HIV infection in Kisumu, Kenya. The outcome was first incident non-ulcerative STI over two years follow-up. STIs examined were laboratory-detected *Neisseria gonorrhoeae* (NG), *Chlamydia trachomatis* (CT) and *Trichomonas vaginalis* (TV).

Results—There were 342 incident infections among 2,655 men followed. Incidences of infection per 100 person-years (PYs) were: 3.48 for NG; 4.55 for CT; and 1.32 for TV. The combined incidence of NG or CT infection was 7.26 per 100 PYs (95% CI: 6.49 – 8.13). The incidence of these STIs, individually or combined, did not differ by circumcision status as a time-dependent variable, or fixed variable based on assignment. Risks for incident STIs in multivariable analysis included: STI at enrollment, multiple sex partners < 30 days, and sex during menses in the past 6 months; condom use was protective.

Conclusions—Circumcision of men in this population did not reduce their risk of acquiring these non-ulcerative STIs. Improved STI control will require more effective STI management, including partner treatment, and behavioral risk reduction counseling.

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The authors have no financial or other conflicts of interest to report. Dr. Bailey receives funds for research and implementation of male circumcision interventions from the U.S Government and the Bill and Melinda Gates Foundation through Family Health International.

Results of this analysis have not been presented previously.

Keywords

circumcision; gonorrhea; chlamydia; trichomonas; Africa; Kenya

Background

Three randomized clinical trials in Africa have shown that adult male circumcision reduces risk of HIV acquisition in heterosexual men by 51–76% [1–3]. The World Health Organization recommends male circumcision as an important strategy for HIV prevention in areas where HIV prevalence in the general population is high and circumcision rates are low, in combination with other HIV preventive and reproductive health programs and services [4]. Several HIV-1 target cells, such as CD4+ T cells, macrophages, and Langerhans cells, are present in dense concentration in the unkeratinzed inner mucosal surface of the foreskins of uncircumcised men [5–7], facilitating pathogen host cell attachment and entry. Other than keratinization of the penile skin, other mechanisms by which circumcision may contribute to reduced risk of HIV acquisition include: decreased inflammation and trauma to the penis [7], increased genital hygiene of the prepuce [8], and decreased retention of secretions containing HIV. It is plausible that some of these mechanisms might also confer protection against acquisition of other sexually transmitted infections (STIs).

There is evidence from observational studies that male circumcision may reduce risk of acquiring certain STIs. A meta-analysis of the association of male circumcision with STIs found statistically and clinically significant reductions in risk for syphilis and chancroid [9]. However, no association has been observed between male circumcision and other bacterial STIs [10–15]. Among men enrolled in a randomized trial of adult male circumcision in Rakai, Uganda, the incidence of self-reported genital ulcer disease was almost halved for circumcised men compared to uncircumcised men, but there was no protective association observed for genital discharge or dysuria symptoms [2]. While the experimental study design is strong, these results represent self-reported rather than laboratory detected infections.

We evaluated the effect of adult male circumcision and behavioral risks on the incidence of three non-ulcerative laboratory diagnosed STIs among adult men participating in a randomized, controlled clinical trial of adult male circumcision to prevent HIV infection in Kisumu, Kenya.

Methods

Study design and participants

The main trial design, circumcision technique, adverse events, and primary outcome (HIV infection) have been described [3]. Briefly, participants were recruited from sexually transmitted disease clinics, workplaces, social events and youth organizations. Interested men were given an appointment for randomization and possible circumcision within one week of screening. For inclusion men had to: be uncircumcised, HIV-negative, sexually active in the last 12 months, and aged 18–24 years; have a hemoglobin ≥ 9.0 mmol/L, and reside in Kisumu District. Exclusion criteria included: foreskin covering less than half of the glans, a bleeding disorder, keloid formation, other conditions that might unduly increase the risks of elective surgery, or a medical indication for circumcision. Institutional Review Boards of the University of Illinois at Chicago, the Kenyatta National Hospital, RTI International, the University of Manitoba, and the University of Washington approved the study.

Clinical procedures and follow-up

Following written informed consent, participants were randomized 1:1 to either immediate circumcision or delayed circumcision after a 2-year follow-up period (the control group). Both groups underwent STI and HIV risk reduction counseling and were provided unlimited supplies of free condoms. Men randomized to intervention underwent a standard "forceps guided procedure" for circumcision, as described previously [3].

Detailed evaluations were conducted at baseline, 1, 3, 6, 12, 18 and 24 months from randomization for both the circumcision and the control groups. At each visit, participants underwent a standardized medical history and physical examination; for planned visits occurring 6 months from randomization or later, subjects underwent personal interview to obtain socio-demographic information and information on sexual behavior. Trained counselors interviewed participants in their language of choice (English, Dholuo or Kiswahili).

Sexually Transmitted Infection Testing

At baseline and at 6, 12, 18, and 24 month follow-up visits, participants were asked to provide urine specimens, which were tested for *Neisseria gonorrhoeae* (NG) and *Chlamydia trachomatis* (CT) by polymerase chain reaction (PCR) assay (AMPLICOR® CT/NG Test, Roche Diagnostics, Montreal, Canada), and for *Trichomonas vaginalis* (TV) by culture (InPouch™ TV test, Biomed Diagnostics, Oregon, United States). Men with urethral discharge also had a urethral swab taken for PCR testing for NG and CT, and culture for NG and TV. Men who presented between study visits with symptoms of infection were also tested, and their results are included in this analysis. Urine, urethral swabs, and blood specimens were sent to the University of Nairobi Department of Medical Microbiology for testing. All tests were conducted according to manufacturers' instructions. Men who tested positive for NG, CT, or TV were traced and given appropriate treatment at the study clinic, as per Kenyan national STI treatment guidelines. HIV testing methods have been reported in detail previously [3].

Data Used for Analysis

Data for this analysis were collected as part of a randomized, controlled trial designed to assess the effect of male circumcision on reducing HIV seroconversion. The trial's target sample size was 2,776 [3]. As a result of an interim analysis conducted in October 2006 (with 87% follow-up), the data and safety monitoring board stopped the trial in December 2006. The data presented here are the trial data with follow-up through October 2006. Of the 1,738 participants randomized at least 24 months plus 2 weeks prior to the October 2006 analysis, 1,501 (86%) had completed their 24 month follow-up visit [3]. The percent of men attending follow-up visits did not differ by treatment arm [3].

Statistical Analysis

To be included in this analysis, participants had to be tested for all three infections during at least one follow-up visit post-randomization. The outcome measure for this analysis was first incident infection, dichotomized as positive versus negative for each infection separately (NG, CT, and TV). Risks for NG and CT were similar, and we additionally examined infection with NG and/or CT as a combined outcome. For each outcome, we calculated incidence by dividing the number of persons with incident infection by the number of person-years at risk. Subjects with multiple incident infections were censored at their first incident infection. Re-infections were examined for descriptive purposes and were defined as infections detected >30 days after the initial infection, provided that the initial infection was treated with appropriate antibiotic therapy. Observation times were calculated

as the time from randomization to individuals' first infection, or their last visit at which they tested negative for an STI. We assumed that subjects who missed interim study visits remained negative during the interim period.

Log-rank tests were used to explore the association of various risk factors individually. Variables significant at the $p<0.05$ level by log-rank test were entered in a Cox proportional hazards regression model. In addition, Cox regression was used to account for time-varying covariates and to compute hazard ratios (HRs) of incident STIs associated with circumcision status, socio-demographics, and behavioral characteristics. Circumcision status was analyzed as a time-varying covariate, to take into account men who crossed over from control to circumcision, and men randomized to intervention but who did not undergo circumcision. Additionally, treatment assignment was analyzed as a fixed variable (intention-to-treat analysis). The assumption of proportionality for Cox proportional hazards was assessed by graphical inspection of Nelson-Aalen curves and by testing for a non-zero slope in a generalized linear regression of the scaled Schoenfeld residuals on functions of time. Statistical significance for the selection of variables to be retained in each multivariable model was determined by Holm adjustment for multiple tests of significance [16]. Standard errors were estimated using a robust variance estimate (sandwich estimator). The Efron method was specified to approximate the exact conditional probability of tied events [17]. Data were analyzed using Stata/SE 9.2 for Windows (Stata Corporation, College Station, Texas).

Results

Study Population

There were 2,784 men enrolled in the trial and 2,655 (95.4%) who were tested for the three infections during follow-up. Among these men, 1,318 were randomized to circumcision and 1,337 were randomized to control. Crossovers from treatment assignment included 16 controls who were circumcised, and 57 men randomized to circumcision who were not circumcised. The control and treatment arms were well-balanced regarding socio-demographic details, behavioral characteristics, baseline STI prevalences, and follow-up [3].

Incidence Rates of Infection

Of 2,655 men with STI testing at follow-up, 361 men had 398 infections: 148 NG infections, 193 CT infections and 57 TV infections. Nearly one-fourth of infected men (n=85; 23.6%) were detected at interim visits. There were 25 men with NG and CT co-infection, 2 with CT and TV co-infection, 8 with NG and TV co-infection, and 1 with NG, CT and TV co-infection. The incidence of first infection per 100 person-years was: 3.48 for NG; 4.55 for CT; and 1.32 for TV (Table 1). The combined incidence of NG and/or CT infection was 7.26 per 100 person-years (95% Confidence Interval [CI]: 6.49 – 8.13). Among 148 men, there were 168 gonorrhea infections. The 20 re-infections were accounted for by 18 men, and 6 of the re-infections occurred within the same follow-up interval as the first infection. Among 193 men, there were 200 chlamydia infections. The 7 re-infections occurred among 7 men, and occurred in follow-up intervals subsequent to the initial infection. There were 61 TV infections detected in 57 men; 1 of the 4 re-infections occurred within the same follow-up interval as an NG infection. Overall, the incidence of first infection with a non-ulcerative STI in this cohort was 8.34 per 100 person-years (95% CI: 7.50 – 9.28), and was minimally impacted by inclusion of re-infections (8.77 cases per 100 person-years; 95% CI: 7.93 – 9.69).

The Effect of Circumcision Status on Incidence of Non-Ulcerative STIs

The incidence of non-ulcerative STIs, individually or combined, did not differ by circumcision status as a time dependent variable or as a fixed variable based on assignment (Table 1). Incidence rate ratios for circumcised versus uncircumcised men (time-dependent circumcision status) were: 0.95 (95% CI: 0.68 – 1.34, p-value = 0.781) for NG; 0.87 (95% CI: 0.65 – 1.16, p-value = 0.325) for CT; 0.89 (95% CI: 0.70 – 1.12; p-value = 0.305) for NG and/or CT combined; and 0.77 (95% CI: 0.44 – 1.36, p-value = 0.346) for TV.

Incidence of Non-Ulcerative STI by Socio-Demographics, Behavioral Characteristics, and Baseline Infection Status

The incidences of NG and CT were increased among men with lower educational attainment, baseline NG or CT infections, multiple sex partners reported in the 30 days previous to the visit at which infection was detected, and having sex with a woman during her menses during the 6 months prior to the visit at which infection was detected (Table 1). For both NG and CT, the incidence rates were highest among men who reported sex during a woman's menses (8.0 NG cases per 100 person-years, and 9.3 CT cases per 100 person-years), and men with baseline NG and/or CT infections (not shown; 9.8 NG cases per 100 person-years; and 9.3 CT cases per 100 person-years). The incidence of TV was low, and few baseline factors distinguished men with infection at follow-up from those who were not infected (Table 1). Men who reported preference for dry vaginal sex had an increased incidence of TV, but not of NG or CT incidence, compared to men who preferred wet vaginal sex. The incidence rate of each infection was lower by 35–50% among men reporting condom use at their last sexual intercourse. Marital status and HSV-2 infection at baseline were not statistically significantly associated with increased incidence of non-ulcerative STI. There were only 7 HIV seroconversions that occurred among men who also had incident non-ulcerative STI; HIV seroconversion was detected in the same follow-up interval as STI for 6 of the cases. Thus HIV-seroconversion was not examined as a predictor of STI.

Cox Proportional Hazards Regression: Risks for Infection

In multivariate regression, risks for NG and CT were similar (Table 2): NG or CT infection at baseline, multiple recent sex partners, and sex with a woman during menses. Condom use at last intercourse remained statistically significantly protective of NG (HR=0.50) and TV (HR=0.52) in multivariable analysis, but not for CT. The only other statistically significant risks for TV were baseline infection with CT or TV. Men who reported that their penis had been abraded or felt sore during intercourse in the 6 months prior to detected infection had increased risk for NG (HR=1.61). There was no statistically significant or meaningful two-way interaction term in any model. Examination of Schoenfeld residuals showed no violation of the assumption of proportionality for each independent variable or for the global test of each model.

Cox Proportional Hazards Regression: Risks for Infection with NG and/or CT

We combined NG and CT infection at follow-up into a single outcome due to similarities in stratified models, and to increase our power to detect statistically significant associations (Table 3). In multivariable Cox regression, NG or CT infection at enrollment (HR=2.31; 95% CI: 1.64 –3.26), multiple sex partners in the past 30 days (HR=2.15, 95% CI: 1.42 – 3.27), and sex during a woman's menstruation (HR=1.67, 95% CI: 1.19 – 2.33) remained statistically significant predictors of NG and/or CT infection (Table 3). Conversely, higher education (HR=0.67; 95% CI: 0.50 – 0.88) and reporting condom use at last intercourse (HR=0.64, 95% CI: 0.50 – 0.82) were protective against infection. There was no statistically

significant or meaningful two-way interaction term, and no violation of the assumption of proportionality for each independent variable or for the global test of the model.

Discussion

We did not find a protective effect of adult male circumcision against any of the non-ulcerative STIs examined (NG, CT or TV) in these sexually active young men in Kisumu, Kenya. There are multiple differences in organism pathogenesis and host immunogenicity that may explain why circumcision may confer protection against HIV but not against these STIs. The HIV-1 target cells that may be protected through increased keratinization resulting from circumcision are specific; HIV-1 must attach to the CD4 receptor for cell entry. Bacterial STIs such as *N. gonorrhoeae, C. trachomatis*, and *T. vaginalis*, however, may bind through multiple ligands and host receptors [18]. Unlike the chlamydia organism, gonococci are not obligate intracellular organisms, and *T. vaginalis* has complex and multiple methods of adhering to and entering host cells. The preferred host cell site is cuboidal or columnar epithelium (internal to the urethra) for both NG and CT; thus it is very unlikely that intact foreskin would provide protection against these infections. Suggestion of protection has stemmed from analysis of some non-experimental study designs [19] rather than biological rationale. Our randomized controlled trial findings of no association between circumcision status and these STIs confirm findings from several other studies with non-experimental designs [11–14]. It is not likely that a longer observation period would have been necessary to observe any potential protective effects; graphical inspection of the estimated cumulative hazard rate appears constant, and biological protective effects would be expected to be gained shortly after circumcision. However, as demonstrated by statistical modeling, the effectiveness of circumcision in reducing HIV burden in the population varies by prevalence of circumcision, HIV prevalence and sexual behavior [20]; thus it is not inconceivable that adult male circumcision may have different effects on non-ulcerative STIs at the population level, varying with population-level sexual practices, and prevalence of STIs and circumcision.

Despite the lack of protective effect on NG, CT, and TV acquisition, adult male circumcision may have other beneficial effects on STIs, such as reduced transmission to sexual partners or decreased acuity or sequelae of infection. Among women enrolled as controls in a cervical cancer study in five countries, self-reported circumcision in male sex partners was strongly protective of CT in the women [21]. Conversely, a cohort study examining hormonal contraception and risk of HIV in women in 3 countries, found that male sex partners' self-reported circumcision status was not associated with women's incident NG, CT or TV infections [22]. However, few studies have examined this issue, and none were specifically designed to assess the association between male circumcision and risk of STIs in female partners. Prospective studies comparing STI incidence among sexual partners and course of infection among circumcised and uncircumcised men are necessary to determine a broader range of potential benefits of adult male circumcision.

Data on the incidence of non-ulcerative STIs among adolescent men in sub-Saharan Africa are limited, but the rates we observed (NG and/or CT combined incidence of 7.26 cases per 100 person-years), seem relatively high. Among truckers aged 16–62 years-old from Mombasa, Kenya, enrolled from 1993–1994 in a cohort study, the incidence of NG was 12.6 per 100 person-years and the incidence of non-gonococcal urethritis was 7.5 per 100 person-years [23]. As part of a 1997–1998 cross-sectional study in 4 sub-Saharan African cities, the prevalence of NG was 0% and CT 2.6% among a representative sample of Kisumu men aged 15–49 years old [24]. Beyond comparison to other populations, the incidence we observed seems high contextually: the young men were enrolled in a study that provided ongoing testing and treatment for STIs, and men received risk-reduction counseling and

free, unlimited numbers of condoms. Men with baseline NG and CT infections were at increased risk for re-infection. This suggests that men may become re-infected by infected partners. Infected men in the trial were given coupons to give to their sex partners to receive free treatment at a nearby clinic, but we do not know how many sought the treatment. Our results suggest that more aggressive partner tracing and treatment might be warranted.

Sex with a woman during her menses was a risk for NG and CT in stratified and combined analyses. In a previous analysis of our data, among men who were excluded from the trial because they were HIV positive at baseline, sex with a woman during her menses was a risk factor for prevalent HIV in multivariable analysis [25]. Some studies have demonstrated increased HIV viral load during the menstrual phase of the menstrual cycle [26–27]. In one study, sex partners of men diagnosed with gonorrhea were more likely to test positive for gonorrhea if they were tested during the menstrual phase compared to other phases of their menstrual cycle [28], possibly through increased organism shedding. There are limited published data quantifying STI organism load and transmission throughout the menstrual cycle. Individual studies suggest potential mechanisms may be increased organism load or increased pathogenicity of organisms during menses due to altered genital flora [29]. While further study is necessary to elucidate female to male transmission of STIs during the menstrual cycle, current counseling and prevention efforts could emphasize avoiding sex during a woman's menses and the use of condoms.

Men who reported coital injuries (their penis had been cut, scratched, or abraded during sex in the 6 months prior to detected infection) had an increased risk for NG. The nature of these injuries and mechanism by which they may increase risk of acquiring infection is unknown. Condom use reduced the risk of infection by more than one-third, emphasizing the importance of promoting condom use.

TV incidence (1.32 cases per 100 person-years) and baseline prevalence (2.1%) in our population was low compared to prevalences detected in cross-sectional studies in other sub-Saharan countries. Among men aged 15–54 in rural Tanzania, the prevalence of trichomonas was 11% [30], and 6.3% among male sex partners of a community based sample of women in Moshi, Tanzania [31]. As the epidemiology of TV among African men is largely unknown, specific behaviors and sexual practices that increase risk may not have been measured in our study.

Limitations of the original trial have been reviewed previously [3], so our discussion of limitations is confined to the current analysis. If a large proportion of infected men sought treatment outside of the study clinic, those infections would not be accounted for in this analysis, potentially leading to an underestimate of incidence, biasing the results towards the null. Some participants did not attend all scheduled follow-up visits, but less than 5% of enrolled men did not have any follow-up testing for STIs. These men were significantly less likely than men with STI testing at follow-up to report coital injuries [results not shown]. However, their baseline characteristics did not differ from men with follow-up with regard to number of sex partners in the past 30 days, baseline infection with NG, CT or TV, sex during a woman's menses, condom use at last intercourse, age, educational attainment or treatment assignment. Finally, behavioral risks were self-reported, and therefore subject to limitations of recall and socially desirable reporting.

In conclusion, we did not observe a protective effect of circumcision on acquisition of these non-ulcerative STIs. Data are lacking on whether adult male circumcision affects transmission of non-ulcerative STI to sexual partners. We measured a high incidence of STIs among a cohort of young men, despite their participation in a clinical trial which included intensive STI diagnosis and treatment, HIV risk-reduction counseling, follow-up,

and a free supply of condoms. This suggests that more effective safer sex counseling content and delivery methods must be identified, especially if circumcision is not a means of STI prevention and control. Increased STI risk among men with previous infections suggests that treatment of partners will also be important.

Acknowledgments

This research was supported by grant number AI50440 from the Division of AIDS, National Institute of Allergies and Infectious Disease of the United States National Institutes of Health, and by grant number HCT 44180 from the Canadian Institutes of Health Research (CIHR). S Moses was supported by a CIHR Investigator Award.

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J Infect Dis. Author manuscript; available in PMC 2011 April 25.

Table 1

Incidence per 100 person-years of follow-up of *Neisseria gonorrhoeae, Chlamydia trachomatis*, and *Trichomonas vaginalis*

Variable	Total Number of Individuals* N (%)	Gonorrhea		Chlamydia		Trichomonas	
		Number of Incident Infections N (%)	Incidence per 100 Person-Years (95% CI)	Number of Incident Infections N (%)	Incidence per 100 Person-Years (95% CI)	Number of Incident Infections N (%)	Incidence per 100 Person-Years (95% CI)
Overall	2,655	148	3.48 (2.96 – 4.09)	193	4.55 (3.95 – 5.24)	57	1.32 (1.02 – 1.71)
Treatment Assignment (Fixed) Control Intervention	1,337 (50.4) 1,318 (49.6)	74 (51.4) 70 (48.6)	3.52 (2.80 – 4.42) 3.39 (2.68 – 4.29)	101 (53.4) 88 (46.6)	4.83 (3.52 – 5.35) 4.34 (3.97 – 5.87)	22 (41.5) 31 (58.5)	1.05 (0.69 – 1.59) 1.45 (1.02 – 2.07)
Reported Age at Baseline+ Age 18–20 years Age 21–24 years	1,352 (50.9) 1,303 (49.1)	71 (48.0) 77 (52.0)	3.32 (2.63 – 4.19) 3.64 (2.91 – 4.55)	105 (54.4) 88 (45.6)	4.93 (4.07 – 5.97) 4.16 (3.38 – 5.13)	24 (42.1) 33 (57.9)	§ 1.10 (0.74 – 1.65) 1.54 (1.09 – 2.16)
Educational Attainment None, Primary 1–8 Secondary 1–4 Post Secondary	910 (34.3) 464 (17.5) 1,281 (48.3)	68 (46.0) 27 (18.2) 53 (35.8)	† 4.75 (3.74 – 6.02) 3.70 (2.54 – 5.40) 2.54 (1.94 – 3.32)	96 (49.7) 29 (15.0) 68 (35.2)	† 6.79 (5.56 – 8.30) 3.93 (2.73 – 5.66) 3.25 (2.56 – 4.12)	26 (45.6) 6 (10.5) 25 (43.9)	1.79 (1.22 – 2.63) 0.79 (0.36 – 1.77) 1.18 (0.80 – 1.75)
Marital Status Not married Married or living as married	2,496 (94.4) 149 (5.6)	127 (87.6) 18 (12.4)	3.51 (2.95 – 4.17) 2.97 (1.87 – 4.71)	158 (83.2) 32 (16.8)	4.37 (3.74 – 5.11) 5.28 (3.74 – 7.47)	44 (84.6) 8 (15.4)	1.20 (0.89 – 1.61) 1.29 (0.64 – 2.57)
Baseline Gonorrhea Results Negative Positive	2,576 (98.0) 53 (2.0)	138 (94.5) 8 (5.5)	† 3.35 (2.83 – 3.95) 10.0 (5.00 – 20.0)	184 (95.8) 8 (4.2)	§ 4.47 (3.87 – 5.17) 9.52 (4.76 – 19.0)	57 (100) 0 (0.0)	1.36 (1.05 – 1.77) --
Baseline Chlamydia Results Negative Positive	2,505 (95.3) 123 (4.7)	126 (86.9) 19 (13.1)	† 3.14 (2.64 – 3.74) 10.1 (6.41 – 15.8)	176 (91.7) 16 (8.3)	§ 4.40 (3.79 – 5.10) 8.40 (5.15 – 13.7)	50 (87.7) 7 (12.3)	† 1.23 (0.93 – 1.62) 3.61 (1.72 – 7.57)
Baseline Trichomonas Results Negative Positive	2,577 (97.9) 56 (2.1)	143 (98.0) 3 (2.0)	3.48 (2.95 – 4.10) 2.94 (0.95 – 9.12)	185 (96.4) 7 (3.6)	4.50 (3.90 – 5.20) 7.18 (3.42 – 15.1)	51 (89.5) 6 (10.5)	† 1.22 (0.93 – 1.60) 6.19 (2.78 – 13.8)
Baseline HSV-2 Results Negative Positive	1,928 (72.7) 722 (27.3)	98 (66.2) 50 (33.8)	3.17 (2.60 – 3.86) 4.35 (3.30 – 5.74)	132 (68.8) 60 (31.2)	4.29 (3.61 – 5.08) 5.19 (4.03 – 6.69)	37 (64.9) 20 (35.1)	1.18 (0.85 – 1.63) 1.71 (1.10 – 2.65)
Prefer Sex Wet Dry No Preference Don't know	1,006 (38.3) 1,245 (47.4) 232 (8.8) 145 (5.5)	47 (32.0) 82 (55.8) 7 (4.8) 11 (7.5)	2.91 (2.18 – 3.87) 4.16 (3.35 – 5.17) 1.88 (0.89 – 3.94) 4.43 (2.45 – 7.99)	67 (35.1) 101 (52.9) 13 (8.1) 10 (5.2)	4.16 (3.28 – 5.29) 5.13 (4.22 – 6.23) 3.50 (2.03 – 6.03) 4.02 (2.17 – 7.48)	16 (28.6) 36 (64.3) 2 (3.6) 2 (3.6)	§ 0.98 (0.60 – 1.59) 1.80 (1.30 – 2.49) 0.53 (0.13 – 2.12) 0.79 (0.20 – 3.14)
Number of sex partners past 30 days None One Two or more	1,162 (43.8) 1,054 (39.8) 435 (16.4)	27 (18.6) 80 (55.2) 38 (26.2)	† 1.70 (1.17 – 2.48) 3.81 (3.06 – 4.74) 6.75 (4.91 – 9.28)	38 (19.8) 118 (61.5) 36 (18.7)	† 2.41 (1.75 – 3.31) 5.62 (4.69 – 6.73) 6.39 (4.61 – 8.86)	16 (28.6) 31 (55.4) 9 (16.1)	1.00 (0.61 – 1.63) 1.45 (1.02 – 2.07) 1.55 (0.81 – 2.99)

Variable	Total Number of Individuals* N (%)	Gonorrhea		Chlamydia		Trichomonas	
		Number of Incident Infections N (%)	Incidence per 100 Person-Years (95% CI)	Number of Incident Infections N (%)	Incidence per 100 Person-Years (95% CI)	Number of Incident Infections N (%)	Incidence per 100 Person-Years (95% CI)
Vaginal sex with a woman during her menstruation							
No	1,893 (85.2)	104 (80.6)	†	145 (83.3)	†	39 (83.0)	1.23 (0.90 – 1.68)
Yes	328 (14.8)	25 (19.4)	3.32 (2.74 – 4.02)	29 (16.7)	4.64 (3.95 – 5.46)	8 (17.0)	2.48 (1.24 – 4.95)
			8.08 (5.46 – 12.0)		9.25 (6.43 – 13.3)		
Sex with a woman the same day as meeting her							
No	1,833 (69.3)	96 (66.2)	§	137 (71.4)	4.35 (3.68 – 5.15)	43 (76.8)	1.35 (1.00 – 1.82)
Yes	814 (30.7)	49 (33.8)	3.04 (2.49 – 3.72)	55 (28.6)	5.04 (3.87 – 6.57)	13 (23.2)	1.16 (0.67 – 1.99)
			4.49 (3.40 – 5.95)				
Gave a woman gifts or money in exchange for sex							
No	1,914 (83.0)	122 (87.1)	3.82 (3.20 – 4.56)	160 (89.4)	5.01 (4.29 – 5.85)	40 (81.6)	1.23 (0.90 – 1.68)
Yes	391 (17.0)	18 (12.9)	5.17 (3.26 – 8.21)	19 (10.6)	5.45 (3.48 – 8.55)	9 (18.4)	2.54 (1.32 – 4.87)
Used a condom the last time you had vaginal intercourse							
No	1,382 (52.1)	81 (55.9)	†	97 (50.5)	†	32 (57.1)	†
Yes	1,269 (47.9)	64 (44.1)	4.74 (3.81 – 5.90)	95 (49.5)	5.71 (4.68 – 6.97)	24 (42.9)	1.85 (1.31 – 2.61)
			2.52 (1.97 – 3.22)		3.74 (3.06 – 4.57)		0.93 (0.62 – 1.39)
Penis ever bleeds during sex							
No	2,201 (83.1)	127 (87.6)	3.26 (2.74 – 3.88)	168 (87.5)	§	50 (89.3)	1.26 (0.96 – 1.67)
Yes	447 (16.9)	18 (12.4)	5.13 (3.23 – 8.14)	24 (22.5)	4.32 (3.72 – 5.03)	6 (10.7)	1.66 (0.75 – 3.74)
					6.82 (4.57 – 10.2)		
Penis ever sore or scratched during sex							
No	947 (35.8)	64 (44.1)	†	109 (57.7)	4.29 (3.56 – 5.18)	31 (55.4)	1.18 (0.83 – 1.68)
Yes	1,648 (64.2)	81 (55.9)	2.49 (1.93 – 3.16)	80 (42.3)	4.96 (3.99 – 6.18)	25 (44.6)	1.48 (1.00 – 2.19)
			4.90 (3.94 – 6.09)				

*Total number of individuals represents baseline values for time-varying covariates: marital status and behavioral risks. Circumcision status is not shown because it is a time varying covariate and at baseline, all men were uncircumcised.

Educational attainment and preference for sex when a woman's vagina is wet or dry were fixed variables, assessed at baseline.

+Age was statistically significantly associated with Trichomonas at the $p<0.05$ level as a continuous fixed and continuous time-varying variable.

Log rank p-values:

†indicates p-value < 0.01;

§indicates 0.01< p-value <0.05

Table 2

Multivariable Cox Proportional Hazards Regression: Relative Hazard of Gonorrhea, Chlamydia, and Trichomonas

Variable	Gonorrhea, N=2,449 Hazard Ratio (95% C.I.), p-value	Chlamydia, N=2,450 Hazard Ratio (95% C.I.), p-value	Trichomonas, N=2,626 Hazard Ratio (95% C.I.), p-value
Reported age in years (continuous)			^1.21 (1.03 – 1.41), 0.017
Educational attainment at baseline None, Primary 1–8 Secondary 1–3 Secondary 4, Post-secondary		ref 0.64 (0.41 – 0.99), 0.044 ^0.58 (0.41 – 0.81), 0.001	
Gonorrhea or chlamydia infection at baseline	^3.04 (1.93 – 4.77), <0.001	1.70 (1.06 – 2.73), 0.029	
Chlamydia infection at baseline			^2.49 (1.07 – 5.78), 0.034
Trichomonas infection at baseline			^5.34 (2.16 – 13.2), <0.001
Number of sex partners past month None One Two or more	ref 1.37 (0.83 – 2.26), 0.220 ^2.25 (1.29 – 3.94), 0.004	ref ^1.81 (1.16 – 2.82), 0.009 1.89 (1.11 – 3.22), 0.018	
Condom used at last intercourse	^0.50 (0.35 – 0.72), <0.001		^0.52 (0.30 – 0.88), 0.015
Vaginal sex with a woman during her menses	1.64 (1.03 – 2.61), 0.036	^1.78 (1.18 – 2.70), 0.006	
Penis ever scratched or sore during sex	^1.61 (1.13 – 2.31), 0.009		

^ = Statistically significant by Holm corrected p-value; C.I. = Confidence Interval

Statistically significant variables entered from univariate analysis that were not statistically significant in the multivariable models are not shown.

Table 3

Univariate and Multivariate Cox Regression Results: Relative Hazards of Incident Gonorrhea or Chlamydia Infection.

Characteristic	Univariate Hazard Ratio [95% CI], P-Value	Multivariate Hazard Ratio, N=2,444 [95% CI], P-Value
Circumcision Status		
Uncircumcised	ref	
Circumcised	0.96 [0.89 – 1.04], 0.329	
Reported Age at Baseline		
Age 18–20 years	ref	
Age 21–24 years	0.92 [0.73 – 1.15], 0.476	
Educational Attainment		
None, Primary 1–8	ref	ref
Secondary 1–4	0.63 [0.45 – 0.87], 0.006	NS
Post Secondary	0.51 [0.40 – 0.66], <0.001	0.67 [0.50 – 0.88], 0.005
Baseline Chlamydia or Gonorrhea Infection		
No	ref	ref
Yes	2.71 [1.97 – 3.75], <0.001	2.31 [1.64 – 3.26], <0.001
Baseline HSV-2 Results		
Negative	ref	
Positive	1.32 [1.02 – 1.68], 0.025	
Number of sex partners past 30 days		
None	ref	ref
One	2.37 [1.76 – 3.19], <0.001	1.64 [1.14 – 2.36], 0.008
Two or more	3.15 [2.21 – 4.51], <0.001	2.15 [1.42 – 3.27], <0.001
Vaginal sex with a woman during her menstruation in the past 6 months		
No	ref	ref
Yes	2.08 [1.51 – 2.86], <0.001	1.67 [1.19 – 2.33], 0.003
Sex with a woman the same day as meeting her in the past 6 months		
No	ref	
Yes	1.26 [0.98 – 1.61], 0.069	
Used a condom the last time you had vaginal intercourse		
No	ref	ref
Yes	0.58 [0.46 – 0.73], <0.001	0.64 [0.50 – 0.82], 0.001
Penis ever bleeds during sex in the past 6 months		
No	ref	
Yes	1.55 [1.10 – 2.19], 0.012	
Penis ever sore or scratched during sex in the past 6 months		
No	ref	
Yes	1.38 [1.09 – 1.73], 0.006	

"ref" = referent category; "NS" = Not statistically significant

All variables presented in multivariable model were statistically significant by Holm adjusted critical p-value.

Variables not significant at the p<0.05 level from univariate analyses are not shown: marital status, baseline trichomonas infection, preference for wet or dry vaginal sex, giving a woman gifts or money in exchange for sex during the past 6 months.