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Changes in the Contribution of Genital Tract Infections to HIV acquisition among Kenyan High-Risk Women from 1993 to 2012

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Abstract

OBJECTIVE—To understand temporal trends in the contribution of different genital tract infections to HIV incidence over 20 years of follow-up in a cohort of high-risk women.

DESIGN—Prospective cohort study.

METHODS—We performed monthly evaluations for HIV, vaginal yeast, bacterial vaginosis (BV), *Trichomonas vaginalis*, *Neisseria gonorrhoeae*, non-specific cervicitis, herpes simplex virus type 2 (HSV-2), genital ulcer disease (GUD) and genital warts. We used Cox regression to evaluate the association between STIs and HIV acquisition over 4 time periods (1993–1997, 1998–2002, 2003–2007, 2008–2012). Models were adjusted for age, workplace, sexual risk

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AUTHORS' CONTRIBUTIONS

RSM, LM, JMB, BAR, GJ-S, EB, SMG, JO, JK and JS conceived the question and designed the study. RSM and JO obtained funding for the study. LM, RSM, JMB, BAR, SMG and JS participated in collection and interpretation of the data. LM, JMB, and BAR conducted the data analyses. All authors participated in preparation of the manuscript and approved the final draft for submission.

behavior, hormonal contraceptive use, and other STIs. The resulting hazard ratios were used to calculate population attributable risk percent (PAR%).

RESULTS—Between 1993 and 2012, 1,964 women contributed 6,135 person-years of follow-up. The overall PAR% for each infection was: prevalent HSV-2 (48.3%), incident HSV-2 (4.5%), BV (15.1%), intermediate microbiota (7.5%), vaginal yeast (6.4%), *T. vaginalis* (1.1%), *N. gonorrhoeae* (0.9%), non-specific cervicitis (0.7%), GUD (0.8%), and genital warts (−0.2%). Across the four time periods, the PAR% for prevalent HSV-2 (40.4%, 61.8%, 58.4%, 48.3%) and BV (17.1%, 19.5%, 14.7%, 17.1%), remained relatively high and had no significant trend for change over time. The PAR% for trichomoniasis, gonorrhea, GUD and genital warts remained <3% across the four periods.

CONCLUSIONS—Bacterial vaginosis and HSV-2 have consistently been the largest contributors to HIV acquisition risk in the Mombasa Cohort over the past 20 years. Interventions that prevent these conditions would benefit women's health, and could reduce their risk of becoming infected with HIV.

Keywords

Genital tract infections; HIV; women; Africa; population attributable risk percent

INTRODUCTION

In sub-Saharan Africa, a substantial geographic overlap between areas with high STI and HIV prevalence has been recognized since early in the HIV epidemic. Recognition of this geographic overlap led to the hypothesis that STIs could influence HIV transmission [1, 2]. However, treatment of STIs has failed to reduce HIV incidence in the majority of clinical trials [3], raising questions about whether STI treatment for HIV control is a feasible prevention tool [4]. In an effort to understand the inconsistency between findings from observational studies and clinical trials, several hypotheses have been advanced [5–8]. The most widely-accepted hypothesis suggests that the contribution of STIs to new HIV infections may change over time as an HIV epidemic matures [6]. In an early epidemic, the proportion of new HIV infections attributable to treatable STIs is much higher than at later stages [9, 10]. As the epidemic matures, there is a shift towards a greater proportion of HIV transmission attributable to chronic STIs such as herpes simplex virus type 2 (HSV-2) [11]. One modeling study has demonstrated that time since introduction of HIV in a community influences the contribution of STIs to HIV acquisition and an increase in the importance of HSV-2 as the HIV epidemic matures. In contrast, a meta-analysis assessing trends in HIV risk concluded that risk factors for HIV have remained relatively unchanged as the epidemic has matured [12].

To address the question of how the role of STIs in HIV acquisition has changed over time in a high-risk population, we sought to determine how the relative contribution of different STIs to HIV acquisition has changed over the past two decades. Our goals were to estimate the PAR% of various genital tract conditions to HIV acquisition in a cohort of HIV-seronegative high-risk women in Mombasa, Kenya. We then tested the hypothesis that the PAR% of different STIs would change significantly over the 20 years of observation.

MATERIALS AND METHODS

We conducted longitudinal follow-up of women participating in the Mombasa Cohort, an open cohort study of high-risk Kenyan women, between February 1993 and December 2012. The eligibility criteria were: age 18–50 years, residing in the Mombasa area, self-identifying as exchanging sex for cash or in-kind payment, and able to provide informed consent. This study was approved by the ethics boards of Kenyatta National Hospital, the University of Washington and the Fred Hutchinson Cancer Research Center. All participants provided informed consent for participation.

Clinic Procedures

At enrollment, a study nurse conducted a standardized interview detailing demographic data, medical, gynecological, and sexual history. A study physician performed a physical examination including a pelvic speculum examination with collection of swabs of cervical and vaginal secretions for STI testing. Blood was collected for HIV and HSV-2 testing. Women were asked to return for their results a week later. Following enrollment, women were scheduled for monthly follow-up visits, updated risk factor data were collected, and repeat testing for STIs and HIV were performed. Participants received free outpatient medical services including treatment of STIs according to WHO [13] and Kenyan national guidelines. Syndromic management was offered during examination visits if indicated. At the results visit one week later, additional treatment was provided if indicated by the laboratory test results.

Laboratory Procedures

HIV-1 serostatus was determined by ELISA (Detect HIV1/2, BioChem Immunosystems, Montreal, Canada [February 1993-January 2010] or PT-HIV 1,2–96, Pishtaz Teb Diagnostics, Tehran, Iran [February 2010 – December 2012]). Positive tests were confirmed using a second ELISA (Recombigen, Cambridge Biotech, Worcester, MA, USA [February 1993-August 2004] or Bio-Rad HIV-1/HIV-2, Bio-Rad Laboratories, Hercules, CA, USA [August 2004-May 2006] or Vironostika HIV-1 Uniform II AG/AB, bioMerieux, Marcy l'Etoile, France [May 2006-December 2012]). Vaginal Gram's stained slides were evaluated for bacterial vaginosis (BV) using Nugent's criteria [14]. Saline wet mounts were examined microscopically at 40X power for the presence of motile trichomonads, clue cells, and yeast. Culture for *Neisseria gonorrhoeae* was performed on modified Thayer-Martin media. Cervical Gram's stained slides were examined microscopically for the number of polymorphonuclear granulocytes, with a count of ≥ 30 being considered as cervicitis. Starting in August 2006, endocervical samples were tested for *N. gonorrhoeae* and *Chlamydia trachomatis* by transcription mediated amplification using the Gen-Probe APTIMA GC/CT Detection System (Hologic/Gen-Probe, San Diego, California, USA). Because the *Chlamydia* data do not span the entire period of cohort participation, they were not used for this study. Serological testing for HSV-2 was performed using a type-specific HSV-2 gG based ELISA (HerpeSelect 2, Focus Diagnostics, Cypress, California, USA). An index value of greater than or equal to 2.1 (the ratio of the optical density [OD] of the sample to the OD of the standard calibrator) was considered positive [15]. Syphilis testing was performed every three months using rapid plasma reagin (RPR). Further testing using

Treponema pallidum hemagglutination (TPHA) was conducted for RPR-positive samples. When present, ulcers were cultured for *Hemophilus ducreyi*. Since syphilis and *H. ducreyi* data were not collected monthly, these data were not included in the analyses.

Data Analyses

This study was conducted between February 1993 and December 2012. This 20-year period was grouped into four time periods of five years each: 1993–1997, 1998–2002, 2003–2007, 2008–2012. Only women who were HIV seronegative at enrolment were included. The primary exposures were vulvovaginal candidiasis, BV (Nugent score 7–10) [14], intermediate vaginal microbiota (Nugent score 4–6), *Trichomonas vaginalis*, *N. gonorrhoeae*, non-specific cervicitis, prevalent HSV-2, incident HSV-2, genital ulcer disease (GUD), and genital warts. The outcome was time to HIV acquisition. We determined the incidence rates of each genital tract condition overall and for each time period, allowing repeat infections for all conditions except HIV and HSV-2.

Person-time was calculated as time from enrollment until first positive HIV test, last clinic attendance, or end of study period. As in prior analyses with this cohort, we assumed the effect of STI on HIV susceptibility would persist for 15 days after the infection was detected at a clinic visit [16]. We also estimated that HIV seroconversion would be detected 45 days after HIV acquisition, assuming that infection would occur, on average, at the midpoint between monthly visits. Thus, the total window of effect for any STI to influence HIV susceptibility was estimated to be 60 days (15+45). That is, if a participant was diagnosed with an STI at visit Y, we assumed that the effect of the infection would last 60 days, so HIV acquired from the date of visit Y until Y + 60 days was considered exposed to this STI.

We used Cox regression models to determine the hazard ratios (HR) and 95% confidence intervals (CIs) for the effect of STIs on time to HIV seroconversion. First, we determined the incidence and correlates of HIV acquisition for the entire 20 year period. We conducted univariate analyses to determine whether individual risk factors were associated with HIV infection. Variables that were significantly associated with HIV in univariate analyses were included in the multivariate model. These included age, place of work, hormonal contraceptive use, number of sexual partners, unprotected intercourse, condom use in the past week, and tobacco use. For each time period, the final Cox model included the confounding factors from the multivariate model for the entire 20-year period. We decided *a priori* to include all genital tract conditions in the final multivariate model.

Population attributable risk percent was calculated from the adjusted HR obtained from the final Cox models. The formula for PAR% = $pc (HR-1/HR) \times 100\%$, where pc is the proportion of cases (at the visit level) that were exposed during the study. For each STI, we performed a linear test of trend to assess change in PAR% across time periods. Analyses were performed using IBM SPSS 19.0 (IBM, Kirkland, WA, USA) and STATA 12 (StataCorp, College Station, TX, USA).

RESULTS

From 1993–2012, we enrolled 2,301 HIV seronegative women, of whom 1,964 returned for ≥ 1 follow-up visit and were included in this analysis. Table 1 shows the baseline characteristics of these participants. Their median age was 28 years (interquartile range [IQR] 24–33). Most (1310, 66%) reported working at a bar or restaurant. Alcohol use was common (1512, 77%). Except for BV (N=642, 33%) and prevalent HSV-2 infection (N=1442, 73%), diagnosis of STIs and other genital tract conditions at baseline was less common.

The enrolled women contributed 6,135 person-years of follow-up. The median duration of follow-up was 1,136 days (IQR 315–2,878). Three hundred and twenty five women acquired HIV (5.3/100 person-years). The numbers of seroconverters in 1993–1997, 1998–2002, 2003–2007, and 2008–2012 were 150, 98, 56, and 21 respectively. The HIV incidence declined from 11.8/100 person-years in the first time period to 1.3/100 person-years in the last time period (Table 2). A pattern of declining incidence across the four time periods was also observed for *T. vaginalis* and non-specific cervicitis. Incidence rates of the other genital conditions demonstrated more temporal variability.

Over the 20-year period, all genital conditions except genital warts were associated with an increased likelihood of acquiring HIV (Table 3). In multivariate analyses, prevalent HSV-2 (HR 2.50 95% CI 1.51–4.13) and incident HSV-2 (HR 2.95 95% CI 1.63–5.34) were both associated with increased risk compared to HSV-2 seronegative status. Bacterial vaginosis (HR 1.86 95% CI 1.40–2.47) and intermediate vaginal microbiota (HR 1.54 95% CI 1.13–2.09) were associated with increased risk compared to normal microbiota. Vulvovaginal candidiasis (HR 2.09 95% CI 1.62–2.70), gonorrhea (HR 2.05 95% CI 1.38–3.04) and GUD (HR 2.23 95% CI 1.14–4.35) also remained significantly associated with increased risk of acquiring HIV. The association between trichomoniasis and HIV acquisition was of borderline significance (HR 1.41 95% CI 0.99–2.02). Neither condom use nor unprotected intercourse was significantly associated with HIV infection in univariate analysis, so these variables were not included in the multivariate model. Overall rates of reported condom use did not change significantly over time (data not shown).

Table 3 also shows the association between genital conditions and HIV acquisition in each of the four time periods. Although the increased risk of HIV acquisition remained for most genital tract conditions, there was less power for these subgroup analyses, and not all associations remained statistically significant.

To calculate PAR%, we first determined the visit-level prevalence of different genital conditions. Herpes simplex virus type 2 (30,860/38,378, 80.4%), BV (12,534/38,378, 32.6%), and intermediate microbiota (8,155/38,378, 21.3%) had the highest prevalence rates for the overall study period (Table 4). Prevalent HSV-2 (48.3%) had the highest overall PAR%, followed in descending order by BV (15.1%), intermediate microbiota (7.5%), vaginal yeast (6.4%), incident HSV-2 (4.5%), *T. vaginalis* (1.1%), *N. gonorrhoeae* (0.9%), GUD (0.8%), non-specific cervicitis (0.7%), and genital warts (–0.2%). Across the four time periods, the PAR% for prevalent HSV-2 (40.4%, 61.8%, 58.4%, 48.3%) and BV (17.1%,

19.5%, 14.7%, 17.1%), remained high, and there was no significant temporal trend for change in the contribution of these conditions to HIV acquisition. The PAR% for trichomoniasis, gonorrhea, GUD and genital warts all remained <3% across the four study periods. Only the PAR% of HIV attributable to candida changed significantly over time, beginning at 7.3% and decreasing steadily across the four time periods (linear test for trend $p=0.04$). Figure 1 is a graphical presentation of the PAR% results.

This analysis excluded 437 women who did not return for follow-up after enrollment. Compared to the 1,964 women included, those lost to follow-up were younger (median age 26 versus 28, $p<0.001$), more educated (9% versus 6% with 8–12 years of education, $p=0.004$), less likely to have ever been married (44% versus 52%, $p=0.002$), had fewer children (median 1 versus 2, $p=0.03$) and were less likely to use oral contraceptive pills (7% versus 12%, $p=0.013$). They were also less likely to report having >1 alcoholic drink per week (71% versus 77%, $p=0.014$) and less likely to have non-specific cervicitis (5% versus 11%, $p<0.001$) or HSV-2 (15% versus 73%, $p<0.001$). Apart from age and HSV-2, none of the other factors that differed between these two groups were significantly associated with HIV acquisition in this population.

DISCUSSION

In this 20-year prospective study of high-risk African women, HSV-2 and BV consistently made the greatest contribution to their risk of HIV acquisition. The PAR% for these two conditions remained relatively high and stable over time, at around 50% for HSV-2, 15% for BV, and 7.5% for intermediate vaginal microbiota. The PAR% contributions for curable STIs were much lower because these conditions were present at far fewer visits. With the exception of candida, there were no significant temporal changes in PAR% across the four time periods for the other genital conditions. As such, our findings generally do not support our original hypothesis that the contribution of these STIs to HIV acquisition has changed over the 20 years observed in this cohort.

Our data suggest that chronic and recurrent genital conditions are larger drivers of transmission than incident STIs of shorter duration. Stated in terms of PAR%, prevalent or recurrent conditions contribute much more to PAR% than short duration incident infections. Of note, many HSV-2 seropositive patients have only asymptomatic shedding or clinically unrecognized genital ulcers [17]. Thus, the contribution of HSV-2 is crucial even when clinically apparent GUD is not identified.

Changes in STI prevalence and incidence, potentially related to control strategies like condom use and syndromic management, could have influenced the PAR% contributed by some STIs. For example, syndromic STI management could have had a major impact on *H. ducreyi*. This organism is the cause of chancroid. This bacterial STI causes tender suppurative inguinal adenopathy and painful genital ulcers [18], and may have played a substantial role in HIV transmission in Africa in the late 1980s and early 1990s [9]. In addition, HIV incidence in many countries began to decline well before antiretroviral therapy became available [19], and strong STI programs in the 1990s may have influenced these trends.

Prior trials of STI control to reduce HIV incidence targeted bacterial STIs. In our population of high-risk women, these STIs appear to be less important as drivers of transmission. Only one clinical trial of STI treatment for HIV-1 prevention demonstrated a statistically significant reduction in HIV incidence [20]. It has been suggested that the relative contribution of curable STIs to HIV acquisition may decline in the later stages of an HIV epidemic [5]. Other plausible explanations for the failure of most RCT interventions to reduce HIV incidence involve technical issues such as low incidence in some studies, greater than anticipated variability in community clusters, contamination between intervention and control communities, high attrition rates, declining rates of curable STIs, inappropriate site selection, and weak/infrequent interventions [21, 22]. Two rigorously conducted trials targeted HSV-2 suppression, and these also failed to demonstrate an effect on HIV incidence [23, 24]. This effect has been attributed to the inability of acyclovir to suppress persistent immune activation triggered by HSV-2 infection that enhances HIV acquisition [25]. In addition, results from an in-vitro study demonstrated that CD4+ and CD8+ T cells persist at sites of HSV-2 reactivation.

Given the finding that HSV-2 and BV were the largest contributors to PAR% for HIV in women, it is interesting to note that there are important interactions between these two genital tract conditions. Women with BV are more likely to acquire HSV-2 [26]. There is also evidence that prevalent and incident HSV-2 infection is associated with increased prevalence of BV [27, 28]. In general, HSV-2 and BV appear to work together, with each driving the acquisition and/or transmission of the other. Devising innovative ways to mitigate the interactions between these conditions could help to reduce women's HIV risk.

While most studies targeting genital tract infections as a strategy to reduce HIV incidence have not demonstrated efficacy, it remains plausible that prevention of herpes and BV could reduce HIV incidence. Possible interventions for HSV-2 control include vaccination, pre-exposure prophylaxis to prevent HSV-2 acquisition, and preventing BV. Despite the disappointing results of the Herpevac trial, a herpes vaccine remains an important research priority [29]. The efficacy of prophylaxis, for example with valacyclovir, for HSV-2-negative individuals with an HSV-2-positive partner has not been tested. This approach to pre-exposure prophylaxis could be useful for reducing the risk of herpes, particularly in high-risk groups such as sex workers and young women in areas with a high incidence of both herpes and HIV.

Although standard antibiotic regimens result in high cure rates for BV, recurrences are common [30]. Interventions that allow women to maintain healthy vaginal microbiota free from BV and intermediate microbiota should be explored as a means of reducing the risk of herpes and other STIs. Periodic presumptive treatment (PPT) as a strategy to reduce the incidence of vaginal infections (candida, BV and trichomoniasis) and improve vaginal health has been evaluated. Data from Mombasa, Kenya have demonstrated that monthly PPT can reduce BV, promote *Lactobacillus* colonization and maintain a healthy vaginal environment [31–33]. This is a fundamental step towards the development of inexpensive, female-controlled, non-coitally dependent HIV risk reduction interventions for women. Clinical trials to assess BV suppression for STI prevention should be considered, and if successful would provide a useful tool for STI prevention.

This study had several strengths. First, we utilized a large dataset that provided sufficient power to assess the associations between STIs and HIV. Second, monthly sampling to detect HIV and STIs, combined with rigorous measurement of potential confounding factors, provided a strong foundation for studying the associations between HIV and STIs. Finally, our 20-year analysis period for the Mombasa Cohort extended back to 1993. Although this may not align perfectly with the early-phase epidemic in Kenya, HIV incidence was still relatively high at that time (17 per 100 person-years during the earliest period of cohort follow-up) [34]. In addition, HIV incidence declined steadily over the two decades that the study was conducted. As a result, we were able to assess trends in the PAR% contributions of different STIs to HIV acquisition during an extended period that incorporated a wide range of HIV incidences.

Our study also had several limitations. First, STIs and HIV share a common mode of acquisition through contact with an infected partner. As such, our HR and PAR% estimates could be inflated due to confounding by sexual risk behavior. We addressed potential confounding by adjusting for reported risk behaviors including frequency of unprotected sex, number of sexual partners, and number of sex episodes. Nonetheless, we recognize the potential for residual confounding. Second, the number of seroconverters decreased over time in the cohort. The modest number of events in the last ten years limited the precision in our PAR% estimates for the last two time periods. This finding may reflect aggressive screening and treatment of STIs in the cohort and behavior change counselling that the women receive once they have joined the cohort, or a general decrease in HIV incidence in the community, possibly as a result of antiretroviral therapy scale-up. Third, as with all observational studies, these results cannot definitively establish the presence causal associations between STIs and HIV acquisition. Fourth, differences in the sensitivity of laboratory methods for diagnosis of the different STIs may have contributed to the observed strength of the associations. However, the greatest difference in PAR% was likely contributed by the chronicity and frequent recurrence of HSV-2 and BV respectively. Fifth, we did not analyze the contribution of STIs such as syphilis and chancroid to HIV acquisition, because these data were not collected monthly. However the overall prevalences of syphilis and chancroid in this cohort were low (2.4% and 0.03% respectively), hence their contribution to HIV acquisition is likely to be minimal. Sixth, we did not evaluate the contribution of clearance of genital warts to HIV acquisition [35] as this would have required a different approach to our analysis than for the other STIs for which PAR% was based on the presence rather than clearance. Finally, our study population was composed of high-risk women whose sexual risk behavior is likely to be different from the general population, and this may limit generalizability. Changes in STI PAR% for HIV acquisition might also differ by geographic location, even for other populations of high-risk women. Despite these limitations, these results make a unique addition to the literature on STI and HIV interactions by directly evaluating trends in the contribution of different STIs to HIV acquisition over 2 decades of observation.

In summary, HSV-2 infection and BV have remained the largest drivers of HIV acquisition in this cohort of high-risk women from 1993 through 2012. While RCTs for prevention and treatment of genital tract infections have mostly failed to reduce HIV incidence, our study highlights the importance of HSV-2 and BV as persistent drivers of HIV transmission. The

findings suggest that strategic interventions that target STIs that are the main contributors to HIV risk could compliment other efficacious prevention approaches such as treatment as prevention [36], pre-exposure prophylaxis [37] and male circumcision [38]. Novel approaches such as HSV-2 vaccination, pre-exposure prophylaxis to prevent HSV-2 acquisition, and interventions that allow women to maintain healthy vaginal microbiota could provide useful strategies for improving women's health and potentially decreasing susceptibility to HIV.

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Figure 1.
Contribution (PAR%) of various genital tract conditions to HIV acquisition by time period

Table 1

Baseline characteristics of 1964 HIV-negative women

Characteristic	Median (IQR) or Number (percent)
Demographics	
Age (years)	28 (24–33)
Education	
8 years	1192 (60.7)
>8 – 12 years	658 (33.5)
12 years	114 (5.8)
Ever married ^a	1029 (52.4)
Work place	
Bar/Restaurant	1310 (66.3)
Night club	507 (25.8)
Home based/other	147 (7.5)
Gynecological	
Parity	2 (1–3)
Hormonal contraceptive use	
OCP	229 (11.7)
DMPA/Norplant	467 (23.9)
Sexual risk behavior reported in an average week	
Unprotected intercourse	178 (9.1)
>1 sex partner ^b	919 (47.4)
>1 sex encounters ^b	1307 (67.4)
Drug use reported at enrollment in the cohort	
Alcohol (1 drink per week)	1512 (77.0)
Tobacco (1 cigarette per day)	338 (17.2)
Laboratory diagnosis of genital tract conditions	
Vulvovaginal candidiasis	280 (14.3)
Bacterial vaginosis	642 (32.7)
<i>Trichomonas vaginalis</i>	95 (4.8)
<i>Neisseria gonorrhoeae</i>	78 (4.0)
Non-specific cervicitis	220 (11.2)
Herpes simplex virus type 2	1442 (73.4)
Genital ulcer disease	36 (1.8)
Genital warts	26 (1.3)
Reported vaginal washing	1841 (93.7)
Water only ^c	491 (26.7)
Soap/Other ^c	1350 (73.3)

OCP – oral contraceptive pills; DMPA – depot medroxyprogesterone acetate

^aIncluded 30 currently married, and 999 widowed or divorced women

^b Analyzed only among 1938 women reporting any sexual activity in the past week

^c Analyzed only among 1841 women reporting vaginal washing

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Table 2
Incidence per 100 person-years of HIV and other genital tract conditions by time period

Genital tract condition	Overall incidence	1993–1997	1998–2002	2003–2007	2008–2012	P value for test of trend
HIV	5.30	11.83	6.19	3.28	1.33	0.03
Candidiasis	62.56	72.11	48.88	71.73	59.93	0.82
Intermediate microbiota	109.10	200.13	94.59	98.49	70.17	0.34
Bacterial vaginosis	168.97	243.28	147.36	186.07	119.21	0.20
<i>Trichomonas vaginalis</i>	18.63	36.22	21.02	15.76	6.58	0.02
<i>Neisseria gonorrhoeae</i>	8.74	21.75	8.64	3.31	5.39	0.15
Non-specific cervicitis	26.88	105.24	10.58	10.14	5.64	0.20
HSV-2	19.58	31.40	23.33	11.87	13.44	0.08
Genital ulcer disease	7.49	9.19	6.74	6.20	8.46	0.75
Genital warts	11.19	27.37	3.70	4.57	14.55	0.56

Table 3

Association between different genital tract conditions and HIV acquisition*

Genital tract condition	Overall ^a	1993–1997 ^b	1998–2002 ^b	2003–2007 ^b	2008–2012 ^b
Candidiasis	2.09 (1.62–2.70) p = <0.001	3.04 (2.12–4.36) p = <0.001	1.65 (0.92–2.95) p = 0.09	1.47 (0.69–3.02) p = 0.32	0.99 (0.21–4.64) p = 0.99
Intermediate microbiota	1.54 (1.13–2.09) p = 0.01	1.76 (1.10–2.82) p = 0.02	1.08 (0.53–2.21) p = 0.83	1.30 (0.50–3.36) p = 0.60	2.35 (0.53–10.35) p = 0.26
Bacterial vaginosis	1.86 (1.40–2.47) p = <0.001	1.90 (1.19–3.02) p = 0.01	2.07 (1.13–3.79) p = 0.02	1.81 (0.90–3.63) p = 0.10	3.32 (0.98–11.17) p = 0.05
<i>Trichomonas vaginalis</i>	1.41 (0.99–2.02) p = 0.06	1.18 (0.70–1.97) p = 0.53	2.10 (1.07–4.10) p = 0.03	2.22 (0.66–7.51) p = 0.20	2.22 (0.25–19.88) p = 0.48
<i>Neisseria gonorrhoeae</i>	2.05 (1.38–3.04) p = <0.001	1.50 (0.84–2.65) p = 0.17	1.91 (0.80–4.54) p = 0.14	7.39 (1.68–32.49) p = 0.01	3.60 (0.41–31.24) p = 0.25
Non-specific cervicitis	1.14 (0.81–1.60) p = 0.45	1.09 (0.74–1.61) p = 0.68	1.64 (0.70–3.83) p = 0.25	— ^c	— ^c
Prevalent HSV-2	2.50 (1.51–4.13) p = <0.001	1.98 (0.98–4.00) p = 0.06	4.74 (1.11–20.19) p = 0.04	3.70 (0.86–15.93) p = 0.08	2.46 (0.30–19.95) p = 0.40
Incident HSV-2	2.95 (1.63–5.34) p = <0.001	3.26 (1.35–7.85) p = 0.01	6.69 (1.46–30.60) p = 0.01	3.42 (0.61–19.24) p = 0.16	1.13 (0.07–19.15) p = 0.93
Genital ulcer disease	2.23 (1.14–4.35) p = 0.02	2.13 (0.67–6.75) p = 0.20	1.80 (0.53–6.18) p = 0.35	— ^c	6.09 (0.71–51.98) p = 0.10
Genital warts	0.92 (0.41–2.10) p = 0.85	0.83 (0.33–2.05) 0.68	— ^c	3.54 (0.46–27.08) 0.22	— ^c

* Adjusted hazard ratios

^a Analyses are adjusted for age, place of work, hormonal contraceptive use, number of sexual partners, tobacco use, calendar year and all sexually transmitted infections/conditions listed in the table.

^b Analyses are adjusted for age, place of work, hormonal contraceptive use, number of sexual partners, tobacco use and all sexually transmitted infections/conditions listed in the table.

^c There were no cases therefore it was not possible to calculate an incidence estimate

Prevalence (proportion of visits exposed) and contribution of genital tract conditions to HIV acquisition (PAR%) by time period

Table 4

Genital tract condition	Overall		1993-1997		1998-2002		2003-2007		2008-2012	
	P	PAR%	P	PAR%	P	PAR%	P	PAR%	P	PAR%
Candidiasis	12.19	6.36	10.91	7.32	12.73	5.01	12.73	4.07	12.42	-0.13
Intermediate microbiota	21.25	7.45	29.52	12.75	24.54	1.82	17.44	4.02	14.55	8.36
Bacterial vaginosis	32.66	15.10	36.07	17.09	37.78	19.53	32.82	14.69	24.53	17.14
<i>Trichomonas vaginalis</i>	3.66	1.06	5.44	0.83	5.38	2.82	2.81	1.54	1.40	0.77
<i>Neisseria gonorrhoeae</i>	1.79	0.92	3.51	1.17	2.23	1.06	0.61	0.53	1.11	0.80
Non-specific cervicitis	5.47	0.67	16.09	1.33	2.70	1.05	1.82	.a	1.19	.a
Prevalent HSV-2	80.42	48.25	81.70	40.44	78.29	61.77	80.00	58.38	81.37	48.29
Incident HSV-2	6.81	4.50	3.50	2.43	7.95	6.76	8.67	6.13	7.03	0.81
Genital ulcer disease	1.49	0.82	1.48	0.79	1.74	0.77	1.09	.a	1.82	1.52
Genital warts	2.15	-0.19	3.93	-0.80	0.94	.a	0.81	0.58	3.00	.a

P=Prevalence; PAR%=Population attributable risk percent

^aThere were no cases therefore it was not possible to calculate PAR%