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Human papillomavirus infection among male adolescents and young adults with perinatally-acquired HIV and without HIV in Thailand

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Abstract

HIV infection may increase the risk of persistent infection and complications. Perinatally HIV-infected (PHIV) and HIV-uninfected male adolescents and young adults (AYA) in Thailand were matched by age and number of lifetime sexual partners. HPV infection at oral, anal, penile, and scrotal sites was detected by polymerase chain reaction. A total of 49 PHIV and 47 HIV-uninfected male AYA (median age 18 [17–20] years) were enrolled (June 2013–September 2014). Overall, 18 were men who had sex with men (MSM) (12% of PHIV and 26% of HIV-uninfected AYA; $P=0.12$). Among the PHIV, the median (IQR) CD4 cell count was 573 (434–747) cells/mm³ and 69% had HIV RNA load <40 copies/mL. The prevalence of any HPV infection was 61% in PHIV and 49% in HIV-uninfected AYA ($P=0.23$); and that of high-risk HPV infection was 33% in PHIV and 28% in HIV-uninfected AYA ($P=0.59$). Among those with HPV, 55% were infected with any high-risk HPV type and 28% had HPV-16 and/or HPV-18. In multivariate models, smoking (OR 6.10, 95% CI, 1.19–31.35, $P=0.01$) and prior history of STI symptoms (OR 5.01, 95% CI, 1.63–15.40, $P=0.004$) were associated with high-risk HPV infection. HPV vaccination in early adolescence presents a valuable but missed prevention opportunity.

Keywords

HIV; human papillomavirus; perinatal; male adolescents; prevalence

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Introduction

Human papillomavirus (HPV) is the most common cause of anogenital cancers in men, with HPV DNA identified in up to 90% of anal cancers and 30–50% of penile cancers.^{1–2} Genital HPV infections are mainly sexually transmitted. Most HPV infections in adults are transient, and approximately 90% resolve without treatment within 12–24 months.^{3–5} While anogenital cancers in the general population are relatively rare, the incidence is substantially higher in HIV-infected men, particularly among men who have sex with men (MSM) compared to heterosexual men.^{6–9} People living with HIV are at further increased risk of HPV infection, and have lower rates of HPV clearance, resulting in persistent infection and long-term complications.^{10–12} Studies in perinatally HIV-infected female adolescents have shown that about half had high-risk HPV infection in cervical samples and one-third had abnormal cervical cytology, despite their younger ages and shorter times since sexual debut compared to older adults.^{13,14}

To date, there has been no published studies focused on HPV infection among Asian perinatally HIV-infected (PHIV) males. The objective of this study was to determine the prevalence of HPV infection in PHIV male adolescents and young adults compared to HIV-uninfected matched peers, as well as explore factors associated with HPV infection in these populations.

Methods

We conducted a prospective observational study of the natural history of oral, anal, and genital HPV infection among PHIV and HIV-uninfected male adolescents and young adults in Thailand. The results from the baseline visit conducted between June 2013 and September 2014 are presented here.

Study participants

PHIV and HIV-uninfected male adolescents and young adults aged 12–24 years were eligible for recruitment in Bangkok at two sites: 1) HIV-NAT, Thai Red Cross AIDS Research Centre and 2) Siriraj Hospital, Mahidol University. Male adolescents and young adults were eligible to participate if they had a history of prior sexual activity, no current symptomatic untreated sexually transmitted infections (STI) (except genital warts), had not previously received HPV vaccine, and were able to independently complete the audio computer-assisted self-interview (ACASI). Participants with HIV were limited to those who had acquired their HIV infections perinatally and had been fully disclosed to about their own HIV status. The perinatal infection was determined by maternal HIV status and the history of HIV-related illness or treatment with onset during childhood. They were matched to HIV-uninfected males by age group (12–15, 16–18, 19–21, 22–24 years) and number of lifetime sex partners (3 or >3). The inclusion criteria of the HIV-uninfected adolescents and young adults were those healthy males with an anti-HIV negative at the screening visit (within 4 weeks before baseline visit) and without any chronic diseases or receiving medications causing immunosuppression.

The study was approved by the institutional review boards of the two participating sites and the coordinating center (TREAT Asia/amfAR, Bangkok). At HIV-NAT, informed consent was obtained from participants aged 18 years or older or from legal guardians for those under the age of 18. Assent was obtained from participants below 18 years of age. At Siriraj Hospital, informed consent was obtained from those aged 18 years or older, and assent from those below 18 years of age; legal guardian consent was waived.

Procedures

Eligible participants visited the clinic at baseline (enrollment) and then annually for three years. At baseline and annual study visits, all participants underwent physical examination, sexual and risk behavioral assessment, completed the study ACASI, and had laboratory testing, including fasting lipid profiles, rapid plasma reagin (RPR) or venereal disease research laboratory (VDRL) tests with confirmatory tests (TP-PA), CD4 and HIV RNA for PHIV, anti-HIV antibody for HIV-uninfected participants, and urine collection for chlamydia and gonorrhea.

Sexual and risk behavioral assessment

Sexual and other risk behaviors were documented among all participants using a sexual behavior questionnaire and an ACASI administered on a tablet device. The ACASI consisted of a maximum of 84 questions for HIV-infected adolescents on demographics, sexual behavior, substance abuse, adherence to ART, stigma associated with HIV infection, and violence, and a maximum of 57 questions for HIV-uninfected adolescents (questions on adherence and stigma were omitted).

HPV testing

Oral rinse, and anal, penile, and scrotal samples were obtained to detect HPV infection. Oral rinses were stored at -20 to -70°C prior to shipment to the Thai Red Cross AIDS Research Centre central laboratory. Specimens were analyzed for HPV DNA by using the LINEAR ARRAY HPV Genotyping test (LA HPV GT, Roche Molecular Systems, Inc.) to identify 37 HPV DNA genotypes including 13 high-risk genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68) and 24 other genotypes (6, 11, 26, 40, 42, 53, 54, 55, 61, 62, 64, 66, 67, 69, 70, 71, 72, 73 [MM9], 81, 82 [MM4], 83 [MM7], 84 [MM8], IS39, CP6108).

Statistical Methods

Due to very limited study available from the LMICs in adolescent males, we use a study in HIV-uninfected male university students with a mean age of 19 years that reported prevalence rates of any HPV on the glans, penile shaft and scrotum of 26%.¹⁵ As there was no report on the difference of the prevalence between HIV-infected and HIV-uninfected male adolescents, we assumed 30% difference reported in female adolescents.¹⁶ With this, 80 subjected (1:1 of HIV-infected and HIV-uninfected male adolescents) would be sufficient to detect the difference of HPV prevalence with 80% power at a 2-sided significance level of 5%.

Statistical analysis was conducted with Stata 14.1 (Statacorp, College Station, TX, USA). Socio-demographic and behavioral characteristics were compared between study groups

(PHIV and HIV-uninfected) using a Wilcoxon test for continuous characteristics, and a Fisher's exact test for categorical characteristics. HPV genotype specific prevalence was compared in anatomical sites, by HIV exposure groups using a Fisher's exact test. Thereafter we assessed associations between HIV exposure group, behavioral characteristics, and the presence of any HPV or any high-risk HPV at any anatomical site using multiple logistic regression. Covariates significant at $P < 0.1$ in univariate models were adjusted for in a multivariate model.

Results

Participant characteristics

A total of 96 sexually active male adolescents and young adults were recruited into the study: 49 were PHIV and 47 were HIV-uninfected (Table 1). The median (interquartile range [IQR]) age was 18 (17–20) years for PHIV males, and 19 (17–20) for HIV-uninfected males ($P=0.33$). All of the PHIV participants were receiving ART; their median (IQR) CD4 count was 573 (434–747) cells/mm³ and 69% had plasma HIV RNA <40 copies/mL. Eighteen (37%) of PHIV and 34 (72%) of HIV-uninfected males were living with one or both parents ($P < 0.001$). In the past three months, 31 (63%) of PHIV compared to 35 (75%) of HIV-uninfected participants reported drinking alcohol ($P=0.29$), 31 (64%) compared to 32 (68%) reported smoking ($P=0.83$), and 11 (44%) compared to 14 (29%) had used recreational drugs ($P=0.67$). Among them, 22% compared to 26% ($P=0.72$) had unsafe or unplanned sex following alcohol or other drug use.

Overall, 18 (19%) participants reported being MSM, six of whom were PHIV (12% of PHIV vs 25.5% of HIV-uninfected males, $P=0.12$). None of the PHIV and seven (15%) HIV-uninfected males were circumcised ($P=0.02$). The PHIV participants were more likely to always use a condom with insertive vaginal intercourse in the past six months (41% vs. 9%, $P=0.001$). Prior history of STI symptoms including but not limited to genital ulcers, genital rash, and genital discharge was reported in 16% of PHIV and 26% of HIV-uninfected males ($P=0.66$).

HPV infection prevalence

The prevalence of any HPV infection identified by HPV DNA detection was 61% in PHIV and 49% in HIV-uninfected participants ($P=0.23$). Overall among HPV-infected adolescents, 55% were infected with any high-risk HPV types, and 28% were infected with HPV-16 and/or HPV-18. The most common high-risk HPV type was HPV-59 (26%), followed by HPV-18 (17%), and HPV-16 and HPV-51 (11% each). High-risk HPV infection was found in 33% of PHIV and 28% of HIV-uninfected participants overall ($P=0.59$), and none of the HIV-uninfected males were infected with HPV-16, Figure 1. The prevalence of any HPV and high-risk HPV infection among MSM regardless of HIV infection were 67% and 33%, and among non-MSM were 52% and 29%, respectively. The rates of any HPV and high-risk HPV detection were 9% and 2% in oral, 22% and 11% in anal, 43% and 22% in penile, and 32% and 13% in scrotal samples. The concordances of HPV serotypes detected at oral, anal, penile, and scrotal compartments were low at 6% between penile and anal samples, and 11% between penile and scrotal samples. PHIV males had a higher rate of oral

HPV infection (16% vs. 2%, $P=0.02$). Three PHIV and none of the HIV-uninfected participants had genital warts.

Factors associated with any HPV and high-risk HPV infection—Overall, 30% of adolescents had high-risk HPV infection at any anatomical site. On regression analysis, this was related to smoking and prior history of STI symptoms, (Table 2; smoking OR 6.10, 95% CI, 1.19–31.35, $P=0.01$; history of STI symptoms OR 5.01, 95% CI, 1.63–15.40, $P=0.004$). Prior history of STI symptoms was also associated with any HPV infection (OR 3.08, 95% CI, 1.01 – 9.37, $P=0.04$). HIV infection status and MSM gender identity were not associated with any HPV infection or high-risk HPV infection ($P=0.7$ and $P=0.74$).

Discussion

This study adds to the very limited available data on HPV infection among sexually active Asian male adolescents and young adults with PHIV infection, reporting a prevalence of any HPV infection of 61% and of high-risk HPV of 33% in Thai PHIV male youth. We also found that high-risk HPV was associated with smoking and a prior history of STI symptoms, which have been reported in the past and are likely markers of high-risk sex behaviors in our context.^{10,17,18} The prevalence of HPV infection among males over 18 years of age varies by study population, age, geographic area, anatomical sites, and HPV DNA detection methods.^{19–22} Data from East Asia showed that adult males without HIV from Japan, China, and South Korea had a relatively lower rate of HPV infection with the range from 8% to 19%.²⁰ In HIV-uninfected adult males with a mean age of 32 years in the US and Latin America from the HPV in Men (HIM) Study,⁵ 50% of participants had genital infection with any HPV types and 30% were infected with oncogenic HPV, data which are comparable to our 49% overall HPV prevalence and 28% high-risk HPV prevalence among our much younger HIV-uninfected male youth.

People living with HIV have an increased risk of new HPV infection, reactivation of latent infection, and decreased ability of clearance.¹⁰ Both HIV and HPV viruses are primarily transmitted by sexual contact. While vertical transmission of HPV has been reported, the rates are relatively low. A meta-analysis of prospective cohort studies showed a pooled relative risk of mother-to-child HPV transmission of 4.8.²³ Data on vertical transmission of HPV, specifically among perinatally HIV-infected children are limited. A study in the US reported that approximately a quarter of pre-sexually active boys and girls with perinatal HIV infection had detectable HPV in oral or genital sites.²⁴ Data of the cohort in Thailand and Vietnam revealed that sexually active PHIV female youth had higher rates of any HPV and high-risk HPV detection than HIV-uninfected counterparts.²⁵ Our study found no statistically significant differences in prevalence of any HPV infection and prevalence of high-risk HPV infection between PHIV and HIV-uninfected male youth, but our cohort was relatively small and prevalence values overall and in every compartment were consistently higher among PHIV. Notably, all of our PHIV participants were on ART, and as a group they had a high median CD4 count (573 cells/mm³) and 69% of them had viral suppression, showing that ART alone may have a limited impact on the epidemiology of HPV infections acquired by PHIV youth.

Among MSM, the prevalence of HPV infection in our study was similar by HIV status. In adults, the rate of HPV detection is higher among MSM and the anal cancer incidence was 20–25 times higher in MSM than in heterosexual men.^{7,26} Moreover, adult MSM with HIV have been reported to have an even higher rate of HPV infection and anal cancer rates twice as high as MSM without HIV.⁹ A study among Thai adult MSM with HIV found the prevalence of any anal HPV infection of as high as 85%,²⁷ but only 10% of participants in that study had undetectable HIV viral load, which was thought to have mediated the high rates of infection. A study from the US reported a prevalence of anal high-risk HPV infection of 61% among adult males with HIV, where 60% were MSM and 61% had a suppressed HIV viral load.²⁸ While the lack of an impact of HIV status on HPV infections among MSM in our younger cohort is likely related to the small size of this sub-group, we cannot rule out variations in sexual behaviors (e.g., receptive anal intercourse) also being a factor.

We found relatively high prevalence of oral HPV detection in our study (9%) compared to other studies in lower and middle income countries (LMICs). This was probably from the different population and specimen collection methods. The HPV exposure would be different by sexual practice in different populations and settings. The recent study in South Africa²⁹ conducted in 181 male adults with the median age of 39 years, 15% reported oral sex practices, and 7% reported ever have sex with men, found oral HPV prevalence of 1.8% in oral rinse samples and 0.6% in swab samples. Another study conducted in 124 healthy volunteer adults in Sao Paulo collected the samples by mouthwash, and found oral HPV in 2.4%. The sexual risk behavior was not reported in that study.³⁰ Our population was male adolescents and young adults with median age of 18 years, relatively higher sexual risk with 18% were MSM, and the specimen collection was by oral rinse.

These data are useful for public health policy makers in Southeast Asia as they consider the inclusion of male children into new and recently implemented HPV vaccination programs. In Thailand in 2017, a 2-dose series of HPV vaccine was included in the national health program, but only for 5th grade girls enrolled in primary school. Moreover, for children with HIV of either sex, a 3-dose series of HPV vaccine is recommended.³¹ Although there have been some discussions around the potential for HPV vaccination coverage among females to offer some degree of “herd immunity” to males, this would not benefit MSM per se nor would it offer population-level protection against HPV infection and prevention of HPV-related cancers for males.

There are several limitations to our study. This was a descriptive study without a sample size calculation, as prior data were not available on HPV prevalence in PHIV in this age group to base the power estimates on. Consequently, the size of our cohort was likely to be insufficient for a thorough comparative analysis. Despite that, we observed consistently higher absolute HPV prevalence in all anogenital compartments and significantly higher rates in oral samples among those with PHIV infection. In addition, due to the nature of study design, the associations observed do not imply causality. Furthermore, the proportion of MSM in the HIV-uninfected group was notably higher than in the PHIV group. Based on HPV data in adult males, this would have been expected to result in higher rates of HPV in the HIV-uninfected group, but this was not the case in terms of absolute prevalence. Had the

sub-populations of young MSM been balanced between the groups, there may have been an even greater difference in HPV infection rates by HIV status.

In conclusion, our study showed over half of sexually active Thai PHIV and HIV-uninfected male adolescents and young adults had HPV infection. Accounting for the possibility of vertical HPV transmission, most HPV infections and associated cancers among males could be prevented by expanding vaccination access to boys and young adolescent males. Early sex education to prevent STIs, HPV vaccination before both males and females become sexually active, and smoking prevention should be emphasized within public health programs for children and youth.

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Figure 1.
High-risk HPV genotypes detected across four anatomical sites (i.e., oral, anal, penile, scrotal), by HIV status (N=96)

Table 1.

Baseline characteristics of 96 male adolescent and young adult study participants, by HIV status

Characteristics	Total (n=96)	Perinatally HIV-infected (n=49)	HIV-uninfected (n=47)	P
Age in years, median (IQR₂₅₋₇₅)	18 (17 – 20)	18 (17 – 20)	19 (17 – 20)	0.33
BMI, kg/m², median (IQR)	20.0 (17.7 – 22.0)	19.6 (17.6 – 21.3)	20.2 (18.4 – 23.9)	0.17
Circumcision				0.02
No	79 (82%)	43 (88%)	36 (77%)	
Yes	7 (8%)	0 (0%)	7 (15%)	
Unknown	10 (10%)	6 (12%)	4 (8%)	
Living situation				<0.001
With One or both parents	52 (54%)	18 (37%)	34 (72%)	
With Relatives	25 (26%)	21 (43%)	4 (9%)	
In a Foster home or shelter	2 (2%)	2 (4%)	0 (0%)	
With a Partner or husband	9 (9%)	1 (2%)	8 (17%)	
Alone	7 (7%)	7 (14%)	0 (0%)	
No response	1 (1%)	0 (0%)	1 (2%)	
Currently employed				0.28
Yes	49 (51%)	28 (57%)	21 (45%)	
No	45 (47%)	21 (43%)	24 (51%)	
No response	2 (2%)	0 (0%)	2 (4%)	
Ever used alcohol				0.80
Yes	91 (95%)	47 (96%)	44 (94%)	
No	4 (4%)	2 (4%)	2 (4%)	
No response	1 (1%)	0 (0%)	1 (2%)	
Ever smoked tobacco				0.45
Yes	75 (78%)	37 (76%)	38 (81%)	
No	20 (21%)	12 (24%)	8 (17%)	
No response	1 (1%)	0 (0%)	1 (2%)	
Ever experienced using other substances				0.05
Yes	26 (27%)	9 (18%)	17 (36%)	
No	69 (72%)	40 (82%)	29 (62%)	
No response	1 (1%)	0 (0%)	1 (2%)	
Sexual behavior				
MSM	18 (19%)	6 (12%)	12 (25.5%)	0.12
Median (IQR) number of lifetime partners	4 (2 – 10)	4 (2 – 9)	4 (2 – 10)	0.54
Median (IQR) number of partners in last 6 months	1 (1 – 2)	1 (1 – 1)	1 (1 – 2)	0.15
Frequency of sexual intercourse in the last 3 months (per month)				0.15
1–5 times	52 (54%)	25 (51%)	27 (57%)	

Characteristics	Total (n=96)	Perinatally HIV-infected (n=49)	HIV-uninfected (n=47)	P
6–10 times	21 (22%)	11 (22%)	10 (21%)	
11–20 times	9 (9%)	5 (10%)	4 (9%)	
More than 20 times	3 (3%)	0 (0%)	3 (6%)	
Almost every day	3 (3%)	1 (2%)	2 (4%)	
No response	8 (8%)	7 (14%)	1 (2%)	
Frequency of condom use				0.003
Always use	31 (33%)	23 (47%)	8 (17%)	
Sometimes use	57 (59%)	21 (43%)	36 (77%)	
Never use	5 (5%)	3 (6%)	2 (4%)	
No response	3 (3%)	2 (4%)	1 (2%)	
Condom use with insertive vaginal sex in the past 6 months				0.001
Always	24 (25%)	20 (41%)	4 (9%)	
Sometimes	43 (45%)	18 (37%)	25 (53%)	
Never	6 (6%)	4 (8%)	2 (4%)	
Not applicable ^a	23 (24%)	7 (14%)	16 (34%)	
Condom use with insertive anal sex in the past 6 months				0.20
Always	3 (3%)	3 (6%)	0 (0%)	
Sometimes	7 (7%)	3 (6%)	4 (9%)	
Never	2 (2%)	2 (4%)	0 (0%)	
Not applicable ^a	84 (88%)	41 (84%)	43 (91%)	
Condom use with receptive anal sex in the past 6 months				0.46
Always	3 (3%)	1 (2%)	2 (4%)	
Sometimes	6 (6%)	0 (0%)	6 (13%)	
Never	2 (2%)	0 (0%)	2 (4%)	
Not applicable ^a	85 (89%)	48 (98%)	37 (79%)	
STI testing				
Syphilis (VDRL,RPR), Positive	3 (3%)	2 (4%)	1 (2%)	1.0
<i>Neisseria gonorrhoea</i> , Positive	2 (2%)	0 (0%)	2 (4%)	0.24
<i>Chlamydia trachomatis</i> , Positive	10 (10%)	6 (12%)	4 (9%)	0.74
Ever experienced STI symptoms (eg. genital discharge, genital rash, or genital ulcer)				0.66
Yes	20 (21%)	8 (16%)	12 (26%)	
No	74 (77%)	40 (82%)	34 (72%)	
No response	2 (2%)	1 (2%)	1 (2%)	

Note: One PHIV adolescent and one HIV-uninfected adolescent had incomplete data on the sexual behavior part in ACASI, one HIV-uninfected adolescent had missing data in ACASI. One PHIV and two HIV-uninfected adolescents reported having both male-female and male-male sexual relationship.

^aNot Applicable: did not use this route or did not have sex in that time interval

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Table 2.

Factors associated with any HPV and high-risk HPV infections

Characteristics	Any HPV infection (N= 51)			High risk HPV infection (N= 28)		
	Univariate analysis		p	Univariate analysis		p
	Unadjusted OR (95%CI)	P		Unadjusted OR (95%CI)	P	
HIV status		0.35			0.70	
Uninfected	(Ref)			(Ref)		
Perinatal infection	1.47 (0.65 – 3.35)			1.19 (0.49 – 2.89)		
MSM		0.26			0.74	
No	(Ref)			(Ref)		
Yes	1.85 (0.63 – 5.43)			1.20 (0.40 – 3.61)		
Circumcision		0.13			0.31	
No	(Ref)			(Ref)		
Yes	0.29 (0.05 – 1.60)			0.36 (0.04 – 3.17)		
N/A						
Number of sex partners in the past 6 months		0.39			0.90	
None	(Ref)			(Ref)		
1	0.48 (0.13 – 1.79)			0.89 (0.24 – 3.38)		
2	0.80 (0.19 – 3.37)			0.74 (0.17 – 3.24)		
ACASI questions						
Type of sex activity						
Insertive vaginal sex		0.43			0.62	
No	(Ref)			(Ref)		
Yes	0.63 (0.19 – 2.05)			0.74 (0.22 – 2.45)		
Insertive anal sex		0.79			0.80	
No	(Ref)			(Ref)		
Yes	1.18 (0.34 – 4.02)			1.19 (0.33 – 4.32)		
Receptive anal sex		0.25			0.49	
No	(Ref)			(Ref)		
Yes	2.04 (0.58 – 7.15)			1.55 (0.46 – 5.23)		

Characteristics	Any HPV infection (N= 51)				High risk HPV infection (N= 28)			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	Unadjusted OR (95%CI)	P	Adjusted OR (95%CI)	p	Unadjusted OR (95%CI)	P	Adjusted OR (95%CI)	p
Number of sex partners in the last 3 months		0.29				0.32		
1	(Ref)				(Ref)			
2	1.61 (0.66 – 3.91)				1.60 (0.63 – 4.05)			
Frequency of condom use		0.75				0.68		
Always	(Ref)				(Ref)			
Sometimes	0.86 (0.36 – 2.08)				1.22 (0.47 – 3.16)			
Never	0.48 (0.07 – 3.30)				-			
Ever experienced STI symptoms *		0.04		0.04		0.008		0.004
No	(Ref)		(Ref)		(Ref)		(Ref)	
Yes	3.08 (1.01 – 9.37)		3.08 (1.01 – 9.37)		4.03 (1.43 – 11.33)		5.01 (1.63 – 15.40)	
Ever tried alcohol		0.84				0.82		
No	(Ref)				(Ref)			
Yes	1.22 (0.17 – 9.09)				1.31 (0.13 – 13.13)			
Ever smoked cigarettes		0.21				0.02		0.01
No	(Ref)				(Ref)		(Ref)	
Yes	1.91 (0.69 – 5.30)				4.60 (0.99 – 21.50)		6.10 (1.19 – 31.35)	
Ever used other substances		0.20				0.28		
No	(Ref)				(Ref)			
Yes	1.83 (0.72 – 4.69)				1.70 (0.65 – 4.43)			

* Past history of sexually transmitted infection symptoms; examples: genital discharge, genital rash, or genital ulcer