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Genital human papillomavirus infection in Indian HIV-seropositive men who have sex with men

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Abstract

Background—The incidence of penile cancer in Indian men is high. Little is known about genital HPV infection in Indian HIV-seropositive men who have sex with men (MSM), a population that may be at particularly high risk of genital human papillomavirus (HPV) infection and potentially, penile cancer. In this study we assessed the prevalence and risk factors for genital HPV infection in this population.

Design &Methods—Three hundred HIV-seropositive MSM were recruited from two clinical sites in India. They were tested for genital HPV infection using L1 HPV DNA PCR with probes specific for 29 types and a mixture of 10 additional types. Participants received an interviewer-administered questionnaire that included questions on demographics and behaviors.

Results—HPV data were available from 299 participants. The prevalence of any HPV type in the penis and scrotum was 55% and 54%, respectively. HPV 35 was the most common oncogenic HPV type followed by HPV16. In multivariate analysis, being the insertive partner with 100+ male partners increased the odds of any penile HPV infection compared with not being insertive with any partners (OR 2.5, 95% CI 1.3-5.1). Circumcision was protective against penile HPV infection (OR 0.39, 95% CI 0.19-0.76).

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Conflicts of Interest:
No conflicts of interests were declared by any of the authors.

Conclusions—The prevalence of penile and scrotal HPV infection was high among Indian HIV-seropositive MSM. The most common oncogenic HPV type in this population, HPV 35, is not included in any currently available HPV vaccines. Insertive anal sex with men and lack of circumcision were the primary risk factors for penile HPV infection in this population.

Keywords

Antiretroviral therapy; penis; scrotum; HPV; MSM; HIV

Introduction

Human papillomavirus (HPV) is a well-known cause of cervical cancer worldwide (1). It is a common sexually transmitted infection in women (2-4), and also affects men (5). In men, HPV infections lead to genital warts and cancers, including cancer of the anus and penis (6). The prevalence of penile cancer is very low in developed countries and accounts only for 0.3% to 0.6% of cancers in these regions. However, it is a substantial health problem in developing countries (7). The incidence of penile cancer in India varies from 0·7/100,000 to 3·0 /100,000 (8) and represents more than 6% of all cancers in Indian men (8).

In developed countries the prevalence of HPV-related cancers is higher in HIV-seropositive individuals than in the general population (9-11). Men who have sex with men (MSM) constitute a susceptible population with studies showing a higher prevalence and incidence of HPV infection and related anogenital cancers than among HIV-seronegative men. It has been estimated that 95% of HIV-seropositive MSM in developed countries have anogenital HPV infection (12). One previous study reported a prevalence of penile HPV infection of 26% among HIV-seropositive MSM (13). Moreover, the prevalence of multiple high-risk HPV types in HIV-seropositive MSM is high (14). Although the risk of scrotal cancer is very low, the scrotum may be a potential reservoir for HPV infection and HPV transmission as the epithelium of the scrotum can harbor HPV (15, 16). HPV may be transmitted during insertive anal or vaginal intercourse, even with the use of a condom and transmission may occur even among those who are circumcised (17). Knowledge of HPV infections in MSM in India is scarce and even less is known in Indian HIV-seropositive MSM (18). The reason for this gap in knowledge is the social stigma associated with this population.

We recently reported that the prevalence of anal HPV infection in Indian HIV-seropositive MSM was 95% (19), similar to the prevalence reported in HIV-seropositive men in the U.S. A better understanding of penile and scrotal HPV infection and HPV-associated disease in Indian HIV-seropositive MSM is needed. Further, MSM in India are largely behaviorally bisexual and bridging to women is a strong possibility. High penile HPV infection rates among HIV-seropositive MSM could therefore have consequences for both men and women's health. Therefore we conducted a cross-sectional study of HIV-infected Indian MSM representing different ethnic and socioeconomic backgrounds to determine the prevalence of type-specific penile and scrotal HPV infection and to identify potentially modifiable risk factors for infection.

Methods

Three hundred HIV-seropositive MSM (150 per site) were recruited from two demographically-distinct study sites, Christian Medical College Vellore, Tamil Nadu, India (a large teaching and referral hospital), and Humsafar Trust (HST) Mumbai, Maharashtra, India (a non-governmental organization (NGO) focusing on the health of MSM in India). Men were recruited through outreach workers and local HIV/AIDS support groups, and were also referred from other NGOs. The study was approved by the Institutional Review Boards of CMC Vellore, Humsafar Trust and the University of California, San Francisco. Participants completed an interviewer-administered questionnaire on demographics, native place, socioeconomic status, medical history, number of sexual partners, sexual practices and circumcision status.

The methodology for HPV DNA sampling was described by Weaver et al (2004) (20). Briefly, 600 grit emery paper was used to gently rub the penile skin and scrotal area followed by swabbing with a moist Dacron swab (20). Separate applicators were used to collect penile and scrotal cells respectively. The two swabs were placed in separate vials of Sample Transport Medium (Qiagen, Inc, Gaithersburg MD). Blood was collected to determine the CD4+ count and HIV viral load.CD4+ count was determined by flow cytometry (Becton Dickinson FACS Count).The plasma HIV viral load was determined by HIV-1 Amplicor (Amplicor HIV Monitor test, Version 1.5, Roche Diagnostics).

HPV testing

HPV DNA extraction was performed on all samples. Briefly, the samples were heat-inactivated followed by addition of Proteinase K and ammonium acetate/ethanol mixture. They were frozen at −20°(C) overnight and then centrifuged to obtain the pellet. The samples were eluted in Tris-EDTA buffer. MY09/MY11 L1 consensus primers were used to amplify HPV sequences. Human beta-globin primers were used as a positive internal control to test for the presence of human DNA as a measure of sample adequacy, and absence of PCR inhibitors. A known positive, negative and no template control were included in each assay. Samples were dot-blotted onto a membrane and probed for HPV DNA using a chemiluminescent procedure with a consensus probe mixture. Samples were then analyzed for the presence of 29 individual HPV types, and a mix of 10 less common types(19, 21). Samples that were negative for beta-globin DNA amplification were considered to be uninterpretable and were excluded from analysis.

Statistical methods

Descriptive statistics were calculated for participant characteristics and HPV status. Penile and scrotal HPV prevalence were calculated along with the corresponding exact 95% binomial confidence intervals. Descriptive estimates for concordance of HPV prevalence at two sites were calculated as percent agreement, with concordance assessed using McNemar’s test and the Kappa statistic.

Risk factors for any HPV infection and oncogenic HPV infection at penile and scrotal anatomic sites in Indian HIV-seropositive MSM were investigated using univariate methods

(chi-square or Wilcoxon Rank Sum test). Multivariable logistic models were fit investigating the following independent variables: age, penile warts, lifetime number of insertive anal male partners (participant was insertive partner), circumcision, CD4 counts, currently on highly active antiretroviral therapy (HAART), number of female vaginal sex partners, and smoking status. In all models the comparison group was those with no HPV infection. The final model was determined through backward elimination and maintained factors that were significant at $p<0.10$ in the multivariable model.

Results

The demographic characteristics of participants are shown in Table 1. The median age was 34 years. The demographic profile of the Tamil Nadu group differed from that of the Maharashtra group. In the Tamil Nadu site, 64% were married, 7% were circumcised and 48% reported >5 lifetime female vaginal partners. Among the Maharashtra men, 31% were married, 27% were circumcised and 12% reported >5 lifetime female vaginal partners.

Overall, receptive sex was reported by 86% of the men, with most having more than 200 lifetime male partners with whom they had receptive anal sex and 22% reporting almost always or always using a condom (data not shown). Sexual contact with females was reported by 61% of participants; 23% of these men reported almost always or always using a condom with their female partners (data not shown). Median (IQR) HIV viral load was 9090 (400-79400) copies/mL, and median (IQR) of self-reported nadir CD4 count was 243 cells/mm^3 (150-415).

Of the 300 participants enrolled in the study, 299 provided samples for HPV testing

Only samples that were beta-globin-positive were included for analysis. Of the 299 samples, 274 (92%) penile samples, 262 (88%) scrotal samples, and 251 of both penile and scrotal (84%) samples were beta-globin-positive respectively.

The prevalence of penile or scrotal HPV infection stratified by age is shown in Figure.1. The prevalence of any type of HPV infection of the penis was 55% (95% CI, 49-61%), while that of the scrotum was 54% (95% CI, 48-60%). The prevalence of HPV infection at one or both sites was 69% (95% CI, 62-74%) (See Table, Supplemental Digital Content 1) and increased with age, although the increase was not statistically significant in multivariate analysis. The prevalence of at least one oncogenic HPV type on the penis, scrotum or either was 15%, 13% and 23% respectively. The prevalence of at least one non-oncogenic HPV type on the penis and scrotum or either was 15%, 13% and 20%, respectively. The most common HPV types seen in the genital region were HPV 35, HPV 16, HPV 6/11, and HPV 70 with prevalence of 8%, 6%, 6%, and 6% on the penis and scrotum or either, respectively (Figure 2). Overall prevalance of HPV by anatomic site is presented in Figure 3.

There was good agreement between penile and scrotal HPV infection with the concordance being 73% (Kappa=0.45) (see Table, Supplemental Digital Content2). Thirty-four participants had at least one matching subtype on their penis and scrotum (excluding those positive with the 10-type probe mixture). Among the participants who had specific HPV types identified on the scrotum, 62% had at least one of the same types on their penis.

Similarly, among the participants who had specific penile HPV types identified, 52% had at least one of the same types on their scrotum. The concordance was 84% for oncogenic HPV infection regardless of subtype (Kappa=0.39).

Table 2a presents the univariate associations for *penile* HPV (any HPV and oncogenic HPV) infection and selects risk factors. Table 3a presents the univariate associations for *scrotal* HPV infection and select risk factors. Similarly, univariate association between risk factor and non-oncogenic HPV is shown in Table, Supplemental Digital content 3. Age in years, age at having first male partner, history of penile warts, circumcision, lifetime number of male partners with whom participant had insertive anal sex, lifetime number of female vaginal partners, and enrollment site were associated in univariate analysis with any penile HPV infection. In multivariate analysis significant risk factors for any penile infection included lack of circumcision, having insertive sex with more than 100 male partners compared with those who had no insertive anal sex with male partners, and being a Tamil Nadu participant (Table 2b).

Age in years, lifetime number of partners with whom participants had insertive anal sex, lifetime number of female vaginal partners, and smoking were associated with oncogenic penile HPV infection in univariate analysis. In multivariate analysis those 26-35 years old were more likely to have oncogenic penile HPV than those 18-25 years old, and those having insertive sex with more than 100 male partners were more likely to have oncogenic penile HPV compared with those with no insertive partners (Table 2b).

In univariate analysis of risks factors for any scrotal HPV infection, significant factors included history of penile warts, lifetime number of male partners with whom the participant had insertive anal sex, and lifetime number of female vaginal partners. In the final multivariable model, risk factors for any scrotal infection included a history of penile warts and having insertive anal sex with>100 lifetime number of male partners compared with having no insertive anal sex partners (Table 3b).

In univariate analysis of risk factors for oncogenic scrotal infection, significant factors included history of penile warts, lifetime number of male partners with whom participant had insertive anal sex, and lifetime number of female vaginal partners. With smoking, there was a higher trend towards scrotal oncogenic HPV infection. In the final multivariable model, those with a history of penile warts were more likely to have oncogenic scrotal HPV than those without a history, and those having insertive anal sex with 1-100 partners and more than 100 partners were more likely to have oncogenic scrotal HPV compared with those with no insertive partners (Table 3b).

Discussion

This is the first study looking at genital HPV infection in an Indian MSM population and in particular, the first study of Indian HIV-seropositive MSM. Participants from the two sites were different in some important demographic factors. Compared with the Maharashtra group, the median age of the Tamil Nadu participants was higher, a higher proportion was married and a higher proportion was uncircumcised; Tamil Nadu participants also had a

higher prevalance of any penile HPV infection,, potentially due to the differences in the age, circumcision and exposure to female partners. Modeling of HPV infection according to the individual study sites was not undertaken due to the high number of positive test results, particularly for oncogenic HPV types.

Men at both sites had many results in common, however. These include a high HPV prevalence of the penis (55%, summary of both sites) and scrotum (54% overall). Based on the high prevalence of HPV and the distribution of HPV genotypes, Indian HIV-seropositive MSM may be at high risk of genital warts, and possibly penile pre-cancer or cancer.

Worldwide, the prevalence of high-risk HPV genotypes in penile and scrotal samples ranges between 22 and 34% among HIV-seronegative MSM(22). While the prevalence of high-risk types in our study (40% and 35% on the penis and scrotum, respectively) was similar to those reported in studies of HIV-seropositive Western populations, if not slightly higher (16, 17), the HPV type distribution was different in our study. In our study, HPV 35 was the most common oncogenic HPV type. This is consistent with our previously published study; HPV 35 was also the most common type of anal HPV infection in this population(23). None of the bivalent, quadrivalent or recently licensed nonavalent HPV vaccines include HPV 35. HPV 35 is found in 6% to 10% of cervical specimens of Indian HIV-seropositive women (24, 25) and the percentage of cervical cancers attributable to HPV 35 is low (<2%) (26). However, little is known of the prevalence of different HPV types in penile cancer among Indian HIV-seropositive men. Notwithstanding some amount of cross-protective immunity provided by the vaccines (27), these vaccines may not be fully effective in preventing cancers in the Indian MSM population. Even if some protection is provided, HPV vaccination is not currently offered through government programs for girls or boys in India (24) and the overall uptake among young women is low. However, new initiatives are underway such as the public health program in the state of Delhi to vaccinate girls in schools (28).

In multivariable analysis, men who were uncircumcised and who had more male anal sex partners with whom the participant was the insertive partner had higher rates of penile HPV infection. Other studies have reported similar findings with increased detection of penile HPV infection associated with increasing number of lifetime sexual partners (29). Older men and men with more male sex partners were more likely to have oncogenic penile HPV infection. Our findings among Indian HIV-seropositive MSMs how a strong independent association between sexual behavior and HPV detection in men similar to data from other populations (5, 29). In addition, those who had a larger number of insertive male anal sex partners and those who had female vaginal sex partners were more likely to have any scrotal HPV infection. The odds of having any scrotal HPV and oncogenic scrotal HPV infection increased when penile infection was also present.

In our study a substantial number of participants reported having sex with female partners, and a higher number of female sex partners were associated with a higher prevalence of genital HPV infection. This study highlights that Indian MSM may have more heterosexual partners than Western MSM populations, and thereby could potentially serve as a bridge population to women. High penile HPV infection rates among MSM could have

consequences for women's health and preventions designed to target MSM could also benefit women.

History of penile warts, number of male partners and insertive anal sex were significantly associated with any genital HPV infection. When the sexual risk factors were analyzed, insertive anal sex was associated consistently with any penile/scrotal HPV infection and oncogenic HPV infection. This finding is similar to other published studies that have shown insertive anal sex as a risk factor for genital HPV infection (22). CD4 level, HIV viral load and currently taking antiretroviral therapy were not associated with penile/scrotal or combined infection. This finding is similar to other published studies on anal and cervical cancer where the incidence of HPV infection had not declined despite antiretroviral therapy (30). Other risk factors such as condom usage and alcohol consumption were not associated with genital HPV infection. Smoking as a risk factor was associated in univariate analysis with oncogenic penile HPV infection but did not retain its significance when adjusted for other factors. Condom usage did not protect against either penile or scrotal HPV infection and this could be due to the presence of HPV in the genitalia not covered by the condom, such as the scrotum. Also, it is inherently difficult to assess condom use in a population as it is limited by the accuracy of reporting by participants (31). Circumcision is known to protect men from the acquisition of HPV, HIV and other sexually transmitted infections (32, 33). Similar to previous studies, we were not able to find any association between circumcision and scrotal HPV infection (34). While circumcision may lead to reduced risk of cervical cancer and has important implications for public health practice, it is culturally problematic in India to study circumcision interventions (35).

This study had several limitations. We did not have a history of other sexually transmitted infections in this population. Since the population was HIV-seropositive, the results may not be generalizable to the population of Indian MSM at large. Our risk factor analysis was limited by the cross-sectional nature of the study, and only a prospective study will help to assess the effects of these variables on the incidence and clearance of HPV infection. Our study did not include assessment of HPV-associated disease of the penis and scrotum.

In conclusion, this study highlights the burden of genital HPV infection in Indian HIV-seropositive MSM. Although many of the oncogenic HPV infections detected would be prevented by currently available HPV vaccines, even the new nonavalent HPV vaccine may not be fully protective in this population since HPV 35 was the most commonly detected HPV type in this population. Further studies are needed to define the burden of HPV-associated disease in this population, including penile cancer, as well as the risk of HPV transmission to male and female sexual partners.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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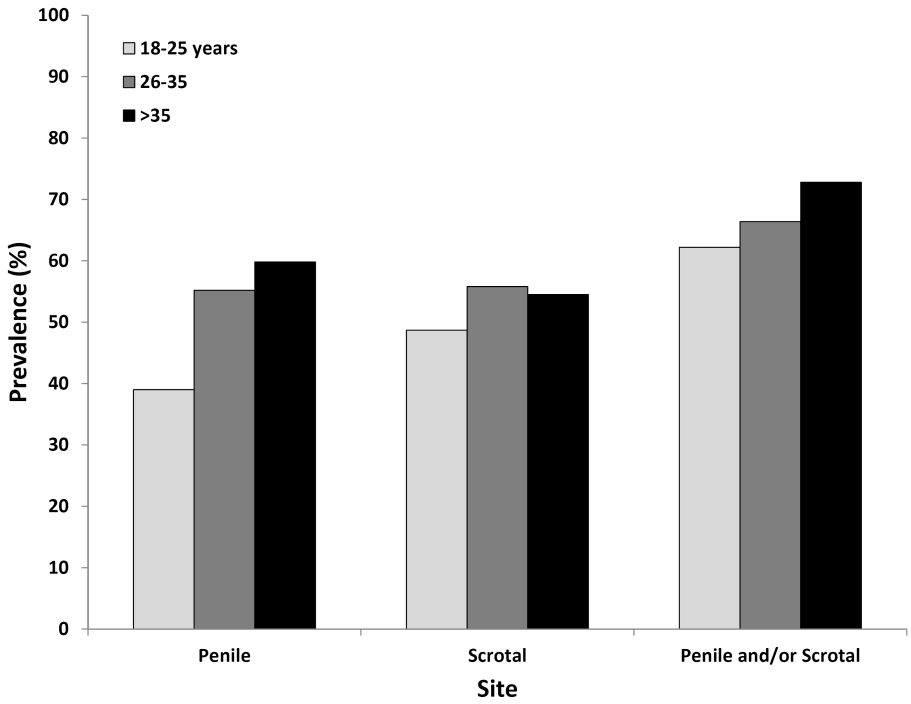

Figure 1.
Prevalence of HPV by age

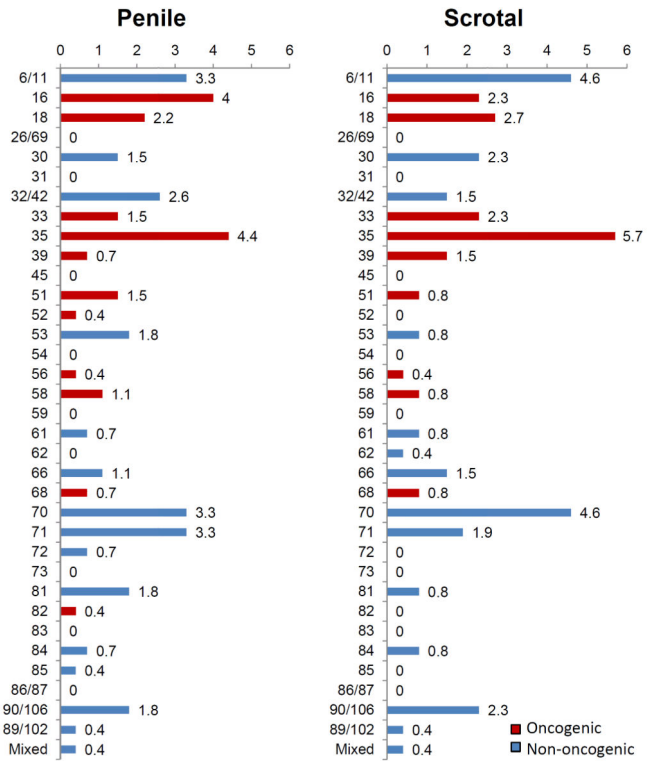

Figure 2.

Prevalence of specific HPV types on the penis and scrotum (% of total)

Mixture of HPV Type includes 7, 13, 40, 43, 44, 55, 74, and 91

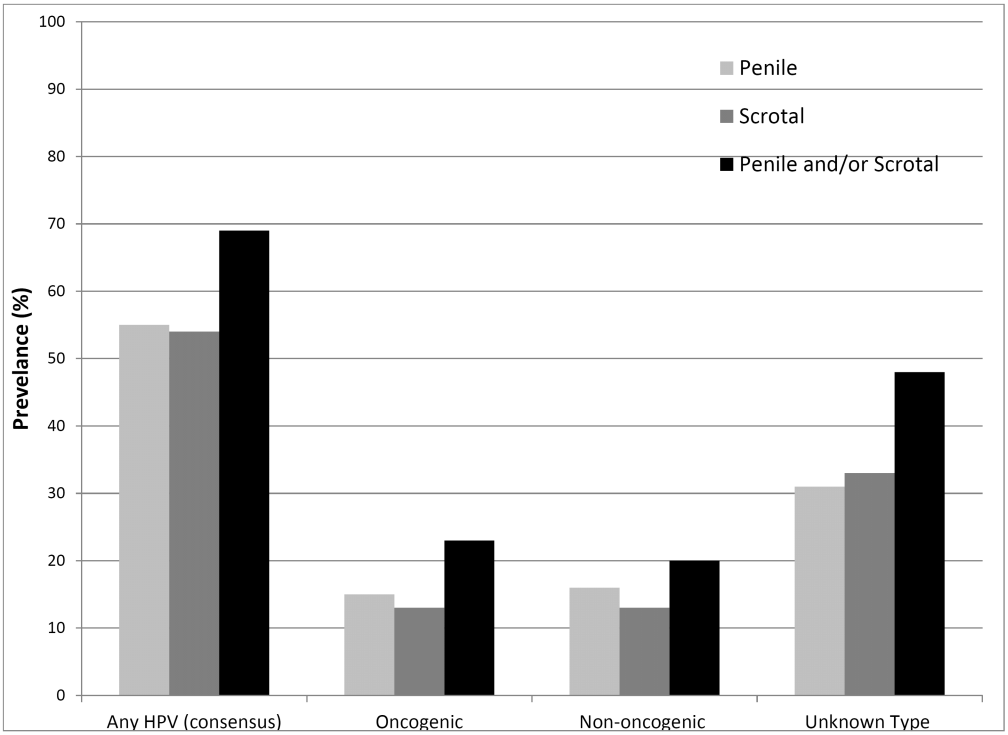

Figure 3.
Prevalence of any, oncogenic, non-oncogenic, and unknown HPV by anatomical site (% of total)

Table 1

Participant characteristics

	Christian Medical College Vellore, Vellore, India n (%)	Humsafar Trust Mumbai, India n (%)	Both sites n (%)	
Total	**150 (100)**	**150 (100)**	**300 (100)**	
Age in years, median (IQR)	37 (32-44)	30 (25-36)	34 (28-40)	<0.001
Marital status				
Married	96 (64)	46 (31)	142 (47)	<0.001
Single/Never married	52 (35)	94 (63)	146 (49)	
Divorced/Separated/Widowed	2 (1)	10 (7)	12 (4)	
Age first had sex with a male (years)				<0.001
≤16	52 (35)	117 (78)	169 (56)	
≥17	98 (65)	33 (22)	131 (44)	
History of penile warts	17 (11)	4 (3)	21 (7)	0.003
Circumcision	10 (7)	40 (27)	50 (17)	<0.001
CD4 absolute count				0.537
<200	16 (11)	22 (15)	38 (13)	
200-500	76 (52)	70 (47)	146 (49)	
>500	55 (37)	58 (39)	113 (38)	
Nadir CD4, median (IQR)	227 (125-398)	260 (151-433)	243 (150-415)	0.094
Currently on HAART	85 (57)	48 (32)	133 (44)	<0.001
Undetectable viral load	62 (42)	45 (30)	107 (36)	0.032
Viral load, median (IQR)	4580 (400-45252)	21800 (400-108000)	9090 (400-79400)	0.003
Lifetime number of male partners with whom participant had insertive anal sex				<0.001
0	70 (47)	42 (28)	112 (38)	
1-100	37 (25)	80 (53)	117 (39)	
>100	41 (28)	28 (18)	69 (23)	
Participant's use of condoms during insertive sex				<0.001
Almost always/always	28 (19)	9 (6)	37 (12)	
Never/occasionally/half time	52 (35)	99 (66)	151 (50)	
Not applicable (no insertive sex)	70 (47)	42 (28)	112 (37)	
Lifetime number of male partners with whom participant received receptive anal sex				<0.001
0	29 (19)	13 (9)	42 (14)	
1-50	37 (25)	16 (11)	53 (18)	
51-200	20 (13)	14 (9)	34 (11)	
>200	63 (42)	107 (71)	170 (57)	
Lifetime number of female				<0.001

	Christian Medical College Vellore, Vellore, India n (%)	Humsafar Trust Mumbai, India n (%)	Both sites n (%)	
vaginal sex partners				
0	44 (30)	72 (48)	116 (39)	
1-4	34 (23)	60 (40)	94 (31)	
≥5	71 (48)	18 (12)	89 (30)	

Table 2a

Univariate Analysis of Risk Factors for Penile HPV infection

			Any HPV				Oncogenic HPV		
	N	%	OR[a]	95% CI	P	%	OR[a]	95% CI	P
Age in years									
18-25	41	39	1			5	1		
26-35	116	55	1.92	0.93-3.98	0.078	20	5.53	1.21-25.32	0.028
>35	117	60	2.33	1.12-3.98	0.023	13	3.99	0.84-18.86	0.081
Age at having 1st male partner (years)									
≤16	154	48	1			13	1		
≥17	120	63	1.87	1.15-3.04	0.012	17	1.82	0.88-3.74	0.104
History of penile warts									
No	255	53	1			14	1		
Yes	19	79	3.33	1.08-10.32	0.037	21	3.33	0.79-14.00	0.100
Circumcision									
No	229	59	1			15	1		
Yes	45	36	0.39	0.20-0.76	0.006	11	0.47	0.17-1.31	0.147
Absolute CD4 count									
<200	36	58	1			6	1		
200-500	128	53	0.81	0.38-1.71	0.580	18	2.88	0.61-13.57	0.182
>500	108	56	0.89	0.42-1.92	0.771	14	2.34	0.48-11.44	0.292
Nadir CD4 count (per 50) [b]	210	-	0.93	0.88-0.99	0.023	-	0.96	0.88-1.05	0.408
Currently on HAART									
No	157	50	1			14	1		
Yes	117	61	1.52	0.94-2.48	0.089	15	1.39	0.67-2.86	0.374
Viral load									
Detectable	178	53	1			15	1		
Undetectable	94	57	0.85	0.51-1.40	0.531	14	1.00	0.47-2.14	0.998
Lifetime #male partners with whom participant had insertive anal sex									
0	101	50	1			11	1		
1-100	108	50	1.02	0.59-1.76	0.943	16	1.46	0.62-3.41	0.383
>100	63	70	2.36	1.22-4.59	0.011	19	2.93	1.11-7.75	0.031
Participant's use of condoms during insertive anal sex									
Almost always/always	30	67	1			7	1		
Never/occasionally/half time	143	56	0.64	0.28-1.45	0.282	19	2.14	0.44-10.44	0.346
Lifetime number of female vaginal sex partners									
0	106	45	1			9	1		
1-4	88	50	1.21	0.69-2.13	0.513	16	1.85	0.75-4.54	0.183

			Any HPV				Oncogenic HPV		
	N	%	OR[a]	95% CI	P	%	OR[a]	95% CI	P
≥5	79	72	3.13	1.68-5.84	<0.001	20	4.22	1.66-10.69	0.002
Smoking status									
Never	189	51	1			12	1		
Current	63	62	1.57	0.88-2.82	0.127	22	2.36	1.06-5.26	0.036
Past	22	68	2.08	0.81-5.32	0.128	14	1.73	0.42-7.22	0.450
Enrolling site									
Christian Medical College	131	66	1			15	1		
Humsafar Trust	143	44	0.40	0.244-0.65	<0.001	14	0.55	0.27-1.13	0.104
Total	274	55				15			

[a] In all cases, odds ratios (OR) were calculated compared to the group that is negative for any HPV; the reference group is indicated by OR=1.

[b] Nadir CD4 was analyzed as a continuous variable with the odds ratio in terms of every 50 units increase in nadir CD4; 64 participants were missing nadir CD4 data. Median (IQR) nadir CD4 was 317 (172-470) for HPV-negative men, 212 (125-390) for men with any HPV, and 286 (160-415) for men with oncogenic HPV..

Table 2b

Multivariable Logistic Regression Models for Any Penile HPV Infection and for Oncogenic Penile HPV Infection

	Odds Ratio[a]	95% Confidence Limits	P-value
Model 1 Outcome: Any Penile HPV Infection (n=271)			
Circumcision			
No	1		
Yes	0.48	0.24-0.96	0.041
Lifetime number of male partners with whom participant had insertive sex			
0	1		
1-100	1.39	0.78-2.50	0.274
>100	2.64	1.34-5.36	0.006
Site			
Christian Medical College	1		
Humsafar Trust	0.45	0.26-0.77	0.004
Model 2 Outcome: Oncogenic Penile HPV Infection (n=164)			
Age in years			
18-25	1		
26-35	5.07	1.33-33.34	0.038
>35	3.23	0.80-21.84	0.144
Lifetime number of male partners with whom participant had insertive sex			
0	1		
1-100	1.39	0.59-3.38	0.454
>100	2.77	1.02-7.72	0.048

[a]Odds ratios (OR) were calculated compared to the group that is negative for any HPV; the reference group is indicated by OR=1. The final multivariable model was determined through backward elimination and maintained factors that were significant at $p<0.10$.

Table 3a

Univariate Analysis of Risk Factors for Scrotal HPV Infection

		Any HPV		95% CI	P	Oncogenic HPV		95% CI	P
	N	%	OR[a]			%	OR[a]		
Age in years									
18-25	39	49	1			15	1		
26-35	113	56	1.33	0.64-2.75	0.448	14	1.07	0.37-3.12	0.906
>35	110	55	1.26	0.61-2.63	0.531	12	0.87	0.29-2.60	0.798
Age at having 1st male partner (years)									
≤16	148	51	1			11	1		
≥17	114	59	1.39	0.85-2.27	0.193	17	1.84	0.86-3.94	0.114
History of penile warts									
No	243	51	1			12	1		
Yes	19	89	8.02	1.82-35.48	0.006	37	14.75	2.91-74.87	0.001
Circumcision									
No	216	56	1			14	1		
Yes	46	43	0.59	0.31-1.13	0.110	9	0.47	0.15-1.44	0.185
CD4 absolute count									
<200	33	64	1			18	1		
200-500	126	52	0.63	0.29-1.39	0.250	14	0.60	0.20-1.83	0.368
>500	100	54	0.67	0.30-1.51	0.335	11	0.48	0.15-1.56	0.221
Nadir CD4 count (per 50) [b]	204		0.92	0.86-0.98	0.009		0.91	0.82-1.00	0.070
Currently on HAART									
No	149	50	1			11	1		
Yes	113	59	1.44	0.88-2.36	0.150	17	1.91	0.89-4.09	0.095
Viral load									
Detectable	167	54	1			15	1		
Undetectable	93	56	0.92	0.55-1.54	0.754	11	1.33	0.58-3.04	0.497
Lifetime #male partners with whom participant had insertive anal sex									
0	96	47	1			4	1		
1-100	106	51	1.18	0.68-2.05	0.564	18	4.66	1.48-14.64	0.009
>100	58	76	2.98	1.48-6.00	0.002	21	9.56	2.70-33.82	0.001
Participant's use of condoms during insertive anal sex									
Almost always/always	28	57	1			25	1		
Never/occasionally/half time	138	59	1.07	0.47-2.42	0.879	17	0.72	0.25-2.06	0.542
Lifetime number of female vaginal sex partners									
0	100	54	1			7	1		
1-4	86	38	0.53	0.30-0.95	0.034	8	0.87	0.28-2.66	0.804

			Any HPV	95% CI	P	Oncogenic HPV		95% CI	P
	N	%	OR[a]			%	OR[a]		
≥5	75	72	2.19	1.16-4.15	0.016	28	6.57	2.42-17.85	<0.001
Smoking status									
Never	183	52	1			10	1		
Current	59	63	1.56	0.85-2.85	0.149	19	2.32	0.96-5.57	0.061
Past	20	50	0.93	0.37-2.33	0.871	25	2.32	0.71-7.56	0.164
Enrolling site									
Christian Medical College	124	58				16	1		
Humsafar Trust	138	51	0.74	0.46-1.21	0.234	11	0.57	0.27-1.23	0.152
Total	262	54				13			

[a] In all cases, odds ratios (OR) were calculated compared to the group that is negative for any HPV; the reference group is indicated by OR=1.

[b] Nadir CD4 was analyzed as a continuous variable with the odds ratio in terms of every 50 units increase in nadir CD4; 70 participants were missing nadir CD4 data. Median (IQR) nadir CD4 was 319 (150-480) for HPV-negative men, 212 (138-371) for men with any HPV, and 212 (158-350) for men with oncogenic HPV.

Table 3b

Multivariable Logistic Regression Models for Any Scrotal HPV Infection and for Oncogenic Scrotal HPV Infection

	Odds Ratio[a]	95% Confidence Limits	P-value
Model 1 Outcome: Any Scrotal HPV Infection (n=256)			
History of penile warts			
No	1		
Yes	5.87	1.50-39.08	0.025
Lifetime number of male partners with whom participant had insertive anal sex			
0	1		
1-100	1.23	0.65-2.36	0.521
>100	2.71	1.23-6.19	0.015
Lifetime number of female vaginal sex partners			
0	1		
1-4	0.42	0.22-0.80	0.010
≥5	1.25	0.59-2.67	0.561
Model 2 Outcome: Oncogenic Scrotal HPV Infection (n=154)			
History of penile warts			
No	1		
Yes	9.98	2.07-74.14	0.008
Lifetime number of male partners with whom participant had insertive anal sex			
0	1		
1-100	4.41	1.49-16.42	0.004
>100	7.85	2.24-32.61	0.002
Site			
Christian Medical College	1		
Humsafar Trust	0.44	0.18-1.08	0.072

[a]Odds ratios (OR) were calculated compared to on the group that is negative for any HPV; the reference group is indicated by OR=1. The final multivariable model was determined through backward elimination and maintained factors that were significant at $p<0.10$