MAJOR ARTICLE

Prevalence of and Risk Factors for Human Papillomavirus (HPV) Infection Among HIV-Seronegative Men Who Have Sex With Men

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Background. We examined the baseline prevalence of penile, scrotal, perineal/perianal, and intra-anal human papillomavirus (HPV) infection in human immunodeficiency virus (HIV)–seronegative men who have sex with men (MSM).

Methods. Data were analyzed from 602 MSM aged 16–27 years with ⩽5 lifetime sexual partners. Serum samples were tested for antibodies to HPV6/11/16/18. Swab samples were collected separately from several anogenital areas for detection of HPV6/11/16/18/31/33/35/39/45/51/52/56/58/59 DNA.

Results. The prevalence of any tested HPV type was 18.5% at the penis, 17.1% at the scrotum, 33.0% at the perineal/perianal region, 42.4% in the anal canal, and 48.0% at any site. Overall, 415 MSM (69.7%) were negative to HPV 6, 11, 16, and 18 at enrollment by both serology and DNA detection. Men residing in Europe and Latin America had significantly increased risk of HPV infection at external genital sites and the anal canal compared to men from Australia. Tobacco use and greater number of lifetime sexual partners was associated with higher HPV infection prevalence.

Conclusions. The prevalence of HPV infection is high among young sexually active MSM, with the anal canal being the most common site of infection. Lifetime number of sexual partners was the most important modifiable risk factor for anogenital HPV infection.

Human papillomavirus (HPV) is the most common sexually transmitted virus and causes a substantial burden of disease in men and women. Several studies have estimated the prevalence of HPV infection among men; however, these estimates vary widely, and the interpretation of these data are complicated by non-standardized HPV sampling methods and differing patient populations[1]. Although many HPV infections in men have been shown to be transient in nature (similar to HPV infections in women), a small percentage persist and can progress to genital warts; preneoplastic and malignant lesions of the anus, penis, and oropharynx; and recurrent respiratory papillomatosis[2].

Previous studies have demonstrated a high prevalence of HPV infection among men who have sex with men (MSM)[3–5]. This high anal HPV prevalence among MSM is associated with an elevated anal cancer

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incidence estimated to be 44 times higher than that among the general population[6]. Human immunodeficiency virus (HIV)–infected MSM are at particularly high risk of anal HPV infection; in fact, it has been estimated that up to 95% of MSM who are HIVinfected also carry anal HPV infection[7]. Accordingly, their risk of anal cancer is approximately 60 times higher than that of the general population[8]. Despite this high risk for anogenital HPV-related disease among MSM, few studies have examined HPV prevalence at multiple anatomic anogenital sites in this population.

Here, we describe the baseline prevalence of HPV infection among HIV-seronegative MSM enrolled in a placebo-controlled randomized trial designed to evaluate the efficacy of a quadrivalent HPV vaccine in young adult men with a limited number of lifetime sexual partners[9]. We also investigated the factors independently associated with HPV prevalence in this global study population.

METHODS

Subjects

Protocol 020 was designed to evaluate the efficacy of quadrivalent HPV (types 6/11/16/18) L1 virus-like particle vaccine in young men (Gardasil, Merck). In addition to 3463 heterosexual men aged 16–24 years, the study enrolled 602 MSM aged 16–27 years with $\leqslant$5 lifetime male and/or female sexual partners. MSM were enrolled from 17 sites in Australia, Brazil, Canada, Croatia, Germany, Mexico, Spain, and the United States and were randomized and vaccinated from 30 November 2004 through 30 May 2007. Participants with $<$1 lifetime male sexual partner must have identified themselves as an MSM and must have engaged in oral sex with another man within the past year. A male sexual partner was defined as a man with whom the participant engaged in receptive or insertive anal intercourse. Men with a history of or with current clinically detectable HPV-related genital lesions or other sexually transmitted diseases were excluded. Participants with known immunodeficiency or HIV infection were also excluded. Participants with HIV infection detected after enrollment were not excluded from the study. HPV or cytologic prescreening was not performed to determine eligibility for enrollment into the study[9].

All enrolled subjects underwent external genital lesion inspection and sampling for HPV DNA detection at baseline. If a lesion observed at baseline was judged by the investigator to be possibly HPVrelated or of unknown etiology, then the subject was excluded from the study.

Study Measurements

Subjects had serum samples collected for HIV and syphilis testing at baseline. Serum samples werealso tested for the presence of antibodies to HPV 6, 11, 16, and 18, as described elsewhere[10–11]. Baseline external genital lesion inspection was conducted using a magnifying glass. Baseline swab specimens were collected separately from the penile, scrotal, perineal/perianal, and anal areas. A metal nail file was used to gently rub the penile skin. A Dacron swab moistened with sterile saline was used to collect cellular debris generated and then placed into a container of Digene (Qiagen) sample transport medium (STM). The procedure was repeated for the scrotum and perineal/perianal regions; each swab was placed in a separate STM vial. A fourth sample from the anal canal was obtained after a sample for cytology by inserting a moistened, nonlubricated Dacron swab a distance of 2–3 cm into the canal. The swab was rotated while moving it in and out several times to retrieve cells. All specimens were tested for the β-globin gene (positive control), and positive samples were tested for a panel of 14 HPV types (HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59). Swab, biopsy, and serum samples were tested at Merck Research Laboratories (Wayne, PA) and Pharmaceutical Product Development (Wilmington, DE). Detailed procedures for DNA detection and serology assays are included in the companion article [12].

ThinPrep anal cytology test specimens were also collected at baseline. All ThinPrep anal cytology tests were analyzed at a central cytology laboratory. Cytology specimens were evaluated using the Bethesda System2001, the same classification used for cervical cytology[13]. In addition, anorectal swab samples were collected at baseline for chlamydia and gonorrhea culture.

Statistical Analysis

Demographic and risk characteristics were analyzed using simple descriptive statistics (mean and standard deviation were calculated for continuous variables, and proportions were calculated for categorical variables). We first conducted univariate analysis using an unconditional logistic regression model to examine the associations between putative risk factors and the detection of HPV DNA (either qHPV types or all 14 HPV types) on day 1 for initial assessment. On the basis of previous literature and expertise, we identified geographic area of residence, age, tobacco use, condom use, age at first sexual intercourse with a male partner, number of lifetime sexual partners, number of new partners in the past 6 months, and circumcision history as putative risk factors. We calculated odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) to estimate the risk of detection of HPV DNA on day 1 in relation to each of the above-mentioned risk factors using the multivariable unconditional logistic regression models by mutually adjusting for other risk factors. Analyses were conducted using the SAS software, version 9 (SAS Institute).

RESULTS

The mean age of subjects in the current analysis was 22 years. Sixty percent described themselves as white, and a majority was enrolled from North America (Table 1). Approximately half the subjects had never smoked prior to enrollment, and 44.4% were circumcised.

Table 1. Selected baseline characteristics among HIV-seronegative men who have sex with men with ≤5 lifetime sexual partners (*N* = 602)

Subject Characteristic	*n* (%)
Age (years)	
Mean (SD)	22.1 (2.5)
Median	22
Range	16–27
Race/Ethnicity	
Asian	33 (5.5)
Black	42 (7.0)
Hispanic American	149 (24.8)
White	363 (60.3)
Other	15 (2.5)
Region	
Australia	89 (14.8)
Europe	122 (20.3)
Latin America	132 (21.9)
North America	259 (43.0)
Smoking Status	
Current user	241 (40.0)
Ex-user	56 (9.3)
Never used	303 (50.3)
Missing or unknown	2 (0.3)
Circumcision	
Yes	267 (44.4)
No	334 (55.5)
Missing or unknown	1 (0.2)

NOTE. Percentages calculated as 100*(*n*/*N*). *N* = number of subjects randomized; *n* = number of subjects with indicated characteristic.

Twenty-three MSM (3.8%) denied prior receptive or insertive anal sex with another man (Table 2); 3 of these subjects reported prior vaginal sex. At enrollment, 67.6% of subjects reported ⩾3 partners for insertive or receptive anal sex, 74.5% reported ⩽1 new partner in the 6 months prior to enrollment, and 42.0% reported always using condoms (Table 3). Overall, 148 subjects (25.0%) engaged in prior vaginal sex, with 89 (15.0%) having 1 female partner and 59 (9.9%) having ⩾2 female partners; 91 (61.5%) reported always using condoms. Only 14 (2.1%) subjects engaged in vaginal sex within 6 months of enrollment.

At enrollment, 80 subjects (13.3%) had at least 1 sexually transmitted infection (STI). HIV, syphilis, rectal gonorrhea, and rectal chlamydia were found in 11 (2.0%), 15 (2.5%), 5 (0.8%), and 54 (9.0%) subjects, respectively (7 subjects had >1 non-HPV-related STI). Overall, 135 subjects (22.8%) had serum antibodies to HPV 6, 11, 16, or 18, with HPV 6 being the most common (*n*=83 [14.0%]). Forty-two subjects (7.1%) were HPV 16 seropositive (Table 3A), and 42 subjects (7.0%) had serological evidence of HPV infection with more than one vaccine HPV type. Only two subjects (0.3%) were seropositive to all 4 vaccine HPV types at baseline (Table 3B).

The prevalence of HPV 6, 11, 16, or 18 DNA detection in any external genital and/or anal swab at enrollment was 30.5% (*n*=180; Table 2A). Only one subject (0.2%) was DNA positive for HPV 6, 11, 16, and 18 at enrollment, but infection with 1, 2, or 3 of these HPV types was found in 124 (21.0%), 45 (7.6%), and 10 (1.1%) of subjects, respectively (Table 3B). Multiple site infections with any of HPV types 6, 11, 16, and/or 18 were common, occurring in 56 subjects (9.4%;data not shown). HPV 6, 11, 16, and/or 18 DNA detection was most prevalent in swabs from the anal canal (25.2% [148]) and perineal/perianal site (19.2% [102]). Overall, 69.7% of MSM subjects (415) were negative to HPV 6, 11, 16, and 18 at enrollment by both serology and DNA detection.

The combined prevalence of DNA detection for any tested HPV type (HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59) at enrollment was 48.1% (*n*=284). Fifty-seven subjects (9.6%) were DNA positive to 4 or more of the 14 tested HPV types at enrollment in any of the external genital and/or anal swabs, and the majority of these cases were related to multiple infections in the anal canal (46 [7.8%]). HPV types 16, 6, and 56 were the most common anal infections detected, found in 13.7% (*n*=81), 13.4% (*n* = 79), and 12.4% (*n*=73) of subjects, respectively.

Table 4 presents the HPV DNA prevalence of individually tested HPV types in all MSM subjects enrolled (with data available) stratified by world region. Individual HPV type prevalence was generally the highest among European men and lowest among men in the North American region. HPV 16 prevalence was between 18 and 19% in all regions except North America, where a prevalence of 7.1% was observed.

Overall, 583 MSM subjects had anal cytology specimens collected at enrollment, and 532 (91.3%) were satisfactory for testing. Of these, 58 (10.9%) were judged as abnormal; 23 (4.3%) were considered atypical squamous cells of undetermined significance,and 35 (6.6%) were considered low-grade squamous intraepithelial lesions. There were no high-grade squamous intraepithelial lesions diagnosed from cytology specimens. Biopsy results were available for 47/58 of these subjects. Among these subjects (scored by the most severe diagnosis) there were 19 cases of anal intraepithelial neoplasia (AIN) 1, 8 cases of AIN 2, 11 cases of AIN 3, 3 cases of condylomaacuminatum, and 6 subjects with negative results.

Table 5A shows the association between HPV positivity at external genital sites and age, smoking status, lifetime number of partners, age at first sex, condom use, circumcision status, and world region. An increased risk of prevalent detection of any one of 14 HPV types approaching significance was seen among men reporting 3–6 lifetime male sexual partners (OR,2.0;95% CI,0.9–4.6). Younger men (aged 15–20 years) were more likely than older men (aged 21–27 years) to have prevalent external genital infection with HPV 6, 11, 16, and 18 (OR,2.0;95% CI,1.1–3.7). Relative to subjects from Australia (lowest composite HPV prevalence in the current study), subjects from Europe were

Table 2. Summary of sexual history at enrollment among men who have sex with men (*N*= 602).

Sexual History	With Males *n* (%)	With Females *n* (%)
Subjects with sexual history data at enrollment	600	592
No partners	23 (3.8)	444 (75.0)
With partners	577 (96.2)	148 (25.0)
Age at first sexual intercourse with a partner among subjects with partners (years)		
Mean (SD)	17.9 (2.9)	16.8 (2.3)
Median	18	17
Range	5–26	6–25
Lifetime number of sexual partners at enrollment among subjects with partners		
1	69 (11.5)	89 (15.0)
2	102 (17.0)	42 (7.1)
3	129 (21.5)	15 (2.5)
4	155 (25.8)	2 (0.3)
5	120 (20.0)	0 (0.0)
>5	2 (0.3)	0 (0.0)
Lifetime number of male sexual partners where the subject engaged in insertive anal intercourse among subjects with male partners		
Unknown*	2 (0.3)	—
0	70 (11.7)	—
1	143 (23.8)	—
2	134 (22.3)	—
3	117 (19.5)	—
4	76 (12.7)	—
5	33 (5.5)	—
>5	2 (0.3)	—
Lifetime number of male sexual partners where the subject engaged in receptive anal intercourse among subjects with male partners		
Unknown*	2 (0.3)	—
0	59 (9.8)	—
1	132 (22.0)	—
2	148 (24.7)	—
3	109 (18.2)	—
4	80 (13.3)	—
5	46 (7.7)	—
>5	1 (0.2)	—
Lifetime condom use with sexual partners at enrollment among subjects with partners		
Unknown	1 (0.2)	1 (0.2)
Never	31 (5.2)	18 (3.0)
Less than half the time	62 (10.3)	10 (1.7)
More than half the time	231 (38.5)	28 (4.7)
Always	252 (42.0)	91 (15.4)
Number of new sexual partners in the 6 months prior to study start among subjects with partners		
Unknown	1 (0.2)	2 (0.3)
0	214 (35.7)	132 (22.3)
1	233 (38.8)	11 (1.9)
2	92 (15.3)	1 (0.2)
3	26 (4.3)	2 (0.3)
4	7 (1.2)	0 (0.0)
5	4 (0.7)	0 (0.0)
Condom usage with male sexual partners in the 6 months prior to study start among subjects with male partners		
Unknown	8 (1.3)	15 (2.5)
Never	162 (27.0)	108 (18.2)
Less than half the time	46 (7.7)	1 (0.2)
More than half the time	107 (17.8)	3 (0.5)
Always	254 (42.3)	21 (3.5)

NOTE. Percentages calculated as 100*(number of subjects with the indicated characteristic/number of subjects with male sexual history data at enrollment).

* Unknown means that the subject had at least one male sexual partner prior to study entry but did not remember or did not document his lifetime number of male sexual partners.

more likely to have prevalent detection of HPV 6, 11, 16, and 18 DNA (OR,3.2;95% CI,1.2–8.6) and any tested HPV type (OR,3.3;95% CI,1.5–7.0) in external genital swabs. Subjects from Latin America had over a 4-fold increase in the detection of DNA from any of the tested HPV types in external genital swabs (OR,4.4;95% CI,2.1–9.3). Subjects from Europe and Latin America were more likely to have tested positive for one of the 14 tested HPV types than those from Australia (OR,2.1 [95% CI,1.1–3.7] and OR,1.7 [95% CI,1.0–3.3], respectively) in intra-anal swabs. Circumcision was not associated with a significantly reduced risk of external genital HPV infection.

Factors associated with prevalent anal HPV detection are presented in Table 5B. The risk of intra-anal HPV 6/11/16/18 detection was marginally higher for those who were past smokers and those who had 3–6 lifetime sexual partners (OR,1.6 [95% CI,1.0–2.4] and OR,2.5 [95% CI, 1.0–6.0], respectively). Subjects with ⩾2 lifetime sexual partners had an almost 3- to 4-fold increased risk for anal HPV prevalence (of any of the 14 tested HPV types[Table 5B]). Europeans and Latin Americans were also at higher risk of anal HPV prevalence when compared to Australia, which had the lowest composite HPV prevalence in the current study (OR,2.1 [95%

Table 3. Summary of anogenital HPV serology and DNA status (A) and multiple HPV exposure (B) at enrollment among men who have sex with men

A. HPV DNA Positivity and Seropositivity

	HPV DNA Positivity *n* (%)					
	External Genital Anatomic Sites					
HPV Type	Penile	Scrotal	Perineal/ Perianal	Anal Canal	External Genital and/ or Anal Sites	Serum *n* (%)
Any tested type*	—	—	—	—	284 (48.1)	135 (22.8)
HPV 6/11/16/18	61 (11.2)	49 (9.2)	102 (19.2)	148 (25.2)	180 (30.5)	135 (22.8)
HPV 16/18	35 (6.4)	24 (4.5)	59 (11.1)	93 (15.8)	112 (19.0)	62 (10.5)
HPV 16	19 (3.5)	13 (2.4)	36 (6.8)	70 (11.9)	81 (13.7)	42 (7.1)
HPV 18	17 (3.1)	11 (2.1)	26 (4.9)	38 (6.5)	48 (8.1)	27 (4.6)
HPV 6/11	33 (6.0)	28 (5.3)	59 (11.1)	87 (14.8)	107 (18.1)	108 (18.2)
HPV 6	24 (4.4)	20 (3.8)	43 (8.1)	65 (11.1)	79 (13.4)	83 (14.0)
HPV 11	11 (2.0)	8 (1.5)	20 (3.8)	31 (5.3)	40 (6.8)	38 (6.4)
HPV 31	9 (1.7)	7 (1.3)	18 (3.4)	33 (5.6)	41 (6.9)	—
HPV 33	3 (0.6)	2 (0.4)	10 (1.9)	16 (2.7)	18 (3.1)	—
HPV 35	4 (0.7)	3 (0.6)	11 (2.1)	24 (4.1)	25 (4.2)	—
HPV 39	7 (1.3)	7 (1.3)	19 (3.6)	36 (6.1)	43 (7.3)	—
HPV 45	10 (1.8)	11 (2.1)	25 (4.7)	39 (6.6)	46 (7.8)	—
HPV 51	11 (2.0)	13 (2.4)	34 (6.4)	46 (7.8)	54 (9.1)	—
HPV 52	5 (0.9)	3 (0.6)	15 (2.8)	29 (4.9)	35 (5.9)	—
HPV 56	17 (3.1)	12 (2.3)	38 (7.1)	60 (10.2)	73 (12.4)	—
HPV 58	5 (0.9)	3 (0.6)	14 (2.6)	24 (4.1)	25 (4.2)	—
HPV 59	6 (1.1)	4 (0.8)	16 (3.0)	32 (5.5)	37 (6.3)	—

* HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 for DNA detection; HPV 6, 11, 16, and 18 for serology.

B. Multiple HPV Positivity (Both DNA Positivity and Seropositivity)

	HPV DNA Positivity *n* (%)					
	External Genital Anatomic Sites					
Number of Types Detected	Penile	Scrotal	Perineal/ Perianal	Anal Canal	External Genital and/ or Anal Sites	Serum *n* (%)
Any tested types*						
0	445 (81.4)	441 (82.9)	357 (67.0)	338 (57.6)	307 (52.0)	—
1	71 (13.0)	71 (13.4)	94 (17.6)	121 (20.6)	128 (21.7)	—
2	22 (4.0)	17 (3.2)	42 (7.9)	47 (8.0)	61 (10.3)	—
3	3 (0.6)	1 (0.2)	24 (4.5)	35 (6.0)	38 (6.4)	—
4+	6 (1.1)	2 (0.4)	16 (3.0)	46 (7.8)	57 (9.6)	—
HPV 6, 11, 16, 18						
0	484 (88.8)	480 (90.7)	427 (80.7)	439 (74.8)	411 (69.5)	457 (77.2)
1	52 (9.5)	46 (8.7)	83 (15.7)	101 (17.2)	124 (21.0)	93 (15.7)
2	8 (1.5)	3 (0.6)	15 (2.8)	39 (6.6)	45 (7.6)	31 (5.2)
3	1 (0.2)	0 (0.0)	4 (0.8)	7 (1.2)	10 (1.1)	9 (1.5)
4	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	2 (0.3)

* HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59.

CI,1.1–3.7]). Circumcision was not associated with a reduced risk of intra-anal HPV DNA prevalence. The prevalence of intra-anal infection with vaccine HPV types was not altered by condom use.

DISCUSSION

To our knowledge this is the first report of HPV prevalence at four different anogenital anatomic sites among HIV-seronegative

Table 4. Summary of HPV prevalence at any site among men who have sex with men stratified by region

HPV Type	Entire Study (*N*=602)		Australia (*N*=89)		Europe (*N*=122)		Latin America (*N*=132)		North America (*N*=259)	
	n/*m*	% (95% CI)	*n*/*m*	% (95% CI)	*n*/*m*	% (95% CI)	*n*/*m*	% (95% CI)	*n*/*m*	% (95% CI)
6	79/589	13.4 (10.8–16.4)	10/83	12.0 (5.93–21.0)	25/122	20.5 (13.7–28.7)	19/132	14.4 (8.9–21.6)	25/252	9.9 (6.5–14.3)
11	40/589	6.8 (4.9–9.1)	7/83	8.4 (3.5–16.6)	14/122	11.5 (6.4–18.5)	6/132	4.5 (1.7–9.63)	13/252	5.2 (2.8–8.66)
16	81/588	13.8 (11.1–16.8)	15/82	18.3 (10.6–28.4)	23/122	18.9 (12.3–26.9)	25/132	18.9 (12.6–26.7)	18/252	7.1 (4.3–11.1)
18	48/589	8.1 (6.07–10.7)	11/83	13.3 (6.8–22.5)	11/122	9.0 (4.6–15.6)	13/132	9.8 (5.4–16.3)	13/252	5.2 (2.8–8.7)
31	41/587	7.0 (5.1–9.4)	7/82	8.5 (3.5–16.8)	15/122	12.3 (7.1–19.5)	15/132	11.4 (6.5–18.0)	4/251	1.6 (0.4–4.0)
33	18/587	3.1 (1.8–4.8)	2/82	2.4 (0.3–8.5)	7/122	5.7 (2.3–11.5)	8/132	6.1 (2.7–11.6)	1/251	0.4 (0.0–2.2)
35	25/587	4.3 (2.8–6.2)	4/82	4.9 (1.3–12.0)	5/122	4.1 (1.3–9.3)	9/132	6.8 (3.2–12.5)	7/251	2.8 (1.1–5.7)
39	43/587	7.3 (5.4–9.7)	9/82	11.0 (5.1–19.8)	10/122	8.2 (4.0–14.6)	11/132	8.3 (4.2–14.4)	13/251	5.2 (2.8–8.7)
45	46/586	7.8 (5.8–10.3)	3/81	3.7 (0.8–10.4)	23/122	18.9 (12.3–26.9)	13/132	9.8 (5.4–16.3)	7/251	2.8 (1.1–5.7)
51	54/587	9.2 (7.0–11.8)	7/82	8.5 (3.5–16.8)	17/122	13.9 (8.3–21.4)	20/132	15.2 (9.5–22.4)	10/251	4.0 (1.9–7.2)
52	35/588	6.0 (4.2–8.2)	6/82	7.3 (2.7–15.2)	6/122	4.9 (1.8–10.4)	17/132	12.9 (7.7–19.8)	6/252	2.4 (0.9–5.1)
56	73/587	12.4 (9.9–15.4)	6/82	7.3 (2.7–15.2)	27/122	22.1 (15.1–30.5)	25/132	18.9 (12.6–26.7)	15/251	6.0 (3.4–9.7)
58	25/587	4.3 (2.8–6.2)	1/82	1.2 (0.0–6.6)	7/122	5.7 (2.3–11.5)	14/132	10.6 (5.9–17.2)	3/251	1.2 (0.3–3.5)
59	38/587	6.5 (4.6–8.8)	3/82	3.7 (0.8–10.3)	12/122	9.8 (5.2–16.6)	20/132	15.2 (9.5–22.4)	3/251	1.2 (0.3–3.5)

NOTE. *N* = number of subjects randomized; *n* = number of subjects positive for HPV type at baseline; *m* = number of subjects with available data for HPV type; CI = confidence interval.

young MSM. With over 600 men from global sites, this also represents the largest HPV-screening study of young adult MSM to date. HPV infection can cause significant pathology in all men, but MSM are at particularly high risk given the high proportion who practice anoreceptive intercourse. The potential for anogenital warts and cancer is also high. HPV infection of the anal canal in MSM is similar to genital infection in heterosexual men (HM), in that infection occurs rapidly in the late teens to early 20s and then persists at ~60% throughout the lifetime[2, 5]. Anal infection, however, is much more common in MSM than HM; prevalence ranges from only 15% in HM to ~60% in HIV-seronegative MSM and almost 100% in HIV-seropositive MSM[14, 15]. Although multiple studies have sought to determine the prevalence of HPV infection in men, few have looked at the subset of HIV-negative MSM alone, and none have evaluated current infection by polymerase chain reaction (PCR) as well as prior infection by serology testing for HPV antibodies.

The prevalence of any tested HPV type in this population of men with a history of few lifetime sexual partners was almost 50% overall, including 18.5% at the penis, 17.1% at the scrotum, 33.0% at the perineal/perianal region, and 42.4% in the anal canal. Factors associated with an increased risk of HPV infection included prior tobacco use (intra-anal detection) and number of lifetime sexual partners (intra-anal detection). Younger age was associated with an almost 2-fold greater risk of external genital infection with HPV 6/11/16/18, but no association was observed when any one of 14 HPV types was evaluated as the endpoint. MSM also had high rates of non-HPV STI, with approximately 2% having undiagnosed HIV or syphilis and rates of anorectal chlamydia infection approaching 10%.

Compared with HM enrolled in Protocol 020 (see accompanying article by Vardas et al.), the MSM were more likely to be from North America (43% vs 24%), circumcised (44% vs 37%), and smokers (40% vs 36%). Twenty-five percent of MSM reported a history of vaginal sex, similar to a previous report from Switzerland [16]. Although 15% of subjects reported that they used condoms less than half the time, it is not possible to know whether these were subjects in monogamous relationships or subjects having sex with multiple partners. MSM were more likely to report using condoms at least half the time than HM (83% vs 69%). This probably results from perceived increased risk of HIV transmission in MSM and safe sex messages geared more to MSM. Increased condom usage in MSM could also result from a larger percentage of MSM subjects enrolling from North America, where safe sex messages may be more common (see accompanying article by Vardas et al.).

When compared with HM, the prevalence of HPV infection at baseline in MSM was much higher. Only 8% of HM were infected with HPV 6, 11, 16, or 18, compared with 30% of MSM (23% when considering only MSM external genital sites). While HM were not tested for anal HPV infection, and the highest prevalence of HPV infections in MSM was intra anal, this does not entirely account for the higher prevalence of total infection, as MSM had consistently higher rates of penile, scrotal, and perineal/perianal infection as well. An increase in persistent HPV infection in and around the anal canal could be a contributing factor, and there is the possibility that the anal canal acts as a reservoir for infection. Additionally, the higher HPV prevalence in MSM when compared to HM could result from the higher numbers of sexual partners for MSM, thereby increasing their exposure to HPV and their risk of infection.

Table 5. Risk factors for prevalent detection of HPV DNA in external genital swabs (A) and anal swabs (B) at enrollment among men who have sex with men

A. External Genital Sites

	Prevalent Detection of HPV 6/11/16/18 DNAin External Genital Swabs		Prevalent Detection of Any Tested HPV DNAin External Genital Swabs*	
Risk Factor	% (no. with infection/ no. of subjects)	Odds Ratio (95%CI)	% (no. with infection/ no. of subjects)	Odds Ratio (95%CI)
Age				
15–20	15.6 (27/173)	2.0 (1.1–3.7)	24.3 (42/173)	1.3 (0.8–2.1)
21—27	9.8 (41/417)	1.0	22.3 (93/417)	1.0
Tobacco use on day 1				
Never used	10.4 (31/297)	1.0	20.9 (62/297)	1.0
Current user	16.4 (9/55)	1.9 (0.8–4.3)	25.5 (14/55)	1.5 (0.7–3.0)
Ex-user	11.8 (28/238)	1.0 (0.6–1.7)	24.8 (59/238)	0.9 (0.6–1.4)
Sex history with MALE partners on day 1				
Age at first intercourse				
<15	16.1 (9/56)	1.1 (0.4–3.0)	25.0 (14/56)	0.6 (0.3–1.4)
15–19	11.8 (43/363)	0.8 (0.4–1.7)	23.7 (86/363)	0.8 (0.5–1.3)
⩾20	10.9 (16/147)	1.0	23.1 (34/147)	1.0
Lifetime sex partners				
⩽1	10.4 (7/67)	1.0	14.9 (10/67)	1.0
2	12.4 (12/97)	1.1 (0.4–3.1)	23.7 (23/97)	1.9 (0.8–4.6)
3–6	12.3 (49/400)	1.1 (0.4–2.8)	25.3 (101/400)	2.0 (0.9–4.6)
Frequency of lifetime condom use				
Never	9.7 (3/31)	0.8 (0.2–2.9)	19.4 (6/31)	1.1 (0.4–3.0)
Less than half of the time	10.3 (6/58)	0.9 (0.3–2.2)	22.4 (13/58)	1.2 (0.6–2.3)
Always/More than half of the time	12.4 (59/477)	1.0	24.1 (115/477)	1.0
Circumcision				
No	11.5 (38/331)	1.0	26.3 (87/331)	1.0
Yes	11.6 (30/259)	1.7 (0.9–3.3)	18.5 (48/259)	1.2 (0.7–2.1)
Region				
Australia	7.1 (6/84)	1.0	13.1 (11/84)	1.0
Europe	17.2 (21/122)	3.2 (1.2–8.6)	31.1 (38/122)	3.3 (1.5–7.0)
Latin America	13.6 (18/132)	2.3 (0.8–6.3)	36.4 (48/132)	4.4 (2.1–9.3)
North America	9.1 (23/252)	1.1 (0.4–3.0)	15.1 (38/252)	1.1 (0.5–2.5)

B. Anal Canal

	Prevalent Detection of HPV 6/11/16/18 DNA in Anal Swabs		Prevalent Detection of Any Tested HPV DNA in Anal Swabs*	
Risk Factor	% (no. with infection/ no. of subjects)	Odds Ratio (95%CI)	% (no. with infection/ no. of subjects)	Odds Ratio (95%CI)
Age				
15–20	21.6 (37/171)	0.9 (0.5–1.4)	34.5 (59/171)	0.7 (0.4–1.1)
21–27	26.7 (111/416)	1.0	45.7 (190/416)	1.0
Tobacco use on day 1				
Never used	20.3 (60/295)	1.0	36.3 (107/295)	1.0
Current user	22.2 (12/54)	1.0 (0.5–2.1)	33.3 (18/54)	0.8 (0.4–1.6)
Ex-user	31.9 (76/238)	1.6 (1.0–2.4)	52.1 (124/238)	1.5 (1.0–2.1)
Sex history with MALE partners on day 1				
Age at first intercourse				
<15	23.6 (13/55)	0.7 (0.3–1.5)	47.3 (26/55)	0.8 (0.4–1.6)
15–19	28.3 (102/360)	1.1 (0.7–1.8)	45.8 (165/360)	1.0 (0.7–1.7)
⩾20	22.3 (33/148)	1.0	39.2 (58/148)	1.0

Table 5. (*Continued*)

B. Anal Canal

Risk Factor	Prevalent Detection of HPV 6/11/16/18 DNA in Anal Swabs		Prevalent Detection of Any Tested HPV DNA in Anal Swabs*	
	% (no. with infection/ no. of subjects)	Odds Ratio (95%CI)	% (no. with infection/ no. of subjects)	Odds Ratio (95%CI)
Lifetime sex partners				
⩽1	11.8 (8/68)	1.0	17.6 (12/68)	1.0
2	22.4 (22/98)	2.0 (0.8–5.1)	37.8 (37/98)	2.7 (1.2–6.0)
3–6	29.9 (118/395)	2.5 (1.0–6.0)	50.4 (199/395)	3.8 (1.8–8.0)
Frequency of lifetime condom use				
Never	16.1 (5/31)	1.0 (0.3–2.9)	35.5 (11/31)	1.5 (0.6–3.8)
Less than half of the time	22.0 (13/59)	1.0 (0.5–1.9)	32.2 (19/59)	0.8 (0.4–1.4)
Always/More than half time	27.5 (130/473)	1.0	46.3 (219/473)	1.0
Circumcision				
No	31.0 (101/326)	1.0	50.6 (165/326)	1.0
Yes	18.0 (47/261)	0.7 (0.4–1.2)	32.2 (84/261)	1.0 (0.6–1.5)
Region				
Australia	31.7 (26/82)	1.0	42.7 (35/82)	1.0
Europe	34.7 (42/121)	1.1 (0.6–2.0)	61.2 (74/121)	2.1 (1.1–3.7)
Latin America	30.8 (40/130)	0.9 (0.5–1.6)	56.9 (74/130)	1.7 (1.0–3.1)
North America	15.7 (40/254)	0.6 (0.3–1.1)	26.0 (66/254)	0.6 (0.3–1.1)

NOTE. CI,confidence interval.

* HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59. The multivariate logistic regression model was adjusted for geographic area of residence, age, tobacco use, age at first sexual intercourse with a male partner, number of lifetime sexual partners, number of new partners in the past 6 months, and circumcision history.

Of note, MSM from Europe and Latin America had a significantly higher prevalence of HPV infection, compared with MSM from Australia. Although higher rates of HPV infection in Latin America are not uncommon, the same cannot be said for Europe. Moreover, the HM subset from Europe and Latin America demonstrated approximately equal or lower baseline HPV prevalence when compared with the North American cohort. Reasons for these findings are unclear.

When analyzing risk factors for HPV infection several interesting findings appear. The lifetime number of sex partners was a significant risk factor for intra-anal detection of any tested HPV type but not for external genital detection of those types. Condom use had inconsistent results for risk of HPV infection in MSM and could substantiate the importance of transmission between partners without penetration or digital autoinoculation. This may also be explained inaccuracies is by the reporting of condom usage or by the presence of HPV in areas of the genitalia not covered by a condom. As in other studies, a past history of smoking significantly increased intra-anal HPV infection risk for the 4 types in qHPV vaccine as well as the composite of any tested type[2, 17]. There was no significant increased risk for current smoking or history of smoking for external genital HPV or for current smoking on intra-anal HPV. This seemingly inconsistent effect could be related to the fact that effects of smoking are primarily mucosal, thus keratinized skin on the external genitalia would not be as prone to the effects of tobacco. Increased prevalence of anal HPV infection and differing effects of baseline characteristics on the risk for prevalent infection may signify biological differences in HPV infection between external genital sites and the anal canal.

Although the present study represents the largest cohort of young adult men screened for both PCR and seroprevalence of HPV infection, it may not be truly representative of the population at large as this cohort had strict limitations placed on number of sexual partners for enrollment and history of STI, including HIV infection. Moreover, subjects could not have a history of or current evidence of an HPV-related lesion. Although the MSM enrolled were, by and large, all sexually active, it stands to reason that a larger percentage of MSM targeted for vaccination before they had anal or vaginal intercourse may be HPV-naive. Although MSM had a higher incidence of HPV infection as evidenced by both PCR and seropositivity, the majority would likely benefit from qHPV vaccine. Moreover, it is still unknown whether those who are PCR-negative but seropositive will derive benefit from qHPV vaccine. Both MSM and HM subjects had similar numbers of sexual partners, but

MSM had much higher HPV prevalence, supporting the paramount importance of early prophylactic vaccination in this population to achieve maximum benefit.

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