Research Article

Cancer Epidemiology, Biomarkers & Prevention

Seroepidemiology of High-Risk HPV in HIV-Negative and HIV-Infected MSM: The H2M Study

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Abstract

Background: Men who have sex with men (MSM), in particular HIV-infected MSM, are at increased risk for diseases related to human papilloma virus (HPV). Our goal was to assess the effect of HIV status on the presence of type-specific antibodies against seven high-risk HPV types in HPV-unvaccinated MSM. Moreover, we compared determinants of HPV seropositivity between HIV-negative and HIV-infected MSM.

Methods: MSM ≥18 years of age were recruited from the Amsterdam Cohort Studies, a sexually transmitted infection clinic, and an HIV-treatment center in Amsterdam, the Netherlands. Participants completed a risk-factor questionnaire; serum samples were analyzed using a fluorescent bead-based multiplex assay.

Results: MSM ($n = 795$) were recruited in 2010 to 2011; 758 MSM were included in this analysis. Median age was 40.1 years (interquartile range 34.8–47.5) and 308 MSM (40.6%) were HIV-infected. Seroprevalence of HPV-16 was 37.1% in HIV-negative and 62.7% in HIV-infected MSM ($P < 0.001$); seroprevalence of HPV-18 was 29.1% in HIV-negative MSM and 42.5% in HIV-infected MSM ($P < 0.001$). Similar patterns of seroprevalence were observed for HPV types 31, 33, 45, 52, and 58. In multivariable analyses, HPV seropositivity was associated with HIV infection [adjusted OR = 2.1; 95% confidence interval, 1.6–2.6]. In multivariable analyses stratified by HIV status, increasing age and number of lifetime male sex partners were significantly associated with HPV seropositivity in HIV-negative, but not HIV-infected MSM.

Conclusions: Seroprevalence of high-risk HPV types is high among unvaccinated MSM.

Impact: HIV infection is a strong and independent determinant for HPV seropositivity, which we hypothesize is because of increased persistence of HPV infection in HIV-infected MSM. *Cancer Epidemiol Biomarkers Prev; 22(10); 1698–708. ©2013 AACR.*

Introduction

Human papilloma virus (HPV) is a common viral sexually transmitted infection (STI). The lifetime risk of genital HPV infection in sexually active people is estimated to be around 80% (1). Estimated prevalence of genital HPV infection in men varies widely, between 1% to 84%, and up to 93% in those who are at high risk, such as men who have sex with men (MSM) and HIV-infected men (2–4).

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The vast majority of HPV infections (>90%) is cleared by the host immune system within 1 or 2 years (5). Time to clearance depends both on virus- and host-related factors (6), with possibly longer persistence of high-risk (oncogenic) HPV types, such as HPV-16, compared to low-risk types (7), and shorter persistence in heterosexual men compared to women (8–11). In immunocompromised people, persistent HPV infection is more common (12, 13).

Cellular immunity plays a major role in clearance of HPV and is often accompanied or followed by a humoral immune response (i.e., development of type-specific antibodies against HPV; ref. 14). Not all HPV infections lead to seroconversion, approximately 60% of women and probably a lower percentage of men seroconvert (15–18). Antibodies may persist for years, even decades, and therefore are reflective of a history of HPV exposure (as well as ongoing infections) at various anatomical locations (15, 19). Persistent HPV infections are more likely to induce a serological response than transient infections (19, 20). Because persistent high-risk HPV infection is related to several types of cancer (e.g., anogenital cancer and a subset of head and neck cancer; ref. 21–23), seropositivity could provide information on clinically relevant HPV infection.

To date, the protective effect of HPV antibodies elicited after natural infection remains elusive (24). Some studies observed a reduced risk of subsequent HPV infection in anti-HPV seropositive individuals (25–27). However, findings have been inconsistent (24, 28, 29) and the immune correlate (i.e., the antibody level which results in effective immunity) is unknown. Antibody levels elicited after HPV vaccination are 1 to 4 logs higher than after natural infection and have been shown to be highly protective against incident infection with vaccine-type HPV (30, 31). Recently, the quadrivalent HPV vaccine, targeting HPV types 6, 11, 16, and 18, has been licensed for use in men. However, few studies have examined HPV antibodies in men (28). Data are especially scarce for HPV seroprevalence in HIV-infected MSM, who are at increased risk for HPV infection and HPV-related diseases.

This study aims to estimate the effect of HIV infection on HPV seropositivity in HPV-unvaccinated MSM. In addition, we compared determinants for seropositivity between HIV-negative and HIV-infected MSM, focusing on the role of sexual behavior and drug use.

Materials and Methods

Study participants

Between July 2010 and July 2011, HIV-negative and HIV-infected MSM were invited to participate in the HIV & HPV in MSM (H2M) study at 3 sites in Amsterdam, the Netherlands: the Amsterdam Cohort Study (ACS) among MSM (Public Health Service of Amsterdam; ref. 32), an STI clinic (Public Health Service of Amsterdam; ref. 33), and an outpatient infectious disease clinic (Medical Center Jan van Goyen). At the ACS mainly HIV-negative participants were recruited, whereas at the latter 2 clinics HIV-infected participants were recruited. Men were eligible for participation if they had had sex with men, were 18 years of age or older, and fluent in Dutch or English. The Medical Ethics Committee of the Academical Medical Center (AMC) Amsterdam approved this study and participants provided written informed consent before enrolment.

Data collection

At the enrolment visit, participants completed an extensive questionnaire about sociodemographic characteristics, general health-related issues (e.g., smoking habits and circumcision status) and lifetime and recent sexual behavior. Venous blood was collected for serum antibody testing. HIV-related data [e.g., CD4 cell count, HIV viral load, and use of combination antiretroviral therapy (cART)] were obtained from the national HIV patients' database of the Dutch HIV Monitoring Foundation.

HPV serum antibody testing

Baseline serum samples were stored at −20°C and transported to the National Institute for Public Health and the Environment (RIVM, Bilthoven, the Netherlands), where samples were stored at −80°C until analysis. HPV-antibody detection against L1 virus-like particles (VLP) for serotypes 16, 18, 31, 33, 45, 52, and 58 was conducted simultaneously using a VLP-based multiplex immunoassay (MIA) as previously described by Scherpenisse and colleagues (34). The HPV–VLPs were coupled to a set of 7 distinct fluorescent microspheres (Luminex Corporation) using an enhanced carbodiimide-mediated coupling procedure that has been described elsewhere (35, 36), but with minor modifications (34). The MIA was conducted as described (37) with modifications. For each analyte, median fluorescent intensity (MFI) was converted to Luminex Units/mL (LU/mL) using a two-fold serial dilution of a reference standard (IVIG, lot LE12H227AF, Baxter, calibrated against reference serum of GSK for all the 7 HPV types) and interpolating the MFI data through a 5-parameter curve-fitting algorithm. Two quality in-house controls (low and high) were added to each plate. Cutoff values were previously determined at ≥9, ≥13, ≥27, ≥11, ≥19, ≥14, and ≥31 LU/mL for types 16, 18, 31, 33, 45, 52, and 58 respectively, based on the results of sera highly likely to be HPV-negative (children 1–10 years of age), using a one-sided 99% prediction interval method (38).

Statistical analyses

Baseline characteristics of HIV-negative and HIV-infected participants were compared using rank-sum tests for continuous data and χ^2 tests for categorical data. The prevalence of antibodies against each of the 7 high-risk HPV types separately, as well as against multiple HPV types, was estimated. Uncertainty was quantified via 95% binomial confidence intervals (95% CI).

We investigated the effect of HIV status on the presence of antibodies against the 7 HPV types in one single model via univariable and multivariable logistic regression analyses. Parameters were estimated using generalized estimating equations (GEE). GEE was applied to account for the analysis of multiple HPV types within the same individual; an exchangeable correlation structure was assumed. In this multivariable model we *a priori* adjusted for age, tobacco smoking, and lifetime male sex partners (39, 40). In addition, we included other potential confounders based on a $P < 0.05$ in univariable analyses, and subsequently obtained a parsimonious model through backward selection. In this overall model, we found a strong and independent effect of HIV infection on HPV seropositivity. We therefore conducted all further analyses stratified by HIV status.

To compare determinants for HPV seropositivity between HIV-negative and HIV-infected MSM, we selected variables based on the literature. Apart from HPV type (merely reflecting differences in seroprevalence between the 7 individual HPV types), the following variables were selected and forced into both stratified models, without conducting backward selection: age, tobacco smoking, recent use of cannabis and poppers, circumcision status, lifetime number of male sex partners, unprotected anal intercourse in the last 6 months, receptive anal intercourse in the last 6 months, and recent receptive fisting. In addition, CD4 cell count and HIV viral load were forced

into the model for HIV-infected MSM. We did not include any interaction between these variables and HPV type.

To minimize loss of observations in multivariable models, an extra category for missings was created for each variable with missing values for >40 participants in overall analyses or >20 participants in stratified analyses. *P* values in the multivariable models were obtained through Wald tests. All analyses were conducted using Stata software package version 11.2 (Stata Intercooled).

Results

Participant characteristics

In total, 795 participants were enrolled in the H2M study. Both questionnaire data and serum sample results were available for 758 MSM, who were included in the current analysis. There were no significant differences in important baseline characteristics (e.g., age, HIV status) between the 37 excluded and the 758 included MSM. Baseline characteristics of the 758 MSM are shown in Table 1, stratified by HIV status. Three hundred and eight MSM (41%) were HIV infected at time of enrolment. The median age was 40.1 years and was significantly higher in HIV-infected than in HIV-negative MSM (45.6 and 37.6 years, respectively). HIV-negative MSM were more likely to be born in the Netherlands and were generally higher educated. HIV-infected MSM were more likely to smoke tobacco and to use cannabis and poppers (alkyl nitrites). In general, HIV-infected MSM reported more sexual (risk) behavior than HIV-negative MSM, for example, higher numbers of lifetime male sex partners and recent anal sex partners. At enrolment, the median CD4 cell count of HIV-infected MSM was high at 535 cells/mm^3; a large majority of MSM (87%) were treated with cART, and 78% had undetectable HIV viral load.

HPV seroprevalence and antibody concentration

In total, 542 of 758 MSM (71.5%) tested positive for antibodies against at least 1 HPV type; seropositivity was significantly higher in HIV-infected compared to HIV-negative MSM (86.4% and 61.3%, respectively; Table 2). Median antibody concentrations were also consistently higher in HIV-infected MSM. Seroprevalence for multiple HPV types was 71.1% in HIV-infected and 37.3% in HIV-negative MSM. Seroprevalence for each specific HPV type was higher in HIV-infected compared to HIV-negative MSM ($P < 0.001$ for each comparison). For example, HPV-16 seroprevalence was 62.7% in HIV-infected and 37.1% in HIV-negative MSM; HPV-18 seroprevalence was 42.5% and 29.1%, respectively (see Fig. 1).

Association between HIV infection and HPV seropositivity

HPV seropositivity was significantly associated with HIV infection in univariable analysis (OR = 2.8; 95% CI, 2.3–3.4); the association remained significant in multivariable analysis [adjusted OR (aOR) = 2.1; 95% CI, 1.6–2.6] after adjusting for age, smoking, and sexual behavior (Table 3).

Risk factors for HPV seropositivity in HIV-negative MSM

In HIV-negative MSM, we observed a significant association in univariable analysis between HPV seropositivity and factors related to age, drug use, and several sexual behaviors (Table 4). In multivariable analysis, the following factors remained significantly associated with HPV seropositivity among HIV-negative MSM: increasing age (aOR = 1.8; 95% CI, 1.2–2.9 for ≥45 years compared to ≤34 years of age; overall $P = 0.021$), increasing number of lifetime male sex partners (aOR = 2.1; 95% CI, 1.4–3.2 for ≥501 compared ≤100 partners; overall $P < 0.001$), and being fisted in the past 6 months (aOR = 1.8; 95% CI, 1.0–3.4). Tobacco smoking and circumcision status were not associated with HPV seropositivity in HIV-negative MSM.

Risk factors for HPV seropositivity in HIV-infected MSM

In HIV-infected MSM, factors about tobacco smoking, drug use, sexual behavior, and HIV viral load were significantly associated with HPV seropositivity in univariable analysis (Table 4). In multivariable analysis, tobacco smoking (aOR = 0.5; 95% CI, 0.3–0.7 for current smokers compared to never smokers; overall $P = 0.002$), unprotected anal intercourse in the past 6 months (aOR = 0.3; 95% CI, 0.2–0.8 for never protected anal intercourse compared to no anal intercourse; overall $P = 0.002$), recently being fisted (aOR = 1.8; 95% CI, 1.1–2.8), and HIV viral load (aOR = 0.5; 95% CI, 0.3–0.9 for ≥50 compared to <50 copies/mL) showed a significant association with HPV seropositivity in HIV-infected MSM.

Discussion

The prevalence of type-specific antibodies against 7 high-risk HPV types among HIV-negative MSM and, in particular, HIV-infected MSM is very high. Determinants for HPV seropositivity differed between HIV-negative and HIV-infected MSM. In HIV-negative MSM, determinants were generally in agreement with well-established risk factors for HPV infection, such as a high number of lifetime male sex partners, which contrasts with our findings in HIV-infected MSM.

Prevalence of antibodies against HPV-16, which is the most carcinogenic and therefore most important HPV type, was high compared to other studies among (mostly heterosexual) males (16, 17, 34, 41), but comparable to data reported for MSM specifically (40, 42). However, comparisons between HPV serology studies are hampered by major differences in characteristics of the study population and in serology methods. A large population-based study in the Netherlands, using the identical serology method as our study, observed an overall seroprevalence of 20% in males 15 to 79 years of age (34). This was substantially lower than the 61% overall seroprevalence observed in HIV-negative MSM in our study, indicating very high HPV exposure in our cohort. Another recent Dutch study, using the identical serology method, found

Table 1. Baseline characteristics of 758 MSM participating in the H2M study, overall and stratified by HIV status (Amsterdam, 2010–2011)[a]

	Overall ($n = 758$)	HIV-negative ($n = 450$)	HIV-infected ($n = 308$)	*P* value[b]
	No. (%)	No. (%)	No. (%)	
A. Sociodemographic characteristics				
Median age in years (IQR)	40.1 (34.8–47.5)	37.6 (33.6–42.3)	45.6 (39.4–52.5)	**<0.001**[c]
Age (years) by category				**<0.001**
≤34	192 (25.3)	150 (33.3)	42 (13.6)	
35–44	335 (44.2)	232 (51.6)	103 (33.4)	
≥45	231 (30.5)	68 (15.1)	163 (52.9)	
Study site				**<0.001**
Amsterdam Cohort Study among MSM	482 (63.6)	448 (99.6)	34 (11.0)	
MC Jan van Goyen	161 (21.2)	0 (0.0)	161 (52.3)	
STI clinic (Public Health Service of Amsterdam)	115 (15.2)	2 (0.4)	113 (36.7)	
Country of birth				**0.034**
The Netherlands	608 (80.9)	371 (83.4)	237 (77.2)	
Any other country	144 (19.1)	74 (16.6)	70 (22.8)	
Education				**<0.001**
Lower education	228 (30.1)	111 (24.7)	117 (38.0)	
Higher education	529 (69.9)	338 (75.3)	191 (62.0)	
Living situation				0.462
Alone	396 (52.7)	239 (53.7)	157 (51.1)	
With steady partner	313 (41.6)	178 (40.0)	135 (44.0)	
With parents/caretakers/others	43 (5.7)	28 (6.3)	15 (4.9)	
B. Health-related characteristics				
Tobacco smoking[d]				**0.007**
Never	253 (36.9)	174 (41.4)	79 (29.7)	
Ever/in the past	180 (26.2)	105 (25.0)	75 (28.2)	
Current smoker	253 (36.9)	141 (33.6)	112 (42.1)	
Tobacco smoking pack years[d,e]				**<0.001**
0–14	459 (79.3)	303 (83.9)	156 (71.6)	
≥15	120 (20.7)	58 (16.1)	62 (28.4)	
Cannabis use last 6 months[f]				**<0.001**
No	498 (69.7)	326 (77.3)	172 (58.9)	
Yes	216 (30.3)	96 (22.7)	120 (41.1)	
Poppers use last 6 months				**<0.001**
No	367 (56.2)	245 (67.9)	122 (41.8)	
Yes	286 (43.8)	116 (32.1)	170 (58.2)	
Circumcised				**0.145**
No	604 (81.1)	366 (82.8)	238 (78.5)	
Yes	141 (18.9)	76 (17.2)	65 (21.5)	
C. Sexual behavior				
Median age first anal sexual experience with male partner (years) (IQR)	21 (18–24)	21 (18–24)	20 (17.5–24)	**0.014**[c]
Age first anal sexual experience with male partner (years) by category				**0.004**
≤19	267 (38.9)	134 (34.4)	133 (44.9)	
20–23	239 (34.8)	155 (39.7)	84 (28.4)	
≥24	180 (26.2)	101 (25.9)	79 (26.7)	

(Continued on the following page)

Table 1. Baseline characteristics of 758 MSM participating in the H2M study, overall and stratified by HIV status (Amsterdam, 2010–2011)[a] (Cont'd)

	Overall ($n = 758$)	HIV-negative ($n = 450$)	HIV-infected ($n = 308$)	*P* value[b]
	No. (%)	No. (%)	No. (%)	
Median lifetime number of male sex partners (IQR)	200 (60–600)	100 (50–400)	300 (100–1000)	**<0.001**[c]
Lifetime number of male sex partners by category				**<0.001**
≤100	287 (40.8)	210 (50.2)	77 (27.0)	
101–500	240 (34.1)	130 (31.1)	110 (38.6)	
≥501	176 (25.0)	78 (18.7)	98 (34.4)	
Unprotected anal intercourse last 6 months				**<0.001**
No anal intercourse	124 (16.6)	73 (16.5)	51 (16.8)	
Anal intercourse, always protected	188 (25.2)	122 (27.5)	66 (21.8)	
Anal intercourse, sometimes protected	307 (41.2)	156 (35.2)	151 (49.8)	
Anal intercourse, never protected	127 (17.0)	92 (20.8)	35 (11.6)	
Receptive anal intercourse last 6 months				0.060
No	252 (33.6)	162 (36.3)	90 (29.7)	
Yes	497 (66.4)	284 (63.7)	213 (70.3)	
Median number of anal sex partners last 6 months (IQR)	2 (1–6)	2 (1–4)	4 (1–10)	**<0.001**[c]
Number of anal sex partners last 6 months by category				**<0.001**
≤1	313 (41.9)	209 (46.7)	104 (34.8)	
2–4	187 (25.0)	135 (30.1)	52 (17.4)	
≥5	247 (33.1)	104 (23.2)	143 (47.8)	
Median number of oral sex partners last 6 months (IQR)	4 (1–11)	4 (1–9)	5 (2–20)	**0.002**[c]
Number of oral sex partners last 6 months by category				**<0.001**
≤2	269 (36.1)	169 (37.6)	100 (33.7)	
3–8	232 (31.1)	162 (36.1)	70 (23.6)	
≥9	245 (32.8)	118 (26.3)	127 (42.8)	
Being fisted last 6 months				**<0.001**
No	665 (89.6)	416 (95.0)	249 (81.9)	
Yes	77 (10.4)	22 (5.0)	55 (18.1)	
D. HIV-related characteristics				
Median CD4 cell count at enrolment (cells/mm^3) (IQR)			535 (410–700)	
CD4 cell count at enrolment (cells/mm^3) by category				
≤350			38 (15.3)	
>350			210 (84.7)	
Median nadir CD4 cell count (cells/mm^3) (IQR)			223 (160–320)	
Nadir CD4 cell count (cells/mm^3) by category				
<200			99 (37.1)	
200–349			114 (42.7)	
≥350			54 (20.2)	
HIV viral load at enrolment (copies/mL) by category				
<50			200 (78.1)	
≥50			56 (21.9)	
Use of cART at enrolment				
No			34 (12.9)	
Yes			229 (87.1)	

NOTE: Significant results ($P < 0.05$) are represented in bold type.

Abbreviation: IQR, interquartile range.

[a]Numbers do not always add up to the total because of missing values.

[b]Based on χ^2 test (except when stated otherwise).

[c]Based on rank-sum test.

[d]Participants who were not current smokers but provided no information on past smoking behavior were counted as missing values.

[e]Never smokers were included in category 0 to 14 pack years.

[f]This concerns cannabis use in general (without specifying route of administration).

Table 2. Antibody concentrations (IgG LU/mL; median and IQR) and seroprevalence against 7 high-risk HPV types separately, HPV-16 and/or HPV-18, at least 1 HPV type, multiple (≥2) HPV types, and 7 high-risk HPV types, in 758 MSM participating in the H2M study, overall and stratified by HIV status (Amsterdam, 2010–2011)

	Overall ($n = 758$)			HIV-negative ($n = 450$)			HIV-infected ($n = 308$)			
Outcome	Median IgG LU/mL (IQR)	No. seropositive	% Positive (95% CI)	Median IgG LU/mL (IQR)	No. seropositive	% Positive (95% CI)	Median IgG LU/mL (IQR)	No. seropositive	% Positive (95% CI)	*P* value[a]
HPV-16	8.1 (1.9–41.6)	360	47.5% (43.9–51.1)	4.3 (1.3–25.8)	167	37.1% (32.6–41.8)	17.0 (4.4–64.3)	193	62.7% (57.0–68.1)	<**0.001**
HPV-18	7.0 (3.1–23.4)	262	34.6% (31.2–38.1)	5.8 (2.6–16.4)	131	29.1% (25.0–33.5)	10.1 (3.8–34.2)	131	42.5% (36.9–48.3)	<**0.001**
HPV-31	4.1 (1.4–14.3)	122	16.1% (13.5–18.9)	2.3 (1.1–7.3)	41	9.1% (6.6–12.2)	9.6 (3.1–30.9)	81	26.3% (21.5–31.6)	<**0.001**
HPV-33	4.9 (1.6–17.4)	260	34.3% (30.9–37.8)	2.9 (1.2–9.6)	101	22.4% (18.7–26.6)	11.8 (3.4–30.7)	159	51.6% (45.9–57.3)	<**0.001**
HPV-45	13.7 (4.8–36.2)	312	41.2% (37.6–44.8)	8.5 (3.3–21.0)	126	28.0% (23.9–32.4)	25.5 (11.2–53.8)	186	60.4% (54.7–65.9)	<**0.001**
HPV-52	4.4 (2.0–11.1)	152	20.1% (17.3–23.1)	3.3 (1.7–7.9)	61	13.6% (10.5–17.1)	6.2 (3.0–18.0)	91	29.6% (24.5–35.0)	<**0.001**
HPV-58	8.0 (2.6–22.3)	144	19.0% (16.3–22.0)	4.7 (1.9–14.5)	54	12.0% (9.1–15.4)	12.9 (5.5–36.2)	90	29.2% (24.2–34.6)	<**0.001**
HPV-16 and/or HPV-18	NA	439	57.9% (54.3–61.5)	NA	219	48.7% (44.0–53.4%)	NA	220	71.4% (66.0–76.4)	<**0.001**
≥1 HPV type(s)	NA	542	71.5% (68.1–74.7)	NA	276	61.3% (56.7–65.9)	NA	266	86.4% (82.0–90.0)	<**0.001**
≥2 HPV types	NA	387	51.1% (47.4–54.7)	NA	168	37.3% (32.8–42.0)	NA	219	71.1% (65.7–76.1)	<**0.001**
All 7 HPV types	NA	32	4.2% (2.9–5.9)	NA	5	1.1% (0.4–2.6)	NA	27	8.8% (5.9–12.5)	<**0.001**

NOTE: Cutoff values were previously determined at ≥9, ≥13, ≥27, ≥11, ≥19, ≥14, and ≥31 LU/mL for HPV types 16, 18, 31, 33, 45, 52, and 58, respectively. Significant results ($P < 0.05$) are represented in bold type.

Abbreviations: IQR, interquartile range; NA, not applicable.

[a]Based on χ^2 test.

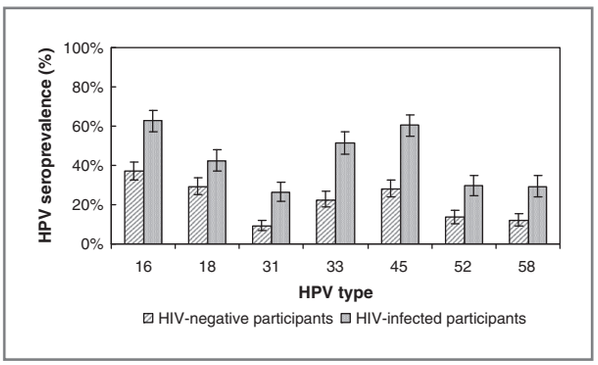

Figure 1. Type-specific HPV seroprevalence and 95% CIs of 7 high-risk HPV types in baseline serum samples from 758 MSM participating in the H2M study, stratified by HIV status (Amsterdam, 2010–2011).

overall seropositivity of 34% among young MSM (16–24 years of age) who visited an STI clinic (43).

We observed a significantly higher HPV-16 seroprevalence among HIV-infected MSM compared to HIV-negative MSM (63% vs. 37%), a similar finding to that of Poynten and colleagues in a recent study among Australian homosexual men (44), but different from observations of others, for example, Hagensee and colleagues (45). In addition, antibody concentrations were higher in HIV-infected than HIV-negative MSM, and HIV infection was independently associated with HPV seropositivity. Thus, our data suggest that HIV infection does not avert the ability to produce HPV antibodies or to remain HPV seropositive. This seems biologically plausible, because HIV infection primarily impairs cellular immunity and to a lesser degree humoral immunity. Our HIV-infected study population was relatively healthy; the majority received cART and had high CD4 cell counts (>500 cells/mm^3) at enrolment; hence, results may not be generalizable to all HIV-infected individuals. Intriguingly, detectable HIV viral load was negatively associated with HPV seropositivity. The increased HPV seroprevalence in HIV-infected MSM observed in our study might be explained by more persistent (vs. none or transient) HPV infections and/or more reactivation of latent HPV

Table 3. Univariable and multivariable logistic regression analyses using GEE to assess the association between HIV status and high-risk HPV seropositivity in 758 MSM participating in the H2M study, adjusting for age, smoking, and sexual behavior (Amsterdam, 2010–2011)

	Univariable		Multivariable ($n = 749$)	
	OR (95% CI)	*P* value	aOR (95% CI)	*P* value[a]
HIV-infected		**<0.001**		**<0.001**
No	1.0		1.0	
Yes	2.8 (2.3–3.4)		2.1 (1.6–2.6)	
Age (years) by category		**<0.001**		**<0.001**
≤34	1.0		1.0	
35–44	1.5 (1.2–2.0)		1.4 (1.1–1.9)	
≥45	2.5 (1.9–3.3)		1.8 (1.3–2.4)	
Tobacco smoking[b]		**0.981**		**0.249**
Never	1.0		1.0	
Ever/in the past	1.0 (0.8–1.3)		0.9 (0.7–1.1)	
Current smoker	1.0 (0.8–1.3)		0.8 (0.6–1.0)	
Lifetime number of male sex partners		**<0.001**		**0.032**
≤100	1.0		1.0	
101–500	1.7 (1.3–2.2)		1.3 (1.0–1.7)	
≥501	2.2 (1.7–2.8)		1.4 (1.1–1.8)	
Unprotected anal intercourse last 6 months		**<0.001**		**<0.001**
No anal intercourse	1.0		1.0	
Anal intercourse, always protected	1.0 (0.7–1.3)		1.0 (0.7–1.4)	
Anal intercourse, sometimes protected	1.7 (1.2–2.2)		1.5 (1.1–2.1)	
Anal intercourse, never protected	0.8 (0.6–1.2)		0.9 (0.6–1.3)	
Being fisted last 6 months		**<0.001**		**0.001**
No	1.0		1.0	
Yes	2.5 (1.8–3.4)		1.7 (1.2–2.3)	

NOTE: High-risk HPV—HPV types 16, 18, 31, 33, 45, 52, and 58. Significant results ($P < 0.05$) are represented in bold type.

[a]Based on Wald test.

[b]Participants who were not current smokers but provided no information on past smoking behavior were counted as missing values.

Table 4. Univariable and multivariable logistic regression model using GEE to assess the association between potential risk factors and high-risk HPV seropositivity in 450 HIV-negative MSM and 308 HIV-infected MSM participating in the H2M study (Amsterdam, 2010–2011)

	HIV-negative MSM				HIV-infected MSM			
	Univariable		Multivariable ($n = 423$)		Univariable		Multivariable ($n = 276$)	
	OR (95% CI)	*P* value	aOR (95% CI)	*P* value[a]	OR (95% CI)	*P* value	aOR (95% CI)	*P* value[a]
Age (years) by category		**<0.001**		**0.021**		0.612		0.614
≤34	1.0		1.0		1.0		1.0	
35–44	1.7 (1.2–2.3)		1.5 (1.1–2.1)		1.1 (0.7–1.7)		1.1 (0.7–2.0)	
≥45	2.1 (1.4–3.2)		1.8 (1.2–2.9)		1.2 (0.8–1.8)		1.3 (0.7–2.2)	
Tobacco smoking[b]		0.628		0.893		**0.011**		**0.002**
Never	1.0		1.0		1.0		1.0	
Ever/in the past	1.1 (0.8–1.6)		1.1 (0.7–1.6)		0.7 (0.5–1.0)		0.5 (0.3–0.8)	
Current smoker	1.2 (0.8–1.6)		1.0 (0.7–1.5)		0.6 (0.4–0.8)		0.5 (0.3–0.7)	
Cannabis use last 6 months[c]		**0.002**		0.077		0.617		0.977
No	1.0		1.0		1.0		1.0	
Yes	1.6 (1.2–2.2)		1.4 (1.0–2.0)		0.9 (0.7–1.2)		1.0 (0.7–1.4)	
Poppers use last 6 months		**0.008**		0.614		**0.018**		0.117
No	1.0		1.0		1.0		1.0	
Yes	1.5 (1.1–2.1)		1.1 (0.8–1.6)		1.4 (1.1–1.9)		1.4 (0.9–2.0)	
Circumcised		0.604		0.980		0.323		0.985
No	1.0		1.0		1.0		1.0	
Yes	1.1 (0.8–1.6)		1.0 (0.7–1.5)		0.8 (0.6–1.2)		1.0 (0.7–1.5)	
Lifetime number of male sex partners		**<0.001**		**<0.001**		0.797		0.959
≤100	1.0		1.0		1.0		1.0	
101–500	1.7 (1.2–2.3)		1.6 (1.1–2.3)		1.1 (0.8–1.6)		1.0 (0.7–1.6)	
≥501	2.6 (1.8–3.7)		2.1 (1.4–3.2)		1.1 (0.8–1.6)		1.0 (0.6–1.5)	
Unprotected anal intercourse last 6 months		**<0.001**		0.053		**0.007**		**0.002**
No anal intercourse	1.0		1.0		1.0		1.0	
Anal intercourse, always protected	1.7 (1.1–2.8)		1.2 (0.6–2.1)		0.6 (0.4–1.0)		0.4 (0.2–0.7)	
Anal intercourse, sometimes protected	2.5 (1.6–3.9)		1.8 (1.0–3.2)		1.1 (0.7–1.6)		0.7 (0.4–1.3)	
Anal intercourse, never protected	1.5 (0.9–2.5)		1.3 (0.7–2.3)		0.6 (0.3–1.0)		0.3 (0.2–0.8)	
Receptive anal intercourse last 6 months		**<0.001**		0.197		0.376		0.075
No	1.0		1.0		1.0		1.0	
Yes	1.7 (1.3–2.3)		1.3 (0.9–1.9)		1.2 (0.8–1.6)		1.6 (1.0–2.7)	
Being fisted last 6 months		**0.002**		**0.047**		**0.004**		**0.018**
No	1.0		1.0		1.0		1.0	
Yes	2.4 (1.4–4.1)		1.8 (1.0–3.4)		1.7 (1.2–2.5)		1.8 (1.1–2.8)	
CD4 cell count at enrolment (cells/mm^3)						0.910		0.754
≤350					1.0		1.0	
>350					1.0 (0.6–1.5)		0.9 (0.6–1.5)	
HIV viral load at enrolment (copies/mL)						**0.008**		**0.009**
<50					1.0		1.0	
≥50					0.6 (0.4–0.9)		0.5 (0.3–0.9)	

NOTE: High-risk HPV—HPV types 16, 18, 31, 33, 45, 52, and 58. HPV type was included in the multivariable models, apart from the variables shown in the table. Significant results ($P < 0.05$) are represented in bold type.

[a]Based on Wald test.

[b]Participants who were not current smokers but provided no information on past smoking behavior were counted as missing values.

[c]This concerns cannabis use in general (without specifying route of administration).

infection because of HIV-induced immunosuppression. In addition, increased HPV acquisition in HIV-infected MSM due to more sexual risk behavior may play a role. In our multivariable analysis we did adjust for sexual behavior, but residual confounding may be present. Longitudinal data assessing HPV DNA and HPV seropositivity are necessary to elucidate the associations between (persistent) HPV infection, HIV infection, and HPV antibodies; such data will be provided by our ongoing cohort study in this group of MSM.

MSM have consistently been shown to have higher HPV seroprevalence compared to heterosexual men (46–48), which could be related to receptive anal intercourse and associated anal HPV infection. One hypothesis is that the mucosal lining of the anal canal provides better access to the immune system than the keratinized epithelium of the penile skin, leading to earlier and stronger antibody responses for anal versus penile HPV infection (14, 48). Our findings support this hypothesis in that men reporting receptive anal intercourse had increased odds for HPV seropositivity, albeit the associations were nonsignificant in multivariable analyses. In addition, receptive fisting, which may facilitate HPV infection through mucosal damage in the anal canal, was a strong and independent risk factor for seropositivity.

Increasing age was significantly associated with HPV seropositivity in HIV-negative MSM. This age-related pattern has consistently been described in serology studies among men (16, 39, 40, 46) and may reflect cumulative lifetime HPV exposure in combination with age-related changes in immunity. An increasing number of lifetime male sex partners is a well-known risk factor for HPV infection (6), and showed a strong and significant association with HPV seropositivity in HIV-negative but not in HIV-infected MSM. This dissimilarity might be explained by a saturation effect in HIV-infected MSM (because they reported significantly more lifetime sex partners than HIV-negative MSM) or an overriding effect of HIV infection on lifetime male sex partners.

Tobacco smoking was negatively associated with HPV seropositivity in HIV-infected MSM. Smoking is a well-established risk factor for HPV infection through modulating effects on local and systemic immunity, but the association between smoking and HPV seropositivity is more ambiguous. A recent study investigating HPV seroconversion following HPV infection in male students found that a history of cigarette smoking was positively associated with seroconversion (18). In contrast, another prospective study observed impaired antibody response following natural HPV-16 or HPV-18 infection among young female smokers compared to nonsmokers (49).

This study has several strengths and limitations. First, our study population was relatively large, and detailed information was obtained on both recent and lifetime sexual behavior. Second, we were able to compare HIV-negative MSM and HIV-infected MSM by using the same serology method. One important limitation is the cross-sectional nature of this study, limiting opportunities to assess time-related effects. Furthermore, although it is very plausible that many of our highly HPV preexposed study participants are seropositive for multiple HPV types, cross-reactivity of phylogenetically related HPV types is likely and may have led to an overestimation of the type-specific seropositivity in our study population (34). Behavioral data in this study were self-reported, and as a consequence may be subject to recall bias or socially desirable answers—although we aimed to limit the latter by using self-administered questionnaires. Some variables contained a relatively large amount of missing data, which we handled by including an extra category for missings in multivariable analyses. Finally, we do not have information on anal disease status. In the future, part of the HIV-infected MSM will undergo high-resolution anoscopy; we therefore hope to publish data on disease status in due course.

Our data confirm that HIV-negative MSM and HIV-infected MSM $\geq$18 years of age are highly exposed to high-risk HPV infections, as antibodies serve as a marker for current and previous HPV infections. The true cumulative lifetime HPV exposure is probably even greater than estimated from seroprevalence data, because not all HPV infections lead to seroconversion and waning of antibodies over time occurs. This study underscores the importance of prevention of HPV infection and sequelae in HIV-negative and HIV-infected MSM, who are at high risk for HPV-related diseases.

Conclusion

In conclusion, we observed a high seroprevalence of 7 high-risk HPV types among HIV-negative MSM and HIV-infected MSM in Amsterdam, the Netherlands. HIV infection was independently associated with HPV seropositivity, which might be explained by more persistent HPV infections or more frequent reactivation of latent infection. Risk factors for HPV seropositivity included increasing age, more lifetime male sex partners (in HIV-negative MSM), and receptive fisting (in both HIV-negative and HIV-infected MSM). Our data indicate that both HIV-negative and HIV-infected MSM are highly exposed to high-risk HPV infections, including HPV-16.

Disclosure of Potential Conflicts of Interest

H. de Vries has received honoraria from the speakers bureau of Benecke and Abvie. Also H. de Vries is a consultant/advisory board member for Willpharma. M. Schim van der Loeff has other commercial research support from Sanfo-Pasteur-MSD and Merck. No potential conflicts of interest were disclosed by the other authors.

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Seroepidemiology of High-Risk HPV in HIV-Negative and HIV-Infected MSM: The H2M Study

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