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Incidence of and risk factors for type-specific anal human papillomavirus infection among HIV-positive MSM

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Abstract

Objective—HIV-positive MSM are at increased risk of anal human papillomavirus (HPV) infection compared with men in the general population, and little is known about the natural history of anal HPV infection in this population. The objective of this study was to determine the incidence of and risk factors for anal type-specific HPV infection.

Design—Prospective cohort study.

Methods—HIV-positive MSM were evaluated for anal HPV DNA, lifestyle factors, and sexual risk behaviors every 6 months for at least 2 years.

Results—The overall incidence rate of detectable type-specific anal HPV infection was 21.3 per 100 person-years [95% confidence interval (CI) 17.7–25.4] and was 13.3/100 person-years (10.5–16.6) for oncogenic HPV types. The most common incident infections were HPV 18 (3.7/100 person-years) and HPV 16 (3.5/100 person-years). An increased number of recent partners with whom the participant was the receptive partner [odds ratio (OR) 2.9 (1.6–5.1) 8+ partners vs. 0–1], an increased number of new partners in which the participant was the receptive partner [OR 1.03 (1.01–1.1) per partner], an increased number of new oral–anal contact partners in which the participant was the receptive partner [OR 1.1 (1.03–1.1) per partner], and the frequency of

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receptive anal intercourse [OR 1.1 (1.03–1.1) per act] all significantly increased the odds of incident HPV infection ($P \leq 0.05$).

Conclusion—HIV-positive MSM have a high incidence of oncogenic anal HPV infection. Recent receptive anal sexual behaviors, including receptive anal intercourse and receptive oral–anal contact, are the most important risk factors for incident anal HPV infection.

Keywords

anus; HIV; HPV; human papillomavirus; incidence; men who have sex with men; receptive anal intercourse

Introduction

The incidence of anal cancer is low among men in the general population, but is considerably increased among MSM. Prior to the HIV epidemic, the incidence of anal cancer among MSM was estimated to be as high as 37 per 100 000 [1], which is similar to the incidence rate of cervical cancer among women in western countries before routine cervical cytology screening was introduced [2]. Among MSM who are also HIV-positive, the incidence rates have been reported to be even higher at 131 per 100 000 [3]. Unlike other virus-associated cancers, the risk of anal cancer has not declined among HIV-positive MSM since the introduction of HAART [4–7]. Instead, the incidence of anal cancer has continued to increase [8], and it is possible that this trend may continue as the HIV-positive population continues to age.

Similar to cervical cancer, anal cancer is associated with human papillomavirus (HPV) infection. Approximately 90% of all anal cancers are attributed to HPV infection [2]. HPV 16 and HPV 18 are responsible for 76 and 9% of anal cancers, respectively [2].

In prevalence studies, anal HPV infection is almost universal among HIV-positive MSM, with reported prevalence estimates between 87 and 98% [9 – 12]. HPV 16 is among the most common types detected, with a greater than 30% prevalence [9–12]. Risk factors for prevalent anal HPV infection include receptive anal intercourse [10], a higher number of male partners [9, 10], inflammation [9, 12], and a lower $CD4^+$ cell count [9, 10, 13]. However, cross-sectional studies are limited in their ability to examine risk factors, given that the prevalent infections are a mix of new and persistent infections. Risk factors for prevalent infection may be factors associated with persistence and not acquisition of new infection.

We conducted a prospective cohort study to assess the natural history of anal HPV infection in MSM in the antiretroviral therapy (ART) era. The goal of this analysis is to report the incidence of detection of type-specific anal HPV infection and to evaluate risk factors for infection.

Methods

HIV-positive MSM were recruited into a prospective cohort study conducted by the University of California, San Francisco (UCSF). Enrollment was completed between

February 1998 and January 2000, and participants were followed every 6 months for at least 2 years. At each visit, participants completed an interviewer-administered questionnaire and a clinical examination, including collection of an anal swab for HPV testing. Blood was collected for $CD4^+$ lymphocyte cell counts that were measured using standardized two or three-color fluorescence methods. HIV plasma viral load (HIV-VL) was measured using the branched-chain Chiron assay (Chiron, Emeryville, California, USA). Written informed consent was collected from participants and the study was approved by the Committee on Human Research at UCSF.

Human papillomavirus testing

Testing for anal HPV infection was performed as described previously using the PCR with L1 consensus primers and probes specific for 29 individual HPV types and a mixture of 10 other types [9]. Beta-globin-negative (indicating insufficient DNA) samples were excluded from analysis. Detection of incident HPV infection was computed for each HPV type individually. Incident HPV infection was defined as a negative test result at baseline for an individual HPV type followed by at least two consecutive positive tests for that type during the follow-up period. Two consecutive positive tests were required because detection on a single occasion is less likely to represent true infection than is two consecutive positive tests 6 months apart, and is consistent with the definition of infection commonly used in vaccine studies [14, 15]. Requiring two positive tests reduces potential outcome misclassification and provides a conservative estimate of incidence. Because of this requirement, participants were included in this analysis only if they had at least two follow-up visits or 1 year of follow-up.

Assessment of potential risk factors

Demographic factors, lifestyle characteristics, medical history including ARTuse, history of treatment for high-grade anal intraepithelial neoplasia (HGAIN), and history of sexual behavior were collected as part of the baseline questionnaire. At each follow-up visit, the interviewer collected information on factors that may have changed since the last interview. Two time periods were included: approximately 6 months prior and in the past 30 days.

We asked if the participant had engaged in each sexual behavior (yes/no); the number of partners with whom he had engaged in the behavior; the number of ‘new’ partners with whom he engaged in the behavior; and the frequency of the behavior. Men were queried about sex with men and women, ‘insertive’ anal intercourse (participant inserts his penis into partner's anus) and ‘receptive’ anal intercourse (participant receives his partner's penis into his anus); oral–anal contact (‘rimming’, participant's anus receives contact from partners mouth).

Statistical analysis

The rate of detection of incident anal HPV infection was computed as number of participants with incident infection detected divided by person-years of follow-up. An incident infection was assumed to have taken place halfway between the previous visit and the current visit, and person-time was assigned as (current visit date minus previous visit

date)/2. Exact Poisson confidence intervals (CIs) were computed for each incidence rate [16].

Participants who had an incident type-specific HPV infection were censored from that type-specific analysis at future time points, but remained in the analyses for other HPV types. Participants could have 'any incident HPV' at multiple visits if they had different type-specific infections at different visits.

We evaluated the bi-variable association of baseline characteristics with any incident infection in participants (n = 376 participants) using the chi-square test for independence for categorical variables, and analysis of variance (ANOVA) or ranked ANOVA for continuous variables, as appropriate. We evaluated bi-variable associations of incident HPV infection with time-dependent characteristics by participant visit (n = 888 participant visits). P-values were generated from generalized linear models estimated through repeated measures with generalized estimating equations (GEE) [17], adjusting for potential correlation from taking repeated measures on participants, as well as reporting robust standard errors. We note that the measure of association obtained from this procedure is the odds ratio (OR) related to the hazard of new infection.

To evaluate the effect of risk factors for incident anal HPV infection, we constructed logistic regression multivariable models estimated through repeated-measures GEE [17]. Four different model sets were created for each risk factor. Model 1 is the unadjusted model and includes only the risk factor. Model 2 additionally includes the baseline value of the risk factor. Model 3 adds six baseline factors identified *a priori* as potential confounders (baseline age, race, education, smoking 100+ lifetime cigarettes, baseline $CD4^+$ cell count, and HPV status at baseline). Model 4 adds the potential time-dependent confounder of $CD4^+$ cell count measured at the previous visit. In all models, the main risk factor is treated as a time-dependent variable.

We also conducted a sub-analysis to determine if treatment for low-grade anal intraepithelial neoplasia (LGAIN) or HGAIN had an effect on our models. We added a variable for treatment at any time during the study to our "Model 4's" (described above). All analyses were conducted using SAS 9.2 (SAS, Cary, North Carolina, USA).

Results

Participants excluded from analysis

Four hundred and ninety-three HIV-positive MSM enrolled in the study at baseline. Of those, 41 (8%) were found to be beta-globin-negative and were excluded from further analyses. Of the remaining 452 considered eligible for our follow-up analysis, 83 (18%) did not return for at least two follow-up visits. The participants who did not return for at least two visits did not differ significantly from those who did by race/ethnicity, education, lifestyle factors, sexual risk behaviors, or HPV prevalence at baseline. Those who did not return were younger in age (41 vs. 45 years; P = 0.001). There was also an important difference between the indicators of HIV disease status between the two groups. Those who did not return had a lower mean $CD4^+$ cell count (365 vs. 459 cells/μl; P = 0.001), a higher

mean HIV-VL (40 242 vs. 10 772 copies/μl; $P < 0.001$), and were less likely to be taking any ART (67 vs. 86%; $P = 0.001$). Table 1 contains a description of the study population.

Incidence of human papillomavirus infection

One hundred and twenty-two men had a detectable type-specific incident anal HPV infection over the 2-year follow-up period and the overall incident detection rate was 21.3 per 100 person-years (95% CI 17.7–25.4) (Table 2). The most common incident HPV type was HPV 18, with an incidence rate of 3.7 per 100 person-years. The incidence of any oncogenic HPV infection was 13.1/100 person-years (95% CI 10.5– 16.6).

Of the 122 men with one or more incident type-specific infections, 97 (80%) had an incident infection with only one HPV type, 19 (16%) had two different HPV type infections, four (3%) had three HPV type infections, one (0.8%) participant had four HPV type infections, and one (0.8%) participant had six different HPV type infections.

Men who had an incident HPV infection were less likely to have had a prevalent HPV infection of any type at baseline (88 vs. 94%; $P = 0.04$) and also were less likely to have had a prevalent HPV 6 infection (32 vs. 43%; $P = 0.04$), the most prevalent HPV type at baseline.

Bi-variable associations between risk factors and incident human papillomavirus infection

Of the demographic, lifestyle, sexual risk, and medical history factors measured over a participant's lifetime, only two were significantly associated with having an incident HPV infection during the follow-up period. Having smoked at least 100 lifetime cigarettes was more common among those without an incident HPV detection (59 vs. 47%; $P = 0.03$). The only other factor associated with incident HPV infection in bi-variable analyses was having been diagnosed with HIV in the past 12 months. Of the men with an incident HPV infection, 4% had a recent diagnosis of HIV infection compared with only 0.8% in those who had been diagnosed with HIV more than 12 months ago ($P = 0.03$). Many sexual behaviors in recent time periods were associated with incident anal HPV infection in bi-variable analyses (Table 3).

Multivariable analyses: effect of recent behaviors on incidence of anal human papillomavirus infection

The results of the four multivariable models are included as Supplemental Digital Content Table 1 (http://links.lww.com/QAD/A502). The results of Model 1 (unadjusted estimates) and Model 4 (fully adjusted estimates) are included in Table 4.

Of the sexual behaviors reported in the past 6 months, many remained significantly associated with incident anal HPV infection after adjusting for the baseline value of the factor, potential baseline confounders and time-dependent confounders. Number of receptive partners (partners with whom the participant was the receptive partner – 8+ vs. 0–1) increased the risk of anal HPV infection by 2.9 [(1.9–5.5), $P = 0.002$] in the fully adjusted model. The frequency of receptive intercourse also was associated with an OR of 2.6 (1.6–4.6, $P = 0.004$) when 1+ times per week was compared with no acts. Having a higher

number of new oral–anal contact partners also increased the odds of HPV infection by a small but significant amount per new partner [OR 1.1 per partner (1.03– 1.1)]. The number of insertive partners (partners with whom the participant was the insertive partner) was not associated with incident HPV infection in the fully adjusted models.

The only behavior reported in the past 30-day recall period that remained significantly associated with incident HPV infection in the fully adjusted model was frequency of receptive intercourse in the past 30 days, which increased the odds of incident HPV infection [OR 1.1 (1.03–1.1) per partner].

A small number (∼1%) of patients in our study were treated for their LGAIN or HGAIN, However, the inclusion of this variable in our multivariable models did not substantively change our findings.

Discussion

Our study represents one of the few natural history studies of a cohort of HIV-positive MSM, followed prospectively for anal HPV infection, together with a detailed evaluation of risk factors for infection during the post-ARTera. We had a high rate of follow-up with 82% of our participants returning for at least two visits and at least 1 year of follow-up.

Overall, the incidence of any anal HPV infection (21.3/100 person-years) and of oncogenic anal HPV infection (13.3/100 person-years) was greater than the reported incidence of other sexually transmitted infections (STIs) among HIV-positive MSM [18–20]. Rates of infection with individual anal HPV types were similar to the increased rates of other STIs commonly seen among MSM. The most common anal HPV type detected was HPV 18, followed closely by HPV 16. These two HPV types are the types most commonly associated with anal cancer and are usually found with the highest prevalences in cross-sectional studies of MSM [9, 21]. Three other oncogenic HPV types (31, 33, and 58) also had high incidence rates (>2.0/100 person-years). Although these types have rarely been detected in anal cancer specimens, they are known to be associated with cervical cancer and may be important in anal disease in HIV-positive populations. The high incidence rates of oncogenic HPV types imply that the prevalences of these types found in cross-sectional studies are not only the result of persistence of infection but also represent an increased rate of acquisition of new infections. Also important to note was that 20% of the men with an incident HPV infection had more than one new HPV type detected during follow-up and many had multiple oncogenic types. An increased number of HPV types have been associated with a greater likelihood of HPV-associated disease [22].

Few published studies are available for comparison with the rates of incident anal HPV infection. Critchlow *et al*. [10] followed HIV-seropositive MSM for 2 years and found that 38% of men positive at baseline for anal HPV had anal HPV DNA of a new type detected during the follow-up period. Our cumulative incidence of any anal HPV (33%) is comparable with this finding. A recent study of HIV-positive MSM in Canada had type-specific incidence rates that were much greater than the rates we found. However, they defined an incident infection as HPV DNA detected at any single visit after a negative test at

baseline. In that study, the incidence rate of HPV 16 was 13.0/100 person-years, compared with our finding of 3.5/100 person-years. When we re-computed our incidence rates using their definition (data not shown), our rates of incident detection were comparably increased (e.g. the rate of HPV 16 infection was 14.8/100 person-years). Because HPV DNA detected from an anal swab sample could be either from an infection in the participant or the result of HPV virus deposited in the anus during anal intercourse, we believe that our stricter definition of an incident infection used in our analyses minimizes potential misclassification of the outcome, which is incident anal HPV. However, we also may be underestimating the true incidence of anal HPV infection.

In our multivariable repeated-measures analyses, recent sex was an important predictor of incident anal HPV infection. Almost all indicators of receptive anal intercourse were significantly associated with incident anal HPV infection. This is to be expected, as receptive anal intercourse is a plausible means of exposure to HPV. However, the association has proved difficult to demonstrate in cross-sectional studies of HIV-positive MSM [9] because most MSM have a history of receptive anal behaviors and there is little variation in the variable. In studies of prevalence, risk factors for prevalent HPV infection may be factors associated with persistence of HPV infection. The findings of these analyses offer convincing evidence that receptive anal intercourse increases the risk of acquiring anal HPV infection among HIV-positive MSM. The number of new oral–anal contact partners, in which the participant's anus receives oral contact, also was associated with incident anal HPV infection. This is an important finding suggesting another potential route of exposure to anal HPV infection. Oral– anal contact also could explain anal HPV infection among men (and women) who deny receptive anal intercourse.

Our study has a number of limitations. We required at least two follow-up visits to be included in our analysis. This produced an important difference between participants included in our analyses and those not included. Men who were excluded had worse measures of HIV disease status than men who were included. It could be that this inclusion criterion induced some selection bias in our study. This may help explain the diminished association between $CD4^+$ cell count and anal HPV incidence seen in our study in comparison with other studies of HIV-positive populations [23–25] given that men with lower $CD4^+$ levels were excluded from the study. Also, men included in our study who had a single positive anal HPV detection were classified as not having an incident anal HPV. If these men had true incident infections that resolved before the following study visit, they would have been misclassified as not having an incident anal HPV infection. It is unlikely that this misclassification is associated with any of the main risk factors and the bias to our estimates would be towards the null value. Another limitation of our study is that we did not collect information on condom use. However, the likely effect of condom use would be to reduce the effect size (by preventing infection in those who have receptive sex). Thus, our results represent a conservative measure of the true association. Also, this study was conducted in the early ART era and treatment of HIV infection has improved since that time. Therefore, our results may not be generalizable to a population of HIV-positive MSM taking improved ART, who may have better health than our participants, and therefore lower incidences of anal HPV infection.

Our current prospective analyses add to the existing evidence from prevalence studies that anal HPV infection is common among HIV-positive MSM, and that the type distribution of incident infection is similar to that seen in prevalence studies. Recent receptive anal intercourse is an important predictor of anal HPV infection and oral–anal contact is also a risk factor for incident infection. HIV-positive MSM should be counseled about anal cancer and risk factors for HPV infection. They also should be counseled about primary prevention measures such as condom use and the HPV vaccine that was recently approved for prevention of anal HPV infection and HPV-associated disease in men aged 9–26 years [26].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline social–demographic, behavioral, and medical characteristics of HIV-positive MSM in San Francisco (*N* = 369).

Characteristic	*N* (%)
Demographics	
Mean age (years) (±SD)	45 (±8)
Race/ethnicity	
Non-Hispanic white	335 (91)
Black	5 (1)
Asian/other	8 (2)
Hispanic	21 (6)
Education	
Did not complete college	144 (39)
Completed college	115 (31)
Completed graduate school	110 (30)
Substance use	
Smoked >100 lifetime cigarettes	202 (55)
History of injection drug use	77 (21)
Medical history	
History anal or genital warts	279 (76)
Mean number of episodes of anal warts	9 (±24)
Prevalent HPV infection at baseline	339 (92)
AIN diagnosed at baseline	463 (±261)
Normal	60 (21)
LGAIN	85 (29)
HGAIN	144 (49)
Mean $CD4^+$ T-cell count (±SD)	463 (±261)
<200	50 (14)
200–500	178 (49)
>500	136 (37)
Mean HIV viral load (±SD)	10619 (±47159)
<500	219 (62)
500–4000	61 (17)
4001–20 000	46 (13)
>20 000	30 (8)
Currently taking antiretroviral medications	319 (86)
HIV diagnosis in past 12 months	7 (2)
Lifetime sexual history	
Number of female partners	
0	134 (36)
1–4	151 (41)
5+	84 (23)

Characteristic	*N* (%)
Number male partners with whom participant was receptive partner	
0–50	147 (40)
51–200	109 (30)
201+	110 (30)
Number male partners with whom participant was insertive partner	
0–50	164 (45)
51–200	115 (31)
201+	89 (24)
Number oral–anal contact partners (participant receives anal contact)	
0–10	142 (38)
11–50	129 (35)
51+	98 (27)

AIN, anal intraepithelial neoplasia; HGAIN, high-grade anal intraepithelial neoplasia; LGAIN, low-grade anal intraepithelial neoplasia. When numbers do not total 369 data were missing.

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Table 2

Incident detection of HPV among HIV-positive MSM in San Francisco (N = 369).

HPV type	*N*[a]	Number incident infections	2-year cumulative proportion[b]	Total PY	Incidence rate (incident infection/100 PY)[c]	(95% CI)[d]
6	221	5	2.3	348	1.4	(0.5–3.4)
11	268	4	1.5	410	1	(0.3–2.5)
16	222	12	5.4	342	3.5	(1.8–6.1)
18	268	15	5.6	407	3.7	(2.1–6.1)
26	360	1	0.3	555	0.2	(0–1)
31	275	9	3.3	417	2.2	(1–4.1)
32	349	4	1.1	538	0.7	(0.2–1.9)
33	278	11	4	423	2.6	(1.3–4.7)
35	354	0	0	551	0	(0–0.7)
39	333	4	1.2	511	0.8	(0.2–2)
40	351	5	1.4	540	0.9	(0.3–2.2)
45	283	8	2.8	433	1.8	(0.8–3.6)
51	305	2	0.7	470	0.4	(0.1–1.5)
52	291	5	1.7	450	1.1	(0.4–2.6)
53	278	8	2.9	428	1.9	(0.8–3.7)
54	333	4	1.2	513	0.8	(0.2–2)
55	357	1	0.3	550	0.2	(0–1)
56	335	8	2.4	518	1.6	(0.7–3.1)
58	283	10	3.5	434	2.3	(1.1–4.2)
59	302	7	2.3	465	1.5	(0.6–3.1)
61	308	13	4.2	474	2.7	(1.5–4.7)
68	312	1	0.3	486	0.2	(0–1.1)
69	358	0	0	555	0	(.-0.7)
70	280	8	2.9	429	1.9	(0.8–3.7)
73	326	3	0.9	506	0.6	(0.1–1.7)
82	359	1	0.3	558	0.2	(0–1)
83	321	2	0.6	496	0.4	(0–1.5)
84	317	8	2.5	489	1.6	(0.7–3.2)

HPV type	N[a]	Number incident infections	2-year cumulative proportion[b]	Total PY	Incidence rate (incident infection/100 PY)[c]	(95% CI)[d]
Any type	369	122	33.1	573	21.3	(17.7–25.4)
Oncogenic types[e]	369	76	20.6	573	13.3	(10.5–16.6)
Nononcogenic types	369	37	10	573	6.5	(4.5–8.9)

CI, confidence interval; HPV, human papillomavirus; PY, person-years. Incident detection infection, negative for type-specific HPV DNA at baseline followed by two consecutive detections of a specific type of HPV.

[a] Participants at risk for HPV type (negative for type at baseline). Participants beta-globin-negative at baseline excluded from analysis.

[b] Number of incident infections/participants negative for type-specific HPV DNA at baseline.

[c] Number of incident infections/person-years at risk.

[d] 95% exact Poisson confidence intervals.

[e] HPV types: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82.

Table 3

Recent lifestyle and behavioral characteristics by incident HPV infection among HIV-positive MSM in San Francisco (*N* = 888 participant visits).

Characteristic	Overall *N* (%)	No HPV (*n*, %)	Incident HPV (*n*, %)	*P*-value[a]
Recall period: past 6 months				
Mean days since last interview	227.3 (±60)	227.2 (±60)	227.6 (±69)	0.94
Smoked any cigarettes	202 (23)	172 (23)	30 (23)	0.84
Drank any alcoholic beverages	753 (85)	634 (84)	119 (88)	0.27
Injected any recreational drugs	19 (2)	14 (2)	5 (4)	0.39
Used rectal drugs	43 (5)	30 (4)	13 (10)	0.03
Number of male partners with whom the participant was the receptive partner				0.03
0–1	566 (64)	491 (65)	75 (55)	
2–7	227 (26)	190 (25)	37 (27)	
8+	95 (11)	71 (9)	24 (18)	
Number of ‘new’ male partners with whom the participant was the receptive partner	2.9 (±9)	2.4 (±8)	5.3 (±14)	0.01
Frequency of receptive intercourse (participant was the receptive partner)				0.03
No receptive intercourse	379 (43)	327 (44)	52 (38)	
1–3 times/month	399 (45)	342 (46)	57 (42)	
1+ times/week	110 (12)	83 (11)	27 (20)	
Number of male partners with whom the participant was the insertive partner				0.09
0–1	589 (66)	509 (68)	80 (59)	
2–7	210 (24)	175 (23)	35 (26)	
8+	89 (10)	68 (9)	21 (15)	
Number of new male partners with whom the participant was the insertive partner	2.6 (±7)	2.4 (±7)	3.4 (±8)	0.18
Number oral–anal contact partners (participant received anal contact)				0.04
0–1	678 (76)	578 (77)	100 (74)	
2–7	169 (19)	148 (20)	21 (16)	
8+	41 (5)	26 (4)	15 (11)	
Number new male oral–anal contact partners (participant received anal contact)	1.7 (±5)	1.5 (±4)	2.9 (±8)	0.04
Objects in anus	243 (27)	197 (26)	46 (34)	0.08
Frequency of object use				0.02
0 times	645 (73)	555 (74)	90 (66)	
1 – 6 times	150 (17)	129 (17)	21 (15)	
7 + times	93 (11)	68 (9)	25 (18)	
Recall period: past 30 days				
Number male partners				0.07
0	194 (22)	164 (22)	30 (22)	
1	303 (34)	267 (35)	36 (26)	

Characteristic	Overall *N* (%)	No HPV (*n*, %)	Incident HPV (*n*, %)	*P*-value[a]
2+	391 (44)	321 (43)	70 (52)	
Number of male partners with whom the participant was the receptive partner	0.9 (±2)	0.8 (±2)	1.2 (±2)	0.07
Frequency of receptive intercourse (participant was the receptive partner)	3.1 (±4)	2.9 (±4)	4.5 (±5)	0.005
Number of male partners with whom the participant was the insertive partner	0.9 (±2)	0.9 (±2)	0.9 (±2)	0.92
Frequency of insertive intercourse (participant was the insertive partner)	3.3 (±6)	3.2 (±5)	4.1 (±8)	0.39
Objects in anus	164 (68)	133 (68)	31 (67)	0.99
Frequency of objects used	3.3 (±4)	3.3 (±4)	3.5 (±2)	0.66
HIV disease status variables				
Mean $CD4^+$ cell count (current visit)	509.5 (±288)	513.2 (±290)	489.1 (±278)	0.36
<200	98 (11)	78 (11)	20 (15)	
200–500	382 (44)	329 (44)	53 (40)	
>500	394 (45)	334 (45)	60 (45)	
Mean $CD4^+$ cell count (previous visit)	495.2 (±280)	494.2 (±280)	500.7 (±281)	0.81
HIV viral load (current visit)				0.85
<500	583 (67)	499 (67)	84 (64)	
500–4000	83 (10)	71 (10)	12 (9)	
4001 –20 000	112 (12)	93 (12)	19 (15)	
>20 000	95 (11)	79 (11)	16 (12)	

HPV, human papillomavirus.

[a] *P*-value from generalized estimating equations (GEE) accounting for correlation from taking repeated measures of participants.

Table 4

Association of time-varying covariates and incident HPV, unadjusted and adjusted for potential confounders among HIV-positive MSM in San Francisco.

Characteristic	Unadjusted		Adjusted[b]	
	OR (95% CI)[a]	*P*-value[a]	OR (95% CI)[a]	*P*-value[a]
Recall period: past 6 months				
Injection drug use	2.0 (0.6–6.7)	0.39	2.1 (0.6–7.0)	0.35
Rectal drug use	2.5 (1.4–4.7)	0.03	2.4 (1.3–4.5)	0.03
Number of male partners with whom the participant was the receptive partner				
0–1	1.0		1.0	
2–7	1.3 (0.8–2.0)	0.03	1.4 (0.9–2.2)	0.006
8+	2.2 (1.3–3.7)		2.9 (1.6–5.1)	
Number of ‘new’ male partners with whom the participant was the receptive partner	1.03 (1.01–1.04)	0.01	1.03 (1.01–1.1)	0.006
Frequency of receptive intercourse (participant receptive partner)				
None	1.0		1.0	
1 –3 times per month	1.1 (0.7–1.6)	0.03	1.3 (0.8–2.0)	0.01
1+ times per week	2.1 (1.3–3.3)		2.6 (1.5–4.6)	
Number of insertive male partners (participant was the insertive partner)				
0–1	1.0		1.0	
2–7	1.3 (0.8–2.0)	0.09	1.3 (0.8–2.0)	0.12
8+	2.0 (1.1–3.4)		2.0 (1.1–3.8)	
Number of ‘new’ male partners with whom the participant was the insertive partner	1.0 (1.0–1.0)	0.18	1.0 (1.0–1.0)	0.22
Number of oral–anal contact partners (participant received anal contact)				
0–1	1.0		1.0	
2–7	1.1 (0.70–1.9)	0.66	1.4 (0.9–2.4)	0.14
8+	1.2 (0.8–2.0)		1.6 (1.0–2.8)	
Number ‘new’ oral–anal contact partners (participant received anal contact)	1.04 (1.01–1.1)	0.04	1.06 (1.03– 1.09)	0.01
Times objects inserted into anus				
0–1	1.0		1.0	
2–7	1.0 (0.6–1.7)	0.02	1.1 (0.6–2.0)	0.11
8+	2.3 (1.4–3.6)		2.1 (1.1–3.8)	
Recall period: past 30 days				
Number of male partners				
0	1.0		1.0	
1	0.7 (0.4–1.2)	0.07	0.8 (0.5–1.3)	0.10
2+	1.2 (0.7–1.9)		1.2 (0.7–2.0)	
Number of male partners with whom the participant was the receptive partner	1.1 (1.0–1.2)	0.08	1.1 (1.0–1.3)	0.07
Frequency receptive intercourse (participant was the receptive partner)	1.1 (1.0–1.1)	0.005	1.1 (1.0–1.1)	0.005

CI, confidence interval; HPV, human papillomavirus; OR, odds ratio.

[a] Generalized linear models estimated with generalized estimating equations (GEE) with a logit link accounting for the correlation between repeated measures on participants.

[b] Adjusted for age at baseline, race, education, smoking 100+ lifetime cigarettes, and baseline $CD4^+$ level, HPV 6 status atbaseline, and $CD4^+$ level at previous visit.