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Anal human papillomavirus infection among Thai men who have sex with men with and without HIV infection: prevalence, incidence, and persistence

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Abstract

Background—HIV-positive men who have sex with men (MSM) have a higher prevalence of anal human papillomavirus (HPV) infection and anal cancer incidence than HIV-negative MSM. High-risk HPV persistence is an important risk factor for the development of anal cancer.

Methods—A total of 123 HIV-positive and 123 HIV-negative MSM were enrolled from the Thai Red Cross AIDS Research Centre in Bangkok, Thailand, and followed for 12 months. Anal sample collection for HPV genotyping was performed at every visit. HPV prevalence, incidence, clearance and persistence were calculated. A logistic regression model was used to study factors associated with high-risk HPV persistence.

Results—The prevalence of any anal HPV infection was 85% in HIV-positive and 58.5% in HIV-negative MSM ($p<0.0001$). The prevalence of high-risk HPV infection was 57.5% in HIV-positive and 36.6% in HIV-negative MSM ($p=0.001$). HPV 16 was the most common high-risk HPV type. HIV-positive MSM had a higher prevalence (22.5% vs. 9.8%, $p=0.008$) and persistence (16.7% vs. 1.3%, $p<0.001$) of HPV 16 than HIV-negative MSM, and a trend for higher incidence (16.1 vs. 6.1 episodes/1000 person-months, incidence rate ratio 2.6, $p=0.058$). HIV infection (OR 4.45, 95% CI 2.11–9.4, $p<0.001$) and smoking in HIV-positive MSM (OR 2.3, 95% CI 1.17–4.5, $p=0.015$) were independently associated with high-risk HPV persistence in multivariate models.

Conclusions—In addition to targeting HIV-positive MSM who are at higher risk for anal high-risk HPV persistence, anal cancer prevention programs should also integrate behavioral interventions such as smoking cessation to modify risk for high-risk HPV persistence.

Keywords

anal; human papillomavirus; persistence; MSM; HIV

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Introduction

Anal infection with human papillomavirus (HPV) is extremely common in men who have sex with men (MSM).[1–3] HIV-positive MSM have a higher prevalence of anal HPV infection than HIV-negative MSM and are more likely to have infection with multiple HPV types.[1,2] Clearance of anal HPV infection has also been shown to be less common among HIV-positive compared with HIV-negative MSM.[2] Persistent anal HPV infection, particularly with high-risk HPV types, is an important risk factor for the development of anal cancer.[4–6]

Compared with HIV-negative MSM, HIV-positive MSM have an approximately 1.5 times higher prevalence of anal HPV infection,[1,2] while their risk for having anal cancer is 5 times higher.[7] In addition to the higher prevalence of anal HPV infection among HIV-positive MSM, reduced clearance[2] may help explain this much higher rate of anal cancer incidence in this population. Data are inconclusive on whether or not the use of highly active antiretroviral therapy (HAART) has an effect on anal HPV infection among HIV-positive MSM.[8,9]

Behavioral risks may also have a role on the prevalence, incidence, and persistence of anal HPV infection. High numbers of lifetime sex partners, unprotected receptive anal sex and cigarette smoking are among behavioral risk factors identified in previous studies on anal HPV infection.[2,10,11] Behavioral modification has been proposed as an intervention to modify anal cancer risk.[11]

Data on anal HPV infection among MSM in Asia are very limited and are mostly derived from HIV-positive MSM in cross-sectional studies.[12,13] We aimed to study the prevalence, incidence and persistence of anal HPV infection in a longitudinal cohort of MSM with and without HIV infection in Bangkok, Thailand. Factors associated with anal HPV persistence among these MSM were also studied.

Methods

Enrollment and follow-up of study participants

Thai men aged 18 years or older who reported a history of anal sex with men were recruited into the study at the Thai Red Cross AIDS Research Centre in Bangkok, Thailand. Men were excluded if they had prior treatment for anal cancer, anal cytology, high-resolution anoscopyor infrared coagulation within 12 months prior to enrollment; trichloroacetic acid or podophyllin application to the intra-anal area in the month prior to enrollment; or evidence of active concurrent intra-anal or perianal bacterial or herpes simplex virus infection at the time of enrollment.

The study was approved by the institutional review board of Chulalongkorn University in Bangkok, Thailand (clinicaltrials.gov identification NCT01637298). All participants gave informed consent. Participants were followed up at 12 months after baseline except for the first 120 participants who were also scheduled for month 6 follow-up. Urogenital and anal examinations were conducted at these visits, along with anal sample collection. Demographic data, smoking history, sexually transmitted infection history, HIV test results, age at sexual debut, lifetime sexual behaviors and sexual behavior in the past three months including condom use were collected at baseline. Additional data on nadir CD4 count, current CD4 count, plasma HIV RNA and use of HAART were also collected in HIV-positive participants.

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HPV genotyping

Anal samples were collected from participants at the baseline, month 6 (for the first 120 participants) and month 12 visits by one study physician (NT). A moistened, non-lubricated flocked swab (Rovers® EndoCervex-Brush®, Rovers Medical Devices B.V., The Netherlands or FLOQSwabs™, Copan Italia S.p.A., Italy) was used to collect anal sample and put in Liqui-PREP™ fluid (LGM International, Inc., Florida, USA). HPV typing was done using the LINEAR ARRAY® HPV Genotyping Test (Roche Molecular Systems, Inc., New Jersey, USA) which amplified target DNA within the polymorphic L1 region of the HPV genome that is approximately 450 base pairs long by the polymerase chain reaction (PCR). The test then utilized nucleic acid hybridization to independently identify 37 anogenital HPV DNA genotypes (6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 62, 64, 66, 67, 68, 69, 70, 71, 72, 73 (MM9), 81, 82 (MM4), 83 (MM7), 84 (MM8), IS39 and CP6108) in cells. The primers for human β-globin gene were used to ensure cell adequacy. Specimens that were negative for β-globin amplification were excluded from analysis.

Statistical Analysis

Statistical analysis was conducted with Stata version 12.1 (Statcorp, College Station, TX, USA). High-risk HPV types included 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68. HPV prevalence was defined as having a specific HPV type at the enrollment visit. HPV incidence was the detection of a specific HPV type at month 6 or month 12 visits that was absent at an earlier visit. HPV clearance was defined as a specific HPV type that was detected at the enrollment and/or month 6 visits which was then undetectable at a later visit. Participant visits with an invalid HPV test were excluded from the analysis. The baseline prevalence of anal HPV infection was calculated together with 95% confidence intervals (95% CI) according to a binomial distribution.

The incidence and clearance densities were calculated per participant-time at risk, along with the incidence rate ratios (IRR) and the clearance rate ratios (CRR) between HIV-positive and HIV-negative MSM. Person-time was calculated using the actual visit dates of participants in the risk set, and 95% CI around the incidence or clearance rate estimates and ratios were calculated using the quadratic approximation to the Poisson log likelihood for the log-rate.

HPV persistence was defined as having the same specific HPV type at two consecutive visits. A logistic regression model was used to study factors associated with any high-risk HPV persistence during the study. Assumptions about linearity of continuous covariates were checked by breaking the variable into quartiles and examining the odds ratio (OR) and 95% CI for each quartile. When these assumptions were not met, categorical groupings were used and adjacent quartiles were collapsed together if appropriate. When testing the following variables, the worst value reached during the study was used in logistic models: CD4 count, log plasma HIV RNA, number of sexual partners during the previous three months, number of sex acts per week in the previous three months and consistent condom use for receptive anal intercourse. Baseline covariates were used for other covariates including age, age at sexual debut, smoking and other socio-demographic covariates. All covariates with $p<0.15$ were included and adjusted for in multivariate models. Additionally, models were developed separately by HIV status at baseline. In HIV-positive MSM, an analysis was performed to model the effect of the above-mentioned covariates and other HIV-specific covariates.

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Results

Participant characteristics

There were 123 HIV-positive MSM and 123 HIV-negative MSM who were enrolled between December 11, 2009 – December 27, 2010 (Table 1). At the end of March 2012, there were a total of 1974 person-months of follow-up (1071 person-months for HIV-positive MSM and 903 person-months for HIV-negative MSM).

The mean (standard deviation, SD) age at enrollment was 28.8 (6.9) years for HIV-positive and 28.9 (7.4) years for HIV-negative MSM (p=0.9). None reported a history of cancers and 14% were current smokers. Mean (SD) age at first sex was 18.0 (3.7) years for HIV-positive and 18.8 (3.7) years for HIV-negative MSM (p=0.11). A history of having >5 lifetime sex partners was reported by 91.1% of HIV-positive MSM and 77.2% of HIV-negative MSM.

During the three months prior to study entry, 25.2% of HIV-negative MSM had at least three sexual partners compared with 8.1% of HIV-positive MSM (p=0.005). Sex acts of ≥3 per week in the past three months was reported by 13.0% of HIV-negative and 9.8% of HIV-positive MSM (p=0.32). Among those who practiced receptive anal sex in the past three months, 63.9% of HIV-positive MSM and 59.0% of HIV-negative MSM reported always using condoms (p=0.82).

Among 123 HIV-positive MSM at baseline, the mean (SD) CD4 count was 353 (146) cells/mm^3, and 10% had plasma HIV RNA <40 copies/mL. At month 12, the mean (SD) CD4 count was 388 (130) cells/mm^3, and 33% had plasma HIV RNA <40 copies/mL. HAART use was reported by 13% of MSM at baseline and 47% of MSM at month 12. Plasma HIV RNA <40 copies/mL was achieved by 69% of those who were on HAART at baseline and 69% of those who reported HAART use at month 12.

Condyloma acuminata was identified in 15.5% of HIV-positive MSM and 13.8% of HIV-negative MSM, and the most common location was the perianal area (12.6%).

Anal HPV prevalence and incidence

Prevalent anal infection with any HPV type was detected in 85% of HIV-positive and 58.5% of HIV-negative MSM (p<0.0001). The median number of HPV types was 3 (interquartile range, IQR 2–5) for HIV-positive MSM and 3 (IQR 2–4) for HIV-negative MSM.

Table 2 shows the prevalence and incidence of type-specific, high-risk, anal HPV infection among MSM, by baseline HIV status. Prevalent infection with any high-risk HPV type was identified in 57.5% of HIV-positive and 36.6% of HIV-negative MSM (p=0.001). The median number of high-risk HPV types was 2.5 (IQR 2–3) for HIV-positive and 2 (IQR 2–3) for HIV-negative MSM.

HPV 16 was the most common high-risk HPV type detected in both HIV-positive MSM (22.5%) and HIV-negative MSM (9.8%). The other common high-risk types in HIV-positive MSM included HPV types 68 (13.3%), 58 (10.3%), 51 (10.3%), 39 (10.0%) and 18 (10.0%). For HIV-negative MSM, the other common high-risk types included HPV types 51 (8.1%), 52 (6.5%), 59 (5.7%) and 39 (5.7%). Compared with HIV-negative MSM, HIV-positive MSM had higher prevalence of high-risk types 16 (p=0.008) and 68 (p=0.015).

Among high-risk HPV types, HPV type 16 had the highest incidence of 16.1 episodes/1000 person-months in HIV-positive MSM while HPV type 68 had the highest incidence of 8.3 episodes/1000 person-months in HIV-negative MSM. The incidence rate of any high-risk HPV type was higher in HIV-positive MSM than in HIV-negative MSM (64.9 vs 28.2/1000

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person-months, IRR 2.3, 95% CI 1.3–4.2, p=0.008). There was a trend for higher incidence of HPV type 16 in HIV-positive MSM (IRR 2.6, 95% CI 0.98–7.1) than in HIV-negative MSM but this was not statistically significant (p=0.058). For non-high-risk HPV types, HPV type 6 was the only type with a significantly higher incidence rate in HIV-positive MSM compared with HIV-negative MSM (11.6 vs. 2.5/1000 person-months, p=0.03).

Anal HPV clearance and persistence

Among HIV-positive MSM, high-risk HPV types 16, 68 and 51, which had the highest prevalence and highest incidence rates, showed low clearance rates of 52.0, 70.2 and 42.9 cleared episodes/1000 person-months, respectively (Table 3). The median time to clearance was 12.6 months for HPV type 16, 10.9 months for HPV type 68, and 11.3 months for HPV type 51. For HIV-negative MSM, HPV 16, the high-risk type with the highest prevalence and incidence rate, had a clearance rate of 101.2 cleared episodes/1000 person-months and a median time to clearance of 11.1 months. The CRR for HPV type 16 was 0.51 (95% CI 0.22–1.22, p=0.15) among HIV-positive compared with HIV-negative MSM. For HPV type 68, HIV-positive MSM had 70.2 cleared episodes/1000 person-months vs. 16.3 cleared episodes/1000 person-months among HIV-negative MSM. The CRR for HPV type 68 was 4.32 (95% CI of 0.66–28.2, p=0.13).

HPV persistence was highest for high-risk HPV types 16 (16.7%), 68 (12.5%) and 51 (11.5%) in HIV-positive MSM and HPV types 68 (7.6%), 18 (3.8%) and 39 (3.8%) in HIV-negative MSM. Persistence of high-risk HPV types 16 (p<0.001) and 51 (p=0.001) was higher in HIV-positive MSM than HIV-negative MSM. In addition, HIV-positive MSM had higher persistence of any high-risk HPV type (49.0% vs. 19.0%, p<0.001) and higher persistence of multiple high-risk HPV types (22.9% vs. 5.1%, p= 0.001) than HIV-negative MSM.

Risk factors for persistence of at least one specific anal high-risk HPV type

In a univariate model, HIV-positive status (OR 4.09, 95% CI 2.05–8.16, p<0.001) and smoking (OR 1.65, 95% CI 1.05–2.60, p=0.029) increased the risk of having any anal high-risk HPV persistence in all MSM (Table 4). Current age, age at sexual debut, condom use for receptive anal intercourse, number of sex acts per week and number of sex partners in the previous three months were not significantly associated with any high-risk HPV persistence in this univariate model. In multivariate analysis, HIV-positive status remained significantly associated with any high-risk HPV persistence with an OR of 4.45 (95% CI 2.11–9.4, p<0.001).

For HIV-positive MSM, a univariate model identified smoking (OR 3.4, 95% CI 1.25–9.22, p=0.016) as a risk factor for persistence of any high-risk HPV infection. Current age between 24–29 years was associated with a trend for an increased risk of any high-risk HPV persistence (OR 4.58, 95% CI 1.28–16.4, p=0.051) but there was no association with HAART use, nadir CD4 count or plasma HIV RNA. Smoking was the only factor with significant association with any high-risk HPV persistence in the multivariate model (OR 2.3, 95% CI 1.17–4.5, p=0.015).

For HIV-negative MSM, persistence of any high-risk HPV infection had a trend for an association with younger age at sexual debut (≤17 years old, OR 3.86, 95% CI 0.99–15.1, p=0.08) in a univariate model, but this was not statistically significant in further analysis.

Discussion

Our study demonstrated a high prevalence of anal HPV infection among Thai MSM -85% among HIV-positive and 58.5% among HIV-negative MSM. In addition, high-risk HPV

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types were identified in 57.5% of HIV-positive MSM and 36.6% of HIV-negative MSM. The higher prevalence of any anal HPV infection and high-risk HPV infection in HIV-positive MSM than HIV-negative MSM was in accordance to previous studies that specifically compared anal HPV prevalence between MSM with and without HIV infection in the US.[1,2]

Although the 85% overall prevalence of anal HPV infection among Thai HIV-positive MSM in our study was slightly lower than those reported from HIV-positive MSM in the US and Canada (ranging from 92–98%),[1,2,8] this prevalence was higher than those reported from Brazil (66%),[14] Taiwan (77%),[13] and China (72%).[12] The 57.5% high-risk anal HPV prevalence in our HIV-positive MSM was higher than the 41% prevalence reported from Taiwan and China[12,13] but was comparable to the 56% prevalence reported from the US.[2] For HIV-negative MSM, previous data were only available from the US and Latin America, where the overall anal HPV prevalence (ranging from 42–66%)[1,2,11,15,16] and high-risk HPV prevalence (ranging from 22–42%)[2,11,15] was comparable to our 58.5% overall anal HPV prevalence and 36.6% high-risk HPV prevalence.

HPV type 16 was the most common high-risk HPV type identified in both HIV-positive and HIV-negative MSM in our study. These data were consistent with previous studies which also reported HPV type 16 to be the most common high-risk HPV type in the anus.[8,11,13] In addition to being the most prevalent high-risk HPV type, HPV type 16 was also the type with highest incidence among HIV-positive MSM in our study. The incidence rate of HPV 16 in our study was comparable to that reported in Canadian HIV-positive MSM,[8] and was higher than that of HIV-negative MSM, although this was not statistically significant (p=0.058). The incidence rate of HPV type 16 among HIV-negative MSM in our study was also similar to the rate reported in the HIM (HPV in Men) Study.[11]

HIV-positive MSM in our study tended to have a lower clearance rate of HPV 16 compared with HIV-negative MSM, although the difference was not statistically significant. Consistent with the lower clearance rate, HPV16 was the most persistent high-risk HPV in HIV-positive MSM, with a significantly higher persistence compared with HIV-negative MSM. We also found higher persistence of at least one high-risk HPV type in HIV-positive MSM than in HIV-negative MSM.

The most common high-risk HPV type identified in anal cancers is type 16.[4,5] Higher prevalence, a trend for higher incidence, and higher persistence of HPV type 16 in the anus of HIV-positive MSM compared with HIV-negative MSM found in our study is consistent with the higher risk of anal cancer in HIV-positive MSM than HIV-negative MSM.[7] Although HPV types from anal swab samples may not truly represent HPV types in the anal tissues, a previous study has demonstrated the concordance of HPV DNA detection between anal biopsy samples and anal swab samples from MSM.[17]

We identified HIV infection to be the main predictor for any high-risk HPV persistence in the anus. However, we could not identify an association between HPV persistence and HAART use. This should be interpreted with caution, as only 13% of HIV-positive MSM in our study reported HAART use at baseline and the proportion increased to 47% over the study duration. This was likely a result of measuring CD4 levels at the baseline visit which subsequently led to linkage to HIV treatment and care, since there were no changes in national guidelines for initiation of HAART during the study period. Although there are currently no data to support this, it is possible that HAART, if initiated early and taken for a long period of time, may lower the risk of HPV persistence. Similar to a previous study from the US,[2] we did not find an association between HPV persistence and CD4 count.

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Smoking significantly increased the risk of high-risk HPV persistence among our HIV-positive MSM. These data are consistent with a recent finding from the HIM study, which identified smoking as an independent risk factor for HPV persistence among MSM.[11] In the 2011 Thai National Statistical Office Smoking and Drinking Behaviour Survey, 35% of men in Bangkok, aged between 20–34 years, were current smokers.[18] Only 14% of MSM participants reported current smoking in our study, which might reflect underreporting or a true difference in smoking patterns in Thai MSM than the general male population The contribution of smoking to HPV persistence may consequently be underestimated in this analysis. Younger age at sexual debut among HIV-negative MSM in our study also showed a trend to be associated with high-risk HPV persistence. As these factors are potentially modifiable, they should be considered targets for interventions to possibly modify anal cancer risk among MSM.

Our study has several limitations. The number of MSM participants with and without HIV infection was small in our cohort, which limited the number of events of interest for statistical analyses. The number of HIV-positive MSM who were on HAART at baseline was small and limited our ability to evaluate the contributions of HAART use and its duration on the HPV endpoints. The short follow-up duration for this report may also limit our understanding of longer term HPV incidence and clearance data. Our definition of HPV clearance based on one negative sample and the inclusion of month 6 data from a subset of participants might also overestimate the clearance rate compared with a more conservative definition of ≥2 consecutive samples. This study, however, is the only study in Asia that prospectively followed HIV-positive and HIV-negative MSM with comprehensive data and sample collection for HPV-related endpoints. As additional follow-up visits occur in our cohort, our estimates should become more accurate.

Information from cohort studies of HIV-positive and HIV-negative MSM at a time when HIV has become a global, chronic disease with potentially long survival time are of great importance. Anal cancer is a non-AIDS-defining cancer with increased incidence since the introduction of HAART [7,19–21] which may be explained by the prolonged survival after HAART and the lack of routine screening for anal precancerous lesions allowing for the progression to anal cancer.[22] As persistent high-risk anal HPV infection is an important risk factor for the development of anal cancer[4–6], anal precancer screening programs should consider integrating interventions such as smoking cessation to modify behavioral risk factors for high-risk HPV persistence whenever possible. Although cessation of smoking has not yet been demonstrated to improve outcomes for anal cancer development, it is plausible and has other health benefits.

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Table 1

Characteristics of 123 HIV-negative MSM and 123 HIV-positive MSM participants at study enrollment.

Characteristic	HIV-negative		HIV-positive		
	N	%	N	%	P
Mean age (SD), years	28.9 (7.4)		28.8 (6.9)		*0.9*
Smoking history					*0.4*
Never smoked	97	79	87	71	
Previously smoked	9	7	15	12	
Currently smokes	15	12	20	16	
No response	2	2	1	1	
Lifetime partners					*0.003*
1	4	3.3			
2–5	22	17.9	9	7.3	
>5	95	77.2	112	91.1	
No response	2	1.6	2	1.6	
Age at sexual debut					*0.69*
≥22 years	21	17.1	17	13.8	
19–21 years	37	30.1	33	26.8	
16–18 years	37	30.1	48	39.0	
≤15 years	23	18.7	21	17.1	
Unknown	5	4.1	4	3.3	
Mean (SD), years	18.8 (3.7)		18.0 (3.7)		*0.11*
Number of sex partners, last 3 months					*0.005*
None	14	11.4	21	17.1	
1	26	21.1	23	18.7	
2	41	33.3	49	39.8	
3–5	23	18.7	9	7.3	
>5	8	6.5	1	0.8	
Number of sex acts per week, last 3 months					*0.32*
None	13	10.6	21	17.1	
<1	51	41.5	44	35.8	

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Characteristic	HIV-negative		HIV-positive		
	N	%	N	%	P
1	17	13.8	25	20.3	
2	26	21.1	21	17.1	
3	15	12.2	12	9.8	
>3	1	0.8	0	0	
No response	0	0	0	0	
Condom use with receptive anal sex, last 3 months					*0.82*
Always	59	48.0	62	50.41	
Sometimes	32	26.0	28	22.76	
Never	9	7.3	7	5.69	
Not applicable	22	17.9	26	21.14	
No response	1	0.8	0	0	
HAART					
Naive			107	87	
Experienced			16	13	
Mean CD4 count, cells/mm^3					
Current CD4 count (SD)			353 (146)		
- On HAART			290 (114)		
- Not on HAART			362 (148)		
Nadir CD4 count (SD)			345 (153)		
Mean baseline plasma HIV RNA					
Baseline $\log_{10}$ copies/mL (SD)			4.27 (1.28)		
- On HAART			1.90 (0.77)		
- Not on HAART			4.59 (0.79)		
N (%) <40 copies/mL			12	10	
N (% of those on HAART) <40 copies/mL			11	69	

MSM, men who have sex with men; SD, standard deviation; HAART, highly active antiretroviral therapy.

Percentages may not always add up to 100% because of rounding.

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Table 2

Prevalence at enrollment and incidence of type-specific, high-risk anal human papillomavirus infection among MSM, by HIV status at baseline.

HPV type	HIV-negative					HIV-positive					IRR (95% CI)	P
	Prevalence, n=123 (%)	Incidence (n)	Person-months	Incidence/1000 person-months	12-month incidence (%)	Prevalence, n=120 (%)	Incidence (n)	Person-months	Incidence/1000 person-months	12-month Incidence (%)		
16	9.8	5	824.3	6.1 (2.5 – 4.6)	7.2 (3.0 – 17.5)	22.5	13	809.3	16.1 (9.3 – 27.7)	19.3 (11.2 – 33.2)	2.6 (0.98 – 7.1)	0.058
18	4.9	5	837.8	6.0 (2.5 – 14.3)	7.2 (3.0 – 17.2)	10.0	8	955.1	8.4 (4.2 – 16.7)	10.1 (5.0 –20.1)	1.4 (0.5 – 4.3)	0.6
31	0	1	903.4	1.1 (0.2 – 7.9)	1.3 (0.2 – 9.4)	2.5	4	1035.3	3.4 (1.5 – 10.3)	4.6 (1.7 – 12.4)	3.5 (0.4 – 27.2)	0.28
33	0.8	1	903.4	1.1 (0.2 – 7.9)	1.3 (0.2 – 9.4)	5.0	5	1002.2	5.0 (2.1 – 12.0)	6.0 (2.5 – 14.4)	4.5 (0.6 – 31.9)	0.15
35	3.3	1	886.1	1.1 (0.2 – 8.0)	1.4 (0.2 – 9.6)	0	5	1053.7	4.7 (2.0 – 11.4)	5.7 (2.3 – 13.7)	4.2 (0.6 – 30.2)	0.18
39	5.7	5	846.2	5.9 (2.5 – 14.2)	7.1 (3.0 – 17.1)	10.0	10	957.6	10.4 (5.6 – 19.4)	12.5 (6.8 –23.3)	1.8 (0.6 – 5.0)	0.3
45	3.3	3	886.2	3.4 (1.1 – 10.5)	4.1 (1.3 – 12.6)	9.2	6	969.3	6.2 (2.8 – 13.8)	7.4 (3.3 – 16.6)	1.8 (0.5 – 7.2)	0.41
51	8.1	3	840.1	3.5 (1.2 – 11.1)	4.3 (1.4 – 13.3)	10.8	10	919.4	10.8 (5.8 – 20.2)	13.1 (7.0 –24.3)	3.0 (0.9 – 10.4)	0.08
52	6.5	3	864	3.5 (1.1 – 10.8)	4.2 (1.3 – 12.9)	9.2	8	941.3	8.4 (4.3 – 17.0)	10.2 (5.1 –20.4)	2.4 (0.7 – 8.8)	0.19
56	1.6	0	896.4	0 (0 – 4.1)	0 (0 – 4.9)	2.5	5	1018.5	4.9 (2.0 – 11.8)	6.0 (2.5 – 14.2)	6.0 (2.5 – 14.2)	**0.04**
58	4.9	3	880.9	3.4 (1.1 – 10.6)	4.1 (1.3 – 12.7)	10.8	11	942.9	6.4 (21.1)	14.0 (7.8 –25.3)	3.4 (1.03 – 11.4)	**0.047**
59	5.7	0	855.8	0 (0 – 4.3)	0 (0 – 5.2)	7.5	9	990.6	9.1 (4.7 – 17.5)	10.9 (5.6 –21.0)	10.9 (3.2 – 18.6)	**0.004**
68	4.1	7	841.9	8.3 (4.0 – 17.4)	10.0 (4.7 – 21.0)	13.3	10	895.7	11.2 (6.0 – 20.8)	13.4 (7.2 –24.9)	1.3 (0.5 – 3.5)	0.6
Any high-risk HPV	36.6	17	602.6	28.2 (17.5 – 45.3)	33.9 (21.1 – 54.5)	57.5	25	385.2	64.9 (43.9 – 96.1)	78.0 (52.7 – 115.4)	2.3 (1.3 – 4.2)	**0.008**

MSM, men who have sex with men; HPV, human papillomavirus; IRR, Incidence rate ratio.

Incidence = incident infections occurring during follow-up; Person-months = person time at risk; Incidence/1000 person-months = incidence density per 1000 patient-months of follow-up; 12-month incidence (%) = yearly incidence percent; P is the probability that the IRR is not equal to 1 (no effect value for a rate ratio). Statistically significant values are indicated in boldface.

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Table 3

Clearance and persistence of type-specific, high-risk anal human papillomavirus infection among MSM, by HIV status at baseline.

HPV type	Clearance								Persistence				
	HIV-negative				HIV-positive								
	Cleared infection (n)	Person-months	Clearance/1000 person-months	Median time (months)	Cleared infection (n)	Person-months	Clearance/1000 person-months	Median time (months)	CRR (95% CI)	P	HIV-negative	HIV-positive	P
16	8	79.1	101.2	11.1	13	249.9	52	12.6	0.51 (0.22 – 1.22)	0.15	1 (1.3%)	16 (16.7%)	**<0.001**
18	4	65.6	61	13.1	7	104.1	67.2	11.3	1.10 (0.32–3.76)	0.9	3 (3.8%)	6 (6.3%)	0.5
31	-	-	-	-	3	23.9	41.8	6.84	-	-	0 (0%)	2 (2.1%)	0.5
33	-	-	-	-	3	57	52.7	11.1	-	-	0 (0%)	4 (4.2%)	0.1
35	2	17.3	115.8	5.6	1	5.6	179.9	-	1.6 (0.14 – 16.8)	0.72	0 (0%)	0 (0%)	-
39	4	57.1	70	11.6	7	101.6	68.9	6	0.98 (0.29 – 3.36)	0.95	3 (3.8%)	6 (6.25%)	0.5
45	1	17.1	58.3	11.7	8	89.9	89	6	1.52 (0.19 – 12.0)	0.77	1 (1.3%)	5 (5.2%)	0.2
51	7	63.2	110.7	10.7	6	139.8	42.9	11.3	0.39 (0.14 – 1.10)	0.1	0 (0%)	11 (11.5%)	**0.001**
52	2	39.3	50.9	11.6	11	117.9	93.3	10.9	1.83 (0.42 – 8.09)	0.46	2 (2.5%)	7 (7.3%)	0.19
56	1	6.9	144.8	-	4	40.7	98.3	6.8	0.67 (0.08 – 5.99)	0.7	0 (0%)	3 (3.1%)	0.25
58	0	22.5	0	-	3	116.3	25.8	-	-	0.6	2 (2.5%)	10 (10.4%)	0.07
59	3	47.6	63	11	6	68.6	87.4	6.4	1.39 (0.35 – 5.51)	0.67	2 (2.5%)	5 (5.2%)	0.46
68	1	61.5	16.3	11.3	11	156.5	70.2	10.9	4.32 (0.66 – 28.2)	0.13	6 (7.6%)	12 (12.5%)	0.33
Any high-risk HPV	12	300.8	39.9	11.6	20	667	30	12.6	0.75 (0.37 – 1.53)	0.44	15 (19.0%)	47 (49.0)	**<0.001**

MSM, men who have sex with men; HPV, human papillomavirus; CRR, Clearance rate ratio.

Cleared infection = cleared infections occurring during follow-up; Person-months = person time at risk; Clearance/1000 person-months = clearance per 1000 patient-months of follow-up; P is the probability that the CRR is not equal to 1 (no effect value for a rate ratio). Statistically significant values are indicated in boldface.

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Table 4

Univariate and multivariate analysis of factors associated with risk of persistence of at least one anal high-risk human papillomavirus type.

Covariates	Univariate				Multivariate			
	HR	Lower CI	Upper CI	P	HR	Lower CI	Upper CI	P
All MSM								
Baseline HIV-positive vs. HIV-negative status	4.09	2.05	8.16	<0.001	4.45	2.11	9.4	<0.001
Smoking	1.65	1.05	2.60	0.029	1.34	0.82	2.19	0.25
Sex acts per week, ≥3	2.04	0.88	4.73	0.097	2.63	0.99	6.98	0.052
Age at sexual debut				0.055				0.17
≥ 20 years	1 (ref)				1 (ref)			
18–19 years	1.06	0.48	2.36		0.95	0.4	2.26	
≤ 17 years	2.32	1.09	4.94		1.94	0.86	4.41	
Baseline HIV-positive MSM only								
Smoking	3.4	1.25	9.22	0.016	2.3	1.17	4.5	0.015
Age group				0.051				0.15
19–23 years	1 (ref)				1 (ref)			
24–29 years	4.58	1.28	16.4		4.19	1.05	16.7	
30–34 years	2.2	0.58	8.28		1.55	0.37	6.59	
≥35 years	1.71	0.46	6.43		1.72	0.41	7.29	
Sex acts per week, ≥3	3.63	0.92	14.4	0.066	3.2	0.7	14.6	0.133
Nadir CD4 count, per 50 cells/mm^3 increase	0.87	0.74	1.03	0.11	0.85	0.71	1.03	0.093
HAART use at baseline	0.88	0.27	2,84	0.83				
Plasma HIV RNA, per log_{10} copies/mL increase	1.05	0.75	1.47	0.78				

HR, hazard ratio; CI, confidence interval.