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BRIEF REPORT

Incidence and Clearance of Anal Human Papillomavirus (HPV)-16 and HPV-18 Infection, and Their Determinants, Among Human Immunodeficiency Virus-Infected Men Who Have Sex With Men in France

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Background. Prospective data on the natural history of anal human papillomavirus (HPV) infection are scarce in human immunodeficiency virus (HIV)-infected men who have sex with men (MSM).

Methods. We analyzed incidence and clearance of HPV-16 and HPV-18 in a French cohort of HIV-infected MSM, aged ≥35 years, followed-up annually (n = 438, 2014–2018).

Results. Human papillomavirus-16 and HPV-18 incidence were similar (~10% incident infections at 24 months). Human papillomavirus-16 incidence was higher among high-grade versus no lesion at baseline (adjusted incidence rate ratio = 3.0; 95% confidence interval, 1.07–8.18). Human papillomavirus-16 cleared significantly slower than HPV-18 (32% versus 54% by 24 months).

Conclusions. In conclusion, anal HPV-16 is more persistent than HPV-18, and its incidence correlates with a prior detection of high-grade lesions.

Keywords. anal HPV infection; human immunodeficiency virus; incidence; men who have sex with men; clearance.

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The incidence of anal cancer has increased in the past decades [1], and the main risk factor is anal exposure to high-risk human papillomavirus (hrHPV) [2], especially HPV-16 [3, 4]. The high burden of anal cancer among men who have sex with men (MSM), especially among human immunodeficiency virus (HIV)-infected MSM, is well characterized [3–5]. However, data on the natural history of anal HPV infections among HIV-infected MSM are scarce.

Among MSM, anal incidence rates (IRs) of HPV-16 can be 2 times higher in HIV-positive MSM compared with HIV-negative MSM, whereas no significant difference in clearance has been found [6, 7]. Among HIV-infected MSM, sexual risk behavior is an important predictor of HPV incidence [7, 8], whereas smoking has been found to be a predictor of HPV persistence [7]. It is unclear whether HIV-related factors are predictors of HPV incidence and/or clearance [6, 9].

In a prospective multicenter study of HIV-infected MSM in France, in which we have previously shown hrHPV and HPV-16 to be highly prevalent at baseline [10], we explore the incidence and clearance of HPV-16 and HPV-18 infection as well as the determinants thereof.

METHODS

Study Participants

As described previously [10, 11], the ANRS EP57 APACHES study concerns an HIV-infected MSM population aged ≥35 years followed up in infectious disease units in 6 hospitals across France. Participants were included between December 2014 and June 2016, with the last visit date in June 2018. In this study, we analyzed annual follow-up visits [10]. Exclusion criteria were anal cancer or histologic high-grade anal intraepithelial lesions treated in the preceding 12 months. The study was approved by the International Agency for Research on Cancer (IARC) Ethics Committee and the Comité de Protection des Personnes de Paris Ile de France VI in accordance with the Declaration of Helsinki.

Data Collection

All participants completed a questionnaire on tobacco use and sexual behavior. Participants' medical records were used to retrieve HIV-related data. The number of new recent sexual partners was asked at every subsequent visit.

Biological Samples

Two anal swabs (Anex Brush) were taken at each visit by a proctologist. Swabs were transferred to PreservCyt medium (Hologic, Boxbourough, MA) to be used for cytology and for HPV deoxyribonucleic acid (DNA) testing. After specimen collection, patients received a standard proctologic examination (including digital anal-rectal examination) and high-resolution anoscopy as described previously [10, 11]. Lesions were classified based on the highest diagnostic category found using either cytology or histology [10]. Currently, (consensus) cytology and histology are only available for the baseline visits. Anal swabs were tested for HPV DNA using the Cobas 4800 system (Roche Molecular Systems, Alameda, CA). This assay provides partial genotyping: HPV-16, HPV-18, and other hrHPV aggregated (-31,-33,-35,-39,-45,-51,-52,-56,-58,-59,-66, and -68).

Statistical Analyses

Incidence rates and clearance rates (CRs) were estimated for HPV-16 and HPV-18 using Poisson regression analyses, assuming a constant rate over time. Cumulative hazard estimates for incidence and clearance were deducted from Kaplan-Meier survival analysis. We included all participants completing ≥2 visits.

Incidence was defined as a positive HPV test result preceded by a negative HPV test. Time at risk for incidence started from the first HPV-negative visit of the HPV type under consideration, and it ended either at the midpoint between the last negative test and the first positive test or at the date of the last HPV-negative sample (if the HPV outcome was not detected). Incident infection with the same HPV type, after clearance of a first infection, was ignored in this analysis.

Clearance was defined as 1 negative test result that was preceded by a positive test result. People entered risk-set for clearance from the first HPV-positive visit, and they left the risk-set either at the midpoint between the last positive test and the first negative test or at the date of the last HPV-positive sample (if the HPV infection had not cleared).

The IR and CR and rate ratios were estimated using Poisson regression. Poisson regression was also used to estimate the incidence/clearance ratio within 1 HPV type.

RESULTS

Description of Study Population

In this study, 438 HIV-infected MSM who had ≥2 visits were included. Baseline HPV-16, HPV-18, other hrHPV, and any hrHPV prevalence were 29%, 12%, 64%, and 71%, respectively; this was similar to the full cohort of participants (n = 490) [10]. The median number of visits was 3 (interquartile range [IQR], 2–4), and the median time interval between 2 visits was 12 (IQR, 12–13) months. Median age at entry was 51 years (IQR, 46–57), and median baseline $CD4^+$ cell count was 682 cells/μL (IQR, 499–884). Most individuals were on cART (95%) and had an undetectable HIV viral load (93%). Eighteen percent had a high-grade lesion detected at baseline (Supplementary Table 1).

Incidence and Clearance of Human Papillomavirus (HPV)-16 and HPV-18

Anal IRs and CRs are presented in Table 1. Incidence rates of HPV-16 and HPV-18 were 4.4 (95% confidence interval [CI], 3.15–6.17) and 4.3 (95% CI, 3.12–5.81) per 1000 person-months, respectively. The incidence of HPV-16 and HPV-18 was similar (the incidence rate ratio [IRR] of HPV-18 versus HPV-16 was 1.0; 95% CI, 0.61–1.52). Clearance rates of HPV-16 and HPV-18 were 16.0 (95% CI, 12.04–21.19) and 31.4 (95% CI, 23.14–42.68) per 1000 person-months, respectively. Human papillomavirus-16 cleared 2.0 (95% CI, 1.30–2.99) times slower than HPV-18. The incidence/clearance ratio was 0.3 (95% CI, 0.18–0.43) for HPV-16 and 0.1 (95% CI, 0.09–0.21) for HPV-18.

Determinants of Human Papillomavirus (HPV)-16 and HPV-18 Incidence

In Table 2, determinants of anal HPV-16 incidence are presented. Significant determinants of HPV-16 incidence were "current" versus "never" tobacco use (adjusted IRR [aIRR] = 3.2;

Table 1. Incidence Rate and Clearance Rate of Anal HPV-16 and Anal HPV-18 Infections Among HIV-Positive MSM (APACHES, France, December 2014–June 2018)[a]

						12 Months		24 Months		36 Months	
	N (Proportion) at Risk	Events	PMO	IR/CR	95% CI	Cumulative Proportion (%)	95% CI	Cumulative Proportion (%)	95% CI	Cumulative Proportion (%)	95% CI
Incidence											
16	337 (77%)	34	7706	4.4	(3.15–6.17)	7.1	(4.83–10.44)	9.5	(6.76–13.23)	15.6	(9.62–24.79)
18	400 (91%)	40	9392	4.3	(3.12–5.81)	6.0	(4.07–8.83)	10.6	(7.84–14.12)	10.6[b]	(7.84–14.12)
Clearance											
16	150 (34%)	48	3006	16.0	(12.04–21.19)	21.4	(15.64–28.87)	32.4	(25.29–40.88)	37.5	(28.08–48.74)
18	79 (18%)	41	1305	31.4	(23.14–42.68)	29.3	(20.54–40.75)	53.7	(42.42–65.92)	69.6	(49.18–87.74)

Abbreviations: CI, confidence interval; CR, clearance rate per 1000 person-months of observation at risk; HIV, human immunodeficiency virus; HPV, human papillomavirus; IR, incidence rate per 1000 person-months of observation at risk; MSM, men who have sex with men; PMO, person-months of observation at risk.

[a]Please note that the number of individuals at risk for incidence and clearance do not add up to 438 because an individual was considered at risk for, for example, incidence, from the first HPV-negative visit and onwards, and thus not from the first (HPV-negative) cohort visit.

[b]No new event between 24 and 36 months.

95% CI, 1.14–8.73), having a new receptive anogenital partner (aIRR = 2.3; 95% CI, 1.06–4.85), and having a high-grade lesion detected at baseline (aIRR = 3.0; 95% CI, 1.07–8.18). Of the 75 individuals with a high-grade lesion, 57% (n = 43) were already HPV-16 positive at baseline, and among the 32 who were HPV-16 negative at baseline, 7 were HPV-16 positive at their next 12-month visit and 1 at his 36-month visit (Table 2). Of note, the 8 individuals with an incident HPV-16 event also tested HPV-16 negative by PapilloCheck at baseline.

Anal HPV-16 incidence was not associated with age nor with most HIV-related variables (cART use, acquired immune deficiency syndrome-defining condition, HIV-viral load at baseline, or $CD4^+$ at baseline and nadir). However, participants with $CD4^+/CD8^+$ ratio ≥1 had lower incidence than those with $CD4^+/CD8^+$ ratio <0.5 (aIRR = 0.3; 95% CI, 0.10–0.87). The only significant determinant for anal HPV-18 incidence, in either bivariable or multivariable analyses, was number of lifetime receptive-anal sexual partners (for 10–39 versus 0–9; aIRR = 5.2; 95% CI, 1.19–22.85) (Supplementary Table 2).

Determinants of Human Papillomavirus (HPV)-16 and HPV-18 Clearance

Determinants of anal HPV-16 and HPV-18 clearance are presented in Supplementary Tables 3 and 4, respectively. Clearance of HPV-16 happened less often after a persistent infection compared with an incident infection (aIRR = 0.3; 95% CI, 0.11–1.01). This association was significant for HPV-18 (aIRR = 0.3; 95% CI, 0.10–0.67). Participants with a high-grade lesion cleared HPV-18 infection less often than participants without a lesion (aIRR = 0.2; 95% CI, 0.06–0.60), but a similar significant effect was not seen for HPV-16 (aIRR = 0.7; 95% CI, 0.31–1.60).

DISCUSSION

Given the limited prospective data on the natural history of anal HPV infections among HIV-infected MSM, we provide a detailed analysis of the incidence and clearance of anal HPV-16 and HPV-18. In a previous study, we showed that one third of the APACHES study population were HPV-16 positive and 12% were HPV-18 positive at baseline [10]. In this study, we show that after 24 months, approximately 10% of all HIV-infected MSM have new HPV-16 or HPV-18 infection detected, and that 32% versus 54% subsequently cleared their HPV-16 or HPV-18 infection, respectively. Furthermore, we found that HPV-16 incidence was significantly higher among individuals with a high-grade lesion at baseline, hinting at the possibility of a small number of HPV-16 infections missed in baseline anal swabs. Furthermore, HIV-related parameters did not show associations with anal HPV clearance, at least not among this contemporary, virally controlled population of HIV-infected MSM.

Incidence rates and CRs of this study are within the range of previous studies [6–9]. Note that studies use different sampling and laboratory techniques, and different definitions of incidence and clearance, hampering direct comparisons between studies. Human papillomavirus-16 is found to have the highest incidence in most studies and to have the lowest clearance in all studies [6–9]. Only a few studies estimate the incidence/clearance ratio of individual HPV types [9, 12], showing—in agreement with our study—the highest incidence/clearance ratio for HPV-16, highlighting the unique carcinogenic potential of HPV-16 [4].

We found a higher incidence of anal HPV-16 among individuals with high-grade lesions at baseline. This association remained strong even after adjustment for sexual activity, and given that 22% (7 of 32) of these incident infections were detected at the next visit, this suggests a small number of missed HPV-16 infections at baseline. Hence, despite the already high correlation found between HPV-16 and high-grade lesions [10], our results suggest that HPV-16 positivity in high-grade lesions might be even higher than that estimated based on a single concurrent anal swab. Although we excluded a small proportion of swabs with inadequate human DNA, sampling procedures of anal swab may need further standardization to ensure quality control given the complexity of sampling the entire anal canal.

Tobacco use was a borderline significant predictor for HPV-16 incidence and showed a positive trend with HPV-18 incidence. This association might be due to residual confounding, but it has also been shown that components of tobacco smoke inflict genotoxic damage in the anal epithelium of smokers [13].

Despite the fact that prevalence/incidence and the sequelae related to HPV infection are more often present among HIV-infected MSM [3, 5, 6], our study, in agreement with others [6, 9], supports the finding that HIV-related parameters are not strongly associated with anal HPV incidence/clearance. Further research needs to clarify whether this is because studies are underpowered and/or other unmeasured factors play a role among HIV-infected MSM. Higher $CD4^+/CD8^+$ ratio was associated with lower HPV-16 incidence; given that it was not consistent with other HIV-related variables, nor with the finding for HPV18, we do not have an explanation for this.

One of the study's limitations is the number of events, which should be kept in mind when interpreting the analysis of the determinants of HPV incidence and clearance. The data did not enable stricter definitions to be applied for incidence (eg, a positive visit preceded by 2 negative visits [0-0-1]) and clearance (eg, a negative visit preceded by 2 positive visits [1-1-0]). Stricter definitions might avoid counting a deposition as an incident infection, rather than an active infection of the anal epithelium [6, 12, 14]. Furthermore, only aggregated data were available for "other hrHPV", hampering a more detailed analysis of hrHPV types beyond HPV-16 and HPV-18. Approximately 70% of this population were hrHPV positive at baseline [10]. Using the aggregated hrHPV positivity, we observe that after 24 months, approximately half of the 30% hrHPV negative acquire a new hrHPV infection, and that one fifth of the hrHPV-positive individuals become hrHPV negative. This high prevalence and

Table 2. Determinants of Anal HPV-16 Incidence: Bivariable and Multivariable Analyses, Among 337 HIV-Positive MSM (APACHES, France, December 2014–June 2018)

	HPV-16 Incidence							
			Bivariable			Multivariable		
	Events	PMO	IRR	95% CI	*P* Value	aIRR[a]	95% CI	*P* Value
Center								
A	8	2385	REF		.26	REF		.16
B	1	428	0.7	(0.09–5.57)		N.E.		
C	5	1235	1.2	(0.39–3.69)		1.4	(0.45–4.60)	
D	10	1246	2.4	(0.94–6.06)		**3.3**	**(1.18–9.08)**	
E	1	836	0.4	(0.04–2.85)		0.4	(0.04–2.95)	
F	9	1576	1.7	(0.66–4.41)		1.6	(0.57–4.72)	
Age (Years)								
35–44	9	1412	REF		.18	REF		.45
45–54	18	3579	0.8	(0.35–1.76)		0.8	(0.35–1.95)	
≥55	7	2716	0.4	(0.15–1.09)		0.5	(0.17–1.49)	
Tobacco Use								
Never	7	2978	REF			REF		
Ever	27	4728	**2.4**	**(1.06–5.58)**	**.04**	**2.7**	**(1.01–7.00)**	**.05**
Former	8	2032	1.7	(0.61–4.62)	**.04**	2.0	(0.63–6.25)	.08
Current	19	2696	**3.0**	**(1.26–7.13)**		**3.2**	**(1.14–8.73)**	
Lifetime Number of Receptive Anal Sexual Partners								
0–9	6	1436	REF		.90	REF		.92
10–39	9	2262	1.0	(0.34–2.68)		0.8	(0.30–2.38)	
≥40	19	3991	1.1	(0.45–2.85)		1.0	(0.39–2.50)	
New Receptive Anogenital Sexual Partners in the Preceding 12 Months (Time Changing)								
No	11	4305	REF		**.02**			**.04**
Yes	18	2781	**2.5**	**(1.20–5.36)**		**2.3**	**(1.06–4.85)**	
Number of Receptive New Anogenital Sexual Partners in the Preceding 12 Months (Time Changing)								
0	11	4305	REF		**.04**			.09
1–4	11	1475	**2.9**	**(1.26–6.73)**		**2.6**	**(1.10–5.97)**	
≥5	7	1306	2.1	(0.81–5.41)		1.9	(0.73–4.99)	
AIDS-Defining Condition								
No	29	5993	REF		.22	REF		.39
Yes	4	1599	0.5	(0.18–1.47)		0.6	(0.17–1.99)	
Currently cART								
Yes	29	7184	REF		.26	REF		.17
No	3	374	2.0	(0.61–6.52)		2.3	(0.69–7.93)	
HIV Viral Load at Baseline								
Undetectable	28	6726	REF		.42	REF		.39
Detectable	3	442	1.6	(0.50–5.36)		1.7	(0.51–5.79)	
CD4 Nadir (Cells/μL)								
<50	4	1005	REF		.85			.75
50–499	24	5659	1.1	(0.37–3.07)		1.3	(0.38–4.58)	
>500	5	908	1.4	(0.37–5.15)		0.9	(0.19–4.28)	
$CD4^+$ Count at Baseline (Cells/μL)								
<350	3	575	REF		.37	REF		.13
350–499	8	1156	1.3	(0.35–5.00)		2.1	(0.44–9.73)	
≥500	21	5426	0.7	(0.22–2.49)		0.9	(0.20–3.73)	
$CD4^+/CD8^+$ Ratio								
<0.50	8	1073	REF		.15	REF		.08
0.50–0.99	13	2928	0.6	(0.25–1.44)		0.5	(0.18–1.26)	
≥1.0	8	2841	0.4	(0.14–1.01)		**0.3**	**(0.10–0.87)**	
Cytology[b] and Histology[c] Combined (Baseline)								
Normal	9	2865	REF		.06	REF		.09
Low grade	17	3788	1.4	(0.64–3.20)		1.3	(0.55–3.17)	
High grade	8	823	**3.1**	**(1.19–8.02)**		**3.0**	**(1.07–8.18)**	

Table 2. Continued

	HPV-16 Incidence							
			Bivariable			Multivariable		
	Events	PMO	IRR	95% CI	*P* Value	aIRR[a]	95% CI	*P* Value
Any Other HPV Positivity in the Preceding 12 Months (Time-Changing Variable)								
Negative	12	2863	REF		.82	REF		.64
Positive	22	4843	1.1	(0.54–2.19)		0.8	(0.39–1.78)	

Abbreviations: AIDS, acquired immune deficiency syndrome; aIRR, adjusted incidence rate ratio; cART, combination antiretroviral therapy; CI, confidence interval; HIV, human immunodeficiency virus; HPV, human papillomavirus; IRR, incidence rate; MSM, men who have sex with men; N.E., not estimated; PMO, person-months of observations at risk; REF, reference.

[a]Multivariable models for anal HPV-incidence were a priori adjusted for age (categorical), tobacco use (never/ever), and number of new receptive anogenital sexual partners in the preceding 12 months (categorical) where appropriate. For example, new anogenital sexual partners was only adjusted for age and tobacco use.

[b]Liquid-based anal cytology slides were prepared and read in local pathology departments, blinded to HPV results. Anal cytology results were categorized according to the 2001 Bethesda System terminology: negative; atypical squamous cells of undetermined significance (ASC-US); low-grade squamous intraepithelial lesion (LSIL); atypical squamous cells, cannot exclude HSIL (ASC-H); high-grade squamous intraepithelial lesion (HSIL); and cancer.

[c]Histological slides were prepared, and initial histological diagnoses were made, in local histology departments. Consensus diagnosis was reached for each slide, reported as negative, anal intraepithelial neoplasia (AIN)1, AIN2, AIN3, or invasive cancer. In case of multiple biopsies, the most severe grade was considered.

NOTE: Bold values indicate significant associations.

turnover highlights how aggregated hrHPV testing (ie, without genotyping) is not a useful marker for triage in this high-risk population.

Although MSM are clearly an important target group for primary prevention, caution is needed when translating epidemiological data on HPV among older MSM to implications for HPV vaccination. Approximately 30% of the men in this population were already HPV-16 positive [11], 68% still had their HPV-16 infection after 24 months, and 10% acquired a new HPV-16 infection within 24 months. Furthermore, a recent study showed that incident infections may be caused by reactivated latent HPV infections rather than new incident infections [14], suggesting that HPV infection was already present. We might expect that a large proportion of any future anal cancer in this MSM population arise from pre-existing infections.

CONCLUSIONS

In conclusion, incidence of HPV-16 and HPV-18 were similar, and HPV-16 clearance was significantly lower, correlating with its known higher carcinogenic potential. In addition to the possibility of high-grade lesions going undetected in HPV-16-positive individuals through the limitations of high-resolution anoscopy [11], our data suggest that the reverse might also be possible, ie, that a small proportion of HPV-16 infections in high-grade lesions may go undetected in a single anal swab. APACHES is currently finalizing study exit outcomes of cytology and histology diagnoses, the future analyses of which will provide more detailed insights into how HPV(-16) incidence and persistence predict the prospective risk for high-grade anal lesions.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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