Research Article

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Risk Factors for Oral HPV Infection among a High Prevalence Population of HIV-Positive and At-Risk HIV-Negative Adults

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Abstract

Introduction: Human papillomavirus (HPV) is an important risk factor for oropharyngeal cancer. Individuals with human immunodeficiency virus (HIV) have higher oral HPV prevalence but the risk factors for oral HPV infection are not well understood for either HIV-positive or HIV-negative individuals.

Methods: This study was nested within the Multicenter AIDS Cohort Study (MACS; men) and Women Interagency HIV Study (WIHS; women) cohorts. Exfoliated oral epithelial cells were collected from 379 HIV-positive and 266 at-risk HIV-negative individuals using a rinse and gargle with Scope mouthwash. Samples were tested for 36 types of HPV DNA using PGMY09/11 consensus primers and reverse line blot hybridization. Risk factors for oral HPV infection were explored using logistic regression with generalized estimating equations in this cross-sectional analysis.

Results: Prevalent oral HPV infection was common (34%), including HPV16 infection in 5.7% of participants. HIV-positive individuals had increased odds of prevalent oral HPV infection compared with HIV-negative individuals [adjusted OR = 2.1; 95% confidence interval (CI), 1.6–2.8]. Risk factors for prevalent oral HPV differed in HIV-positive and HIV-negative participants. Among HIV-negative individuals, higher number of recent oral sex or rimming partners were strong risk factors for prevalent oral HPV infection (each $P_{trend} < 0.01$). In contrast, among HIV-positive individuals, lower CD4 T-cell count ($P_{trend} < 0.001$) and higher number of lifetime sexual partners ($P_{trend} = 0.03$) were strong risk factors.

Conclusions: Oral HPV prevalence was elevated in HIV-positive individuals after controlling for differences in cigarette smoking and sexual behavior, supporting the possibility that HIV may affect the natural history of oral HPV.

Impact: Immunosuppression may contribute to increased persistence or progression of oral HPV infection.
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Introduction

Human papillomavirus (HPV) infection has recently been identified as a causal factor in a subset of head and neck squamous cell cancers, primarily oropharyngeal cancers (1–4). These HPV-positive tumors represent a growing cancer burden; the incidence of oropharyngeal cancers has increased over the past several decades (5–8), in stark contrast to the decreasing incidence of other head and neck cancer subsites (8, 9). It has been hypothesized that changes in sexual behavior may have caused this increase, although this has not been well evaluated.

Initial studies suggest that HIV-positive individuals have an elevated risk of oropharyngeal cancer, as well as other HPV-related cancers (8, 10–13). This increase could be explained by the effects of HIV-related immunosuppression on HPV but alternatively might be explained by higher rates of smoking (14) and the shared sexual risk factors between HIV and HPV.

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The prevalence of oral HPV16 infection, the HPV type which accounts for the majority of HPV-positive oropharynx cancers (1), has been estimated to be approximately 1.3% among healthy adults (15). Higher oral HPV16 prevalence has been reported among HIV-positive individuals (2%–6%; refs. 16–18). In initial studies, oral HPV prevalence was associated with cigarette use, higher number of recent and lifetime oral sexual partners, and immunosuppression (17, 19–22); however, the relative contribution of each of these factors on the higher prevalence of oral HPV among HIV-positive individuals is unclear.

The effect of immunosuppression on oral HPV natural history is unknown. Recent research suggests that highly active antiretroviral therapy (HAART) may not decrease oral HPV prevalence (16, 22) or oral warts (23, 24). This contrasts with the HAART era reductions seen in other oral lesions (24) and HIV shedding in saliva (25). Lower CD4 T-cell count is known to be associated with increased cervical HPV incidence, persistence, and progression to pre-cancer, but the effect of immunosuppression on oral HPV has not been evaluated (26, 27). The current study evaluated differences in risk factors for prevalent oral HPV infection in HIV-positive and HIV-negative individuals. Understanding these differences may shed light on whether the increased oral HPV prevalence and higher incidence of oropharyngeal cancers among people with HIV may be due to differences in sexual behavior (HPV acquisition), tobacco use (a known cause of head and neck cancer), or HIV-related immunosuppression.

Methods

Study population and study design

This cross-sectional study was based within 2 multisite U.S. cohort studies of HIV-positive and at-risk HIV-negative individuals: one cohort of women, the Women Interagency HIV Study (WIHS; refs. 28, 29) and one cohort of men who have sex with men (MSM), the Multicenter AIDS Cohort Study (MACS; refs. 30–32). These cohorts were designed to be methodologically similar and include HIV-negative individuals at risk for HIV infection based on their sexual or injection drug use behaviors. The current study is the initial phase of a larger natural history study of oral HPV infection in these 2 cohorts.

Briefly, the MACS and WIHS began in 1984 and 1994, respectively, with additional enrollment in 1987 to 1991 (MACS-only), and 2001 to 2003. MACS and WIHS participants undergo a semi-annual interview which includes medical history, demographic, and behavioral questions. There is also a physical examination and venipuncture, where the blood is tested for CD4 T-cell count and HIV viral load. Between April 2009 and March 2010, we enrolled a convenience sample of 365 men and 280 women.

The study design stratified enrollment by cohort (365 MACS and 280 WIHS), HIV status (379 HIV-positive and 266 HIV-negative), and among HIV-positive individuals by ever/never HAART use (312 HAART experienced and 67 never HAART users). To enrich for HAART-naive participants; all interested HAART-naive participants at these sites were enrolled. We enrolled 192 HIV-positive and 173 HIV-negative men from the Baltimore, Chicago, and Pittsburgh MACS sites and 187 HIV-positive, 93 HIV-negative women from the Brooklyn, Bronx, and Chicago WIHS sites. This sample represents 25% of current MACS and 26% of current WIHS participants at the sites enrolled. The study protocol was approved by the MACS and WIHS executive committees as well as the Institutional Review Boards at each site. Written informed consent was received from each participant.

An oral rinse sample was collected as part of this substudy using a 30-second swish and gargle of 10 mL of Scope mouthwash, as previously described (33). Relevant behavioral measures routinely collected by the MACS and WIHS were also evaluated in this study. Self-reported lifetime use and past 6 months use (called recent use hereafter) of recreational and therapeutic drugs, alcohol, cigarettes, and sexual behavior were collected by interview-administered questionnaire in the WIHS and computer-assisted self-interview (CASI) in the MACS. Fellatio (conducting oral sex on a man) was defined as "he put his penis in your mouth" in the MACS and "a blow job or putting his penis in your mouth" in the WIHS. Cunnilingus (conducting oral sex on a woman) was defined as "you used your tongue to touch or lick her genitals (vagina, clitoris)" in the MACS and any reported sexual activity with a female in the WIHS. The number of male or female partners an individual conducted fellatio or cunnilingus on is referred to as the number of oral sex partners hereafter. Data on rimming, collected only in the MACS, were defined as "you used your tongue to touch or lick his or her anus/butt." Updated information on lifetime oral sex history was acquired for most participants, but the complete history was not acquired for a proportion of MACS (44%) and WIHS (21%) participants. The updated number of lifetime oral sex partners for these individuals was imputed (see statistical methods below). Recent cigarette smoking was defined as using at least one cigarette per day for the past 6 months. Recent alcohol use was defined as drinking at least once in the past month.

The definition of HAART was guided by the DHHS/Kaiser Panel (34) and is defined as: the reported use of 3 or more antiretroviral medications, one of which has to be a protease inhibitor (PI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), one of the NRTIs abacavir or tenofovir, an integrase inhibitor, or an entry inhibitor. Nadir CD4 was the lowest CD4 T-cell count observed while in the MACS/WIHS study.

Laboratory analyses

After collection, oral rinse samples were stored at 4°C and shipped to a laboratory run by M.L. Gillison at the Ohio State University, Columbus, OH, for processing and testing. DNA was isolated from Scope oral rinse samples by centrifugation, resuspended in PBS, and purified using a magnetic bead–based automated platform (QIAsymphony SP, Qiagen), as previously described (35).

The purified DNA was then analyzed for 36 different HPV types using PGMY09/11 PCR primer pools and reverse line blot hybridization. Samples were considered evaluable if β-globin positive and considered insufficient and excluded from the analysis if β-globin negative. HPV types detected were classified into nononcogenic (low-risk) and oncogenic (high-risk) type categories as previously established by the World Health Organization's International Agency for Research on Cancer (IARC; refs. 36–38). Oncogenic HPV types included HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, and 73. All other types detected were considered nononcogenic including HPV6, 11, 26, 40, 42, 53, 54, 55, 61, 62, 64, 66, 67, 69, 70, 71, 72, 81, 82, 83, 84, and 89.

Statistical analyses

Characteristics of HIV-positive and HIV-negative individuals were compared using χ^2 tests for categorical data and *t* tests for continuous variables. Overall oral HPV status was defined as positive for anyone who had any of the 36 HPV types detected, whereas all others were considered HPV negative. In addition, type-specific HPV prevalence was estimated where participants were categorized as positive or negative for each of the 36 different types of HPV tested.

While the number of lifetime sexual partners at MACS and WIHS study baseline was collected for all participants, 34% of the 645 participants were not asked about their updated number of lifetime number of oral sex partners. Therefore, an updated number of lifetime oral sex partners were imputed for these individuals by calculating the average increase in lifetime oral sexual partners from baseline to current visit among the 425 participants with complete sexual behavioral data. These increases were averaged within subgroups defined by gender, years of follow-up, and number of oral sex partners in the past 6 months and then imputed to individuals without updated lifetime sexual data within each strata. Results were similar when the 220 individuals without an updated measure of lifetime number of oral sex partners were excluded from the analysis.

Risk factors for oral HPV infection were assessed using logistic regression models with robust variance and generalized estimating equations (GEE) to adjust for within-individual correlations related to multiple observations of the same person (i.e., multiple HPV types) using previously described methods (39, 40). Crude and adjusted ORs (OR & aOR) and 95% confidence intervals (CI) were reported. Type-specific risk factors for oral HPV16 infection and multiple HPV infection were calculated using standard logistic regression models. Factors statistically significant ($P < 0.05$) in the univariate analysis and those considered relevant based on previous literature (age, sexual behavior, and gender) were included in multivariate models. Models were stratified by HIV status, per the study design. The final multivariate model for HIV-negative subjects included age, gender, recent cigarette use, number of recent (last 6 months) and lifetime oral sex partners, and education level. The final multivariate model for HIV-positive subjects included these variables as well as current CD4 T-cell count (called current CD4 hereafter), study site, and recent alcohol use. Analyses that stratified by cohort (MACS vs. WIHS) study were also conducted. Fourteen individuals had incomplete covariate information. Therefore, our multivariate analyses were based upon 631 individuals.

Trends in the ORs were tested using continuous data when available (age, current CD4, HIV viral load, number of recent and lifetime oral sexual partners) and considering ordinal values as a single continuous variable when data were collected ordinally (education, recent cigarette and alcohol use). Correlation between variables was tested using Pearson correlation coefficient. All statistical tests were 2-sided and considered significant at α level of 0.05. STATA software (version 10.0; Stata Corp.) was used for all statistical analyses.

Results

Participant characteristics

Characteristics of the 645 participants enrolled are shown in Table 1, stratified by HIV status and gender. Participants in this study sample were similar to those in the MACS and WIHS cohorts. Participants in the MACS sample were similar to the larger MACS population with regard to median current CD4 (550 vs. 557 cells/μL), median age (52 vs. 54 years), proportion White (66% vs. 66%), and proportion sexually active (71% vs. 66%, each $P > 0.05$). Participants in the WIHS samples were similar to the larger WIHS population with regard to median age (45 vs. 46 years) and the proportion White (11% vs. 15%), but those in the WIHS study sample had lower median current CD4 (458 vs. 510 cells/μL) and were more likely to be sexually active in the past 6 months (71% vs. 63%, each $P < 0.05$) than the entire WIHS cohort. By design, the proportion of HIV-infected participants who were HAART naive was larger in our sample (19%) than the current MACS (6%) or WIHS (7%) study populations.

In this study, most HIV-positive participants were receiving HAART, with median nadir and current CD4 of 266 and 524 cells/μL, respectively. HIV-positive individuals were less educated and less likely to have recently conducted oral sex or to drink alcohol than HIV-negative individuals (each $P < 0.05$; Table 1). HIV-positive individuals were also more likely to be from the WIHS, to be African American, and to smoke cigarettes than HIV-negative individuals (each $P < 0.05$; Table 1).

Oral HPV prevalence

Oral HPV prevalence (34%), including infection with multiple HPV types (14%) was high in this study population (Table 2). The overall prevalence of oncogenic oral HPV infections was lower than that of nononcogenic infections (18% vs. 23%, $P = 0.03$). However, HPV16 was the most common HPV type detected in the study (prevalence of 5.7%), detected in 2.2% and 5.4% of HIV-negative

Table 1. Characteristics of men from the MACS and women from the WIHS at the time of their enrollment into this study between April 2009 and March 2010

		Women: WIHS (%)		Men: MACS (%)	
Demographics	**Overall (*N* = 645)**	**HIV-positive (*N* = 187)**	**HIV-negative (*N* = 93)**	**HIV-positive (*N* = 192)**	**HIV-negative (*N* = 173)**
Age, y					
<45	198	44	61	17	16
45–54	231	37	26	44	30
≥54	216	19	13	39	54
Race and ethnicity					
White non-Hispanic	271	11	10	59	74
African American non-Hispanic	322	70	76	40	25
Hispanic (any race)	40	15	12	0	1
Other race	12	4	2	1	1
Education					
Any college education	397	30	37	80	89
High school degree	126	30	32	16	6
<High school degree	119	40	32	5	4
Study site					
Chicago (MACS and WIHS)	177	32	34	27	19
Baltimore (MACS)	175	NA	NA	41	55
Pittsburgh (MACS)	105	NA	NA	32	27
Bronx (WIHS)	93	32	34	NA	NA
Brooklyn (WIHS)	95	35	31	NA	NA
Behavioral					
Number of cigarettes smoked per day past 6 mo					
<1 ("non-smoker")	419	54	52	68	82
1–9	126	31	31	12	10
10–19	67	13	14	11	5
≥20	31	2	3	10	3
Number of alcoholic drinks consumed past 6 mo					
<1 month ("non-drinker")	307	67	54	41	31
1/month to <2/wk	167	19	24	27	34
2–14/wk	110	12	17	24	24
≥15 or more/wk	44	2	5	8	12
Sexual activity					
Any sexual activity in last 6 mo					
No	188	32	23	32	27
Yes	455	68	77	68	73
Number of male or female partners conducted oral sex on in last 6 mo					
0	335	77	60	39	35
1	162	20	32	25	28
2–4	95	4	8	20	25
≥5	52	0	0	16	13
Among those conducting oral sex in last 6 mo: always used barrier					
No	280	72	97	90	98
Yes	27	27	3	10	2
Number of rimming partners in last 6 mo[a]					
0	248			67	69
1	60			17	16
2–4	35			8	11
≥5	20			7	4

(Continued on the following page)

Table 1. Characteristics of men from the MACS and women from the WIHS at the time of their enrollment into this study between April 2009 and March 2010 (Cont'd)

		Women: WIHS (%)		Men: MACS (%)	
Demographics	**Overall (*N* = 645)**	**HIV-positive (*N* = 187)**	**HIV-negative (*N* = 93)**	**HIV-positive (*N* = 192)**	**HIV-negative (*N* = 173)**
Lifetime number of oral sex partners					
0–4 partners	218	66	67	8.0	9
4–19 partners	120	21	19	18	17
20–99 partners	140	7	9	29	38
≥100 partners	159	6	4	45	35
HIV related					
Current HAART use					
No	101	27		27	
Yes	278	73		73	
Current CD4 cell count, cells/μL					
>500	200	46		60	
200–500	139	40		34	
<200	40	14		6.8	
Current HIV viral load, copies/mL					
<50	288	54		72	
50–20,000	61	32		18	
≥20,000	46	14		9	
Nadir[b] CD4 cell count, cells/μL					
>500	52	18		11	
200–500	200	57		53	
<200	112	26		37	

[a]Data on number of rimming partners were only available in the MACS.
[b]This was the nadir (lowest) CD4 cell count observed while in the MACS/WIHS study.

and HIV-positive women ($P = 0.21$), respectively, and in 6.9% and 6.8% of HIV-negative and HIV-positive MSM ($P = 0.95$), respectively. HPV16 constituted a larger proportion of infections detected among HIV-negative than HIV-positive participants (16% vs. 8%, $P = 0.04$). The distribution of all oral HPV types detected by HIV status are displayed in Supplementary Table S2, including the most commonly detected oncogenic (HPV16, 59, and 33) and nononcogenic (HPV55, 62, and 53) types.

Risk factors for prevalent oral HPV infection

HIV-positive individuals were significantly more likely than HIV-negative participants to have a prevalent oral HPV infection detected (aORs = 2.1; 95% CI, 1.6–2.8). This

Table 2. Oral HPV prevalence in HIV-positive and HIV-negative individuals

	Oral HPV prevalence							
	HIV-positive			HIV-negative				
Oral HPV infection	**Women (*N* = 187), %**	**Men (*N* = 192), %**	**Total (*N* = 379), %**	**Women (*N* = 93), %**	**Men (*N* = 173), %**	**Total (*N* = 266), %**	***P*, χ^2 HIV$^+$ vs. HIV$^-$**	**Overall (*N* = 645), %**
Any	35	45	40	18	28	25	<0.001	34
Nononcogenic	27	31	29	11	16	14	<0.001	18
Oncogenic	18	23	21	8.6	17	14	0.033	23
HPV 16	5.4	6.8	6.1	2.2	6.9	5.3	0.665	5.7
Other oncogenic	17	20	18	7.5	11	10	0.004	15
Multiple concurrent	18	19	19	7.5	6.4	6.8	<0.001	14

Table 3. Risk factors associated with prevalent oral HPV infection in univariate and multivariate analysis, by HIV status

		OR (95%CI)[d]			
		HIV-positive		HIV-negative	
Risk factors	Overall oral HPV prevalence, %	Univariate	Multivariate	Univariate	Multivariate
Age, y					
<45	31	1	1	1	1
45–54	36	0.92 (0.63–1.3)	0.84 (0.57–1.2)	1.7 (0.85–3.2)	1.2 (0.54–2.7)
≥54	35	1.1 (0.71–1.6)	1.2 (0.77–1.8)	1.8 (1.0–3.4)	2.1 (1.0–4.4)
P_{trend}		0.48[a]	0.30[a]	0.02	0.01
Gender					
Female (WIHS)	30	1	1	1	1
Male (MACS)	38	1.2 (0.82–1.6)	3.0 (1.7–5.1)	1.2 (0.71–2.2)	0.97 (0.45–2.1)
Education					
Any college	33	1	1	1	1
High school degree	33	1.3 (0.87–2.1)	1.8 (1.0–3.1)	1.2 (0.53–2.5)	1.3 (0.56–2.9)
<High school degree	38	1.5 (1.0–2.3)	2.1 (1.2–3.5)	0.94 (0.44–2.0)	0.90 (0.34–2.3)
P_{trend}		0.02	<0.001	0.99	0.66
Behavioral					
Smoked cigarettes in past 6 mo					
No (<1/d)	29	1	1	1	1
Yes	44	1.8 (1.3–2.5)[a]	1.7 (1.2–2.3)[a]	1.8 (1.1–2.9)[a]	2.8 (1.8–4.4)[a]
Consumed alcoholic drinks in past 6 mo					
No (<1/mo)	37	1	1	1	
Yes	31	0.73 (0.51–1.0)	0.74 (0.49–1.1)	1.2 (0.70–2.0)	
Sexual activity					
Number of oral sex partners in last 6 mo					
0	32	1	1	1	1
1	32	0.92 (0.63–1.3)	0.90 (0.60–1.4)	0.95 (0.49–1.8)	1.4 (0.69–2.9)
2–4	36	0.84 (0.47–1.5)	0.85 (0.50–1.5)	1.7 (0.92–3.1)	2.9 (1.5–5.8)
≥5	46	1.3 (0.71–2.3)	1.2 (0.63–2.1)	1.8 (0.92–3.4)	2.7 (1.3–5.8)
P_{trend}		0.46	0.88	0.01[a]	0.003[a]
Lifetime number of oral sex partners					
0–4 partners	28	1	1	1	1
5–19 partners	32	1.2 (0.74–1.9)	1.2 (0.72–1.9)	1.4 (0.61–3.0)	1.4 (0.59–3.1)
20–99 partners	34	1.3 (0.78–2.1)	1.5 (0.82–2.7)	1.0 (0.51–2.1)	0.87 (0.33–2.3)
≥100 partners	44	1.4 (0.94–2.2)	1.8 (1.0–3.2)	1.6 (0.83–3.1)	1.3 (0.52–3.4)
P_{trend}		0.05[a,c]	0.03[a,c]	0.03[c]	0.11[c]
Number of rimming partners in last 6 mo[b]					
0	33	1	1	1	1
1	43	1.1 (0.68–1.8)	1.3 (0.75–2.1)	1.6 (0.81–3.1)	2.4 (1.1–5.0)
2–4	46	1.0 (0.51–1.9)	1.0 (0.51–1.9)	2.1 (1.0–4.4)	2.7 (1.2–6.1)
≥5	50	1.0 (0.31–3.2)	1.0 (0.31–2.9)	2.5 (1.4–4.7)	3.0 (1.6–5.9)
P_{trend}		0.67	0.51	<0.001	0.002
HIV related					
Current CD4 T-cell count, cells/μL					
>500	37	1	1		
200–500	41	1.7 (1.2–2.4)	1.6 (1.1–2.3)		
<200	58	2.6 (1.7–4.1)	2.1 (1.3–3.2)		
P_{trend}		<0.001	<0.001		

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Table 3. Risk factors associated with prevalent oral HPV infection in univariate and multivariate analysis, by HIV status (Cont'd)

Risk factors	Overall oral HPV prevalence, %	OR (95%CI)[d] HIV-positive Univariate	HIV-positive Multivariate	HIV-negative Univariate	HIV-negative Multivariate
Nadir CD4 T-cell count, cells/μL					
>500	26	1			
200–500	38	1.8 (1.0–3.2)			
<200	50	2.2 (1.2–4.1)			
P_{trend}		0.003			
Current HAART					
No	34	1			
Yes	43	1.1 (0.73–1.6)			
Current HIV viral load, copies/mL					
<50	38	1			
50–20,000	39	1.3 (0.90–2.0)			
≥20,000	59	2.3 (1.5–3.5)			
P_{trend}		0.001			

[a]Effect modification by MACS/WIHS study cohort not included in this model but is reported in Table 4.

[b]The data for rimming presented are in analysis among MACS participants only (because rimming was not measured in the WIHS) and number of recent oral sex partners was not adjusted for in this model because number of recent oral and rimming partners were strongly correlated ($r = 0.65$). Rimming was not adjusted for in the other variables presented in the table.

[c]Lifetime oral sex partners P_{trend} excludes 46 individuals with >500 lifetime sex partners. When these individuals were included, P_{trend} is attenuated.

[d]Model adjusted for age, gender, education, current cigarette use, and number of recent and lifetime oral sex partners. HIV-positive model was also adjusted for alcohol use, study site, and current CD4 T-cell count.

was true for both oncogenic (aOR = 1.8; 95% CI, 1.3–2.7) and nononcogenic (aOR = 2.3; 95% CI, 1.6–3.4) types of oral HPV. Oral HPV16 infection, however, was similarly common among HIV-positive and HIV-negative individuals (aOR = 1.3; 95% CI, 0.62–2.7).

Recent cigarette smoking was associated with significantly increased odds of oral HPV among both HIV-positive and HIV-negative individuals. There were, however, notable differences between HIV-positive and HIV-negative participants in other risk factors for oral HPV infection (Table 3). The number of recent oral sex partners was the strongest risk factor for prevalent oral HPV among HIV-negative ($P_{trend} = 0.003$) but not HIV-positive ($P_{trend} = 0.88$) participants. In the MACS, where data on rimming (oral-anal contact) were collected, number of recent rimming partners was also significantly associated with oral HPV among HIV-negative MSM. However, the number of recent oral sex and rimming partners were highly correlated ($r = 0.65$). In contrast to that observed for recent sex behavior, *lifetime* oral sex behavior was associated with oral HPV prevalence in HIV-positive ($P_{trend} = 0.03$) but not in HIV-negative ($P_{trend} = 0.11$) individuals. Odds of oral HPV also increased significantly with older age among HIV-negative individuals (Table 3; $P_{trend} = 0.01$). Always using a condom during oral sex, race/ethnicity, cigarette smoking intensity and duration, and recent marijuana use were not associated with odds of oral HPV in HIV-positive or HIV-negative individuals (data not shown).

Severity of immunosuppression was the strongest risk factor for prevalent oral HPV among those with HIV (Fig. 1; Tables 3 and 4; $P_{trend} < 0.001$) including an association with lower current and nadir CD4 and higher HIV viral load (Table 3). Current CD4 was moderately correlated with current HIV viral load ($r = 0.48$) and with nadir CD4 ($r = 0.28$). However, when modeled together, current CD4 was a stronger predictor than either nadir CD4 or current HIV viral load (Supplementary Table S1). HIV-positive individuals with current CD4 > 500 remained at significantly increased odds of oral HPV (aOR = 1.6; 95% CI, 1.1–2.3) but had similar odds of HPV16 (aOR = 0.47; 95% CI, 0.16–1.4) compared with HIV-negative participants. Oral HPV prevalence was similar among HIV-positive HAART ever users and never users (42% vs. 34%, $P = 0.24$) and current HAART users and nonusers (43% vs. 34%, $P = 0.11$).

A strong dose response with lower current CD4 was observed among both HAART-naive ($P_{trend} = 0.03$) and HAART-experienced ($P_{trend} = 0.002$) individuals. This trend was especially strong for HPV16 infection where

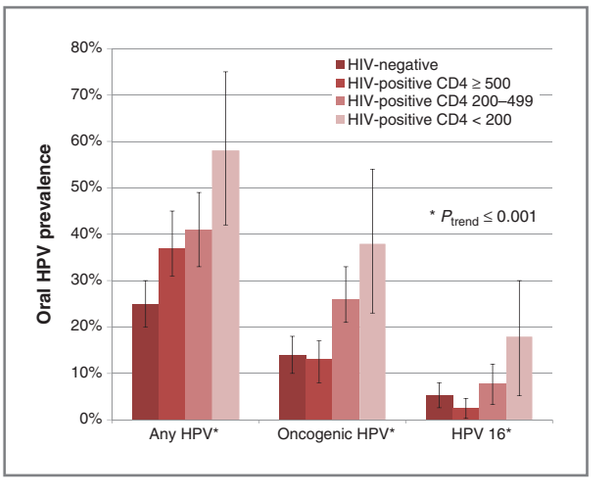

Figure 1. Oral HPV prevalence (unadjusted) by HIV status and current CD4 T-cell count among 379 HIV-positive individuals.

the median current CD4 was 238 cells/μL among those with HPV16 infection compared with 481 cells/μL among those infected with other HPV types ($P = 0.002$). The association between current CD4 and oral HPV16 was significantly stronger than the association of current CD4 with all other HPV types ($P = 0.02$). Contrasting individuals with current CD4 < 200 to HIV-positive individuals with current CD4 $\geq$ 500, the OR for HPV16 was more than 4-fold greater than the OR for all other HPV types (aOR = 4.5; 95% CI, 1.3–16).

When the study population was stratified by MACS/WIHS cohort, current CD4 remained influential among HIV-positive individuals in both cohorts, but there were differences by cohort in other risk factors. The associations of cigarette smoking and lifetime number of oral sexual partners with oral HPV prevalence were more notable among WIHS participants, whereas recent number of oral sex partners was more notable among MACS participants (Table 4).

Conclusions

The prevalence of oral HPV observed in this study is one of the highest ever reported in a non-cancer population. Specifically, this prevalence was higher than that reported in previous studies of HIV-positive (40% vs. 16%–37%; refs. 16, 17, 21, 22, 41) and HIV-negative (25% vs. 4%–18%; refs. 15, 19, 42–44) individuals. This may be explained, at least in part, by the older age and higher number of past and recent sexual partners of our population (45, 46). The findings suggest that the higher oral HPV prevalence among HIV-positive individuals is not fully explained by differences in sexual behavior and cigarette smoking. Indeed, after controlling for cigarette smoking and sexual behavior, odds of oral HPV remained significantly elevated in HIV-positive compared with HIV-negative individuals and were strongly associated with reduced current CD4. These findings are consistent with there being a strong independent association of HIV-related immunosuppression with the burden of oral HPV infection.

Risk factors for prevalent oral HPV infection differed among HIV-positive and HIV-negative individuals in this study. While odds of oral HPV infection were associated with *recent* number of oral sex partners in HIV-negative individuals, they were associated with *lifetime* number of oral sex partners and current CD4 in HIV-positive individuals. These differences are consistent with the hypothesis that prevalent oral HPV infections may represent primarily recently acquired infection among HIV-negative adults but in HIV-positive adults may be more likely to represent persistent or previously acquired reactivated oral HPV infections. The strong association between current CD4 and oral HPV prevalence in this study is consistent with previous research showing an association between immunosuppression and increased risk of *cervical* HPV persistence (27, 47, 48) and progression to cervical cancer (26, 49, 50). In longitudinal follow-up of this study population, we will explore whether HIV-related immunosuppression may have a similar effect on oral HPV natural history.

Our findings suggest that reduced current CD4 may have a stronger effect on oral HPV16 prevalence than other HPV types. This is in contrast to a previous study on cervical HPV in the WIHS which reported a weaker effect of reduced current CD4 on cervical HPV16 infection than on other cervical HPV types (39, 51). It is unclear whether there may be immunologic differences between the cervix and the oral cavity which might affect the relationship between CD4 and HPV type–specific clearance. Considering the relatively higher prevalence of oral HPV16 in this population (5.7%) and that HPV16 constitutes a larger percentage of HPV-positive oropharyngeal cancers than cervical cancers (1, 52), further exploration is warranted.

The significant association of recent oral sexual behavior with increased odds of oral HPV among HIV-negative participants in this study is consistent with several previous studies (19, 21, 41), although no association with oral sex was reported in one other recent study (53). To our knowledge, this is the first study to identify rimming (oral anal contact) as a potential transmitter of oral HPV. As anal HPV prevalence is high among MSM (54, 55), it is conceivable that rimming could lead to oral HPV exposure. However, while 32% of MACS participants reported rimming in the past 6 months, the behavior was highly correlated with oral sex behavior. Thus, it is difficult to determine whether there is an independent role for rimming in the transmission of oral HPV infection.

This study included participants from 2 high-risk cohorts, the MACS and the WIHS, with distinct study populations. While the findings were similar in the 2 cohorts, the associations between prevalent oral HPV with cigarette smoking and recent and lifetime sexual behavior differed between WIHS and MACS participants. Reasons for these differences are unclear and

Table 4. Multivariate risk factors for prevalent oral HPV infection among HIV-positive and HIV-negative subjects, stratified by study cohort (MACS men compared with WIHS women)

	aOR (95% CI)[c]			
	HIV-positive		HIV-negative	
Risk factors	**Men**	**Women**	**Men**	**Women**
Age, y				
<45	1	1	1	1
45–54	0.65 (0.39–1.5)	0.84 (0.48–1.5)	1.1 (0.43–2.6)	1.2 (0.37–3.9)
≥54	0.76 (0.43–1.3)	1.8 (1.0–3.4)	1.9 (0.74–4.7)	1.0 (0.20–5.6)
P_{trend}	0.44	0.03	0.07	0.31
Education				
Any college	1	1	1	1
High school degree	1.8 (0.81–4.0)	1.5 (0.75–3.1)	1.5 (0.42–5.3)	1.0 (0.25–4.1)
<High school degree	1.7 (0.73–3.9)	1.7 (0.94–3.1)	1.5 (0.44–4.8)	0.54 (0.15–1.9)
P_{trend}	0.02	0.07	0.20	0.38
Behavioral				
Smoked cigarettes in past 6 mo				
No (<1/d)	1	1	1	1
Yes	1.2 (0.73–2.0)	2.2 (1.4–3.7)	1.7 (0.84–3.5)	14 (3.2–64)
Consumed alcoholic drinks in past 6 mo				
No (<1/mo)	1	1		
Yes	0.76 (0.49–1.2)	0.95 (0.47–1.9)		
Sexual activity				
Number of oral sex partners in last 6 mo				
0	1	1	1	1
1	1.0 (0.55–1.8)	0.93 (0.48–1.8)	1.4 (0.57–3.3)	1.1 (0.33–3.8)
2–4	1.0 (0.57–1.9)	[a]	3.3 (1.6–6.8)	[a]
≥5	1.4 (0.74–2.5)	[a]	3.1 (1.5–6.3)	[a]
P_{trend}	0.75	0.31	0.005	[a]
Lifetime number of sex partners				
0–4	1	1	1	1
5–19	0.81 (0.32–2.1)	1.0 (0.55–1.8)	1.8 (0.48–6.4)	1.1 (0.32–3.6)
20–99	0.68 (0.22–2.1)	2.3 (1.4–3.9)[e]	1.0 (0.31–3.2)	1.5 (0.16–14)[e]
≥100	0.82 (0.26–2.6)		1.5 (0.46–4.7)	
P_{trend}	0.42[b]	<0.001[b]	0.16[b]	0.09[b]
Number of rimming partners in last 6 mo[d]				
0	1		1	
1	1.3 (0.75–2.1)		2.4 (1.1–5.0)	
2–4	1.0 (0.51–1.9)		2.7 (1.2–6.1)	
≥5	1.0 (0.31–2.9)		3.0 (1.5–5.9)	
P_{trend}	0.51		0.002	
HIV related				
Current CD4 T-cell count, cells/μL				
>500	1	1		
200–500	1.6 (0.93–2.8)	1.6 (0.92–2.6)		
<200	1.9 (1.1–3.4)	2.1 (1.2–3.6)		
P_{trend}	0.06	<0.001		

[a]These categories had <10 individuals and therefore were not included in the models.

[b]Lifetime oral sex partners P_{trend} excludes 46 individuals with >500 lifetime sex partners. When these individuals were included, P_{trend} is attenuated.

[c]Models adjusted for age, education, current cigarette use, number of recent and lifetime oral sex partners. HIV-positive models also adjusted for study site, current alcohol use, and current CD4 T-cell count.

[d]The data for rimming presented are in analysis among MACS participants only (as rimming was not measured in the WIHS) and number of recent oral sex partners was not adjusted for in this model as number of recent oral and rimming partners were strongly correlated ($r = 0.65$). Rimming was not adjusted for in other models presented in the table.

[e]Analyzed as 20 or more lifetime partners due to spare data.

may be explained by the small sample sizes in stratified analyses. Alternatively, the effects of cigarette smoking on oral HPV persistence, if any, may be small in comparison with the risk of new acquisition with sexual risk taking and might therefore be harder to observe in a population such as the MACS with high median number of sexual partners (and thus heavier HPV exposure) than in the WIHS. In addition, the impact of age- and tobacco-related immunosuppression may be expected to be less apparent among HIV-positive individuals, which might explain the lack of association among HIV-positive MACS participants, who were older and had lower nadir CD4 than WIHS participants. The higher number of lifetime sexual partners in the MACS may have led to saturation of risk that could explain why this association was significant in the WIHS but not in the MACS. The higher level of sexual risk taking in the MACS likely also explains why recent sexual behavior was more notable in the MACS than in the WIHS.

There are several limitations to this study. The HIV-positive and HIV-negative populations studied were selected because of their high risk and may not be representative of others in the general population. Second, while we report heterogeneity in some risk factors by HIV status and gender, some of these stratified analyses were underpowered. In addition, as oral HPV infection was only measured at one time point, we cannot differentiate between transient newly acquired infection and persistent or reactivated latent infections. Third, while oral HPV infections detected with the oral rinse have been strongly associated with odds of oropharyngeal cancer (3) and shown to have a higher DNA yield and quality than other oral sampling techniques such as focal brush sampling (56–58), oral rinse sampling cannot differentiate the site of infection, that is, oral cavity or oropharynx. Finally, while a strength of MACS and WIHS data is their extensive characterization of sexual risk behavior over time, each study relies upon self-reported data and missing values were imputed for lifetime number of oral sex partners which could lead to misclassification. Strengths of this study include the detailed biologic and behavioral data collected, the optimized oral rinse processing and HPV testing technique (35), and the inclusion of both HIV-positive and risk-matched HIV-negative individuals of both genders.

This study suggests that oral HPV infection is common in HIV-positive and at-risk HIV-negative women and MSM. HIV-positive individuals had a higher prevalence of oral HPV infection and different risk factors associated with infection than HIV-negative individuals. Whether HIV-related immunosuppression has an effect on oral HPV natural history, similar to that known for cervical HPV, will need to be explored longitudinally.

Disclosure of Potential Conflicts of Interest

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