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Oral human papillomavirus prevalence, persistence, and risk-factors in HIV-positive and HIV-negative adults

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ABSTRACT

Background: HIV has been shown to increase the likelihood of oral HPV infection. In this study, we evaluated the risk of oral HPV in HIV infected patients compared with HIV-negative controls.
Methods: 101 healthy adult volunteers (HIV-) and 245 adults living with HIV infection (HIV+) were recruited from 5 academic medical centers. Questionnaires and saliva samples were obtained every 3–8 months over a period of 2 years (2015–2017). DNA was isolated from the saliva samples and tested for 18 high- and low-risk genotypes.
Results: Oral HPV was detected in 23% of HIV + vs. 10% of HIV- participants ($p < 0.0001$). Men had a higher oral HPV prevalence than women (27% vs. 15% HIV+, $p = 0.03$, 16% vs. 5% HIV-, $p = 0.01$). Risk factors among HIV + participants included more lifetime deep kissing and oral sex partners, and history of AIDS. Persistent oral HPV was detected in 23% of HIV + vs. 5% of HIV- participants ($p < 0.001$). Among 8 HIV + participants with CD4 counts <200 cell/μL none had cleared their HPV infection during the study.
Conclusions: Risk of oral HPV infection and persistence was significantly higher in HIV + adults with a history of poorly controlled HIV, which may put them at increased risk of HPV-associated cancer.

1. Introduction

Oropharyngeal cancer caused by human papillomavirus (HPV) infection is now recognized as an increasing public health issue worldwide [1]. In the late 1980s, HPV was associated with only 16.3% of oropharyngeal cancers in the United States [2]. However, since the early 2000s that proportion has significantly increased to 71.7% [1]. Among high-income countries, 21,000 oropharyngeal cancers per year are estimated to be attributable to HPV [3]. Therefore, understanding the dynamics of HPV infection, risk of persistent infection, and potential for

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HPV prevention are critical to curtailing future oropharyngeal malignancies.

People living with HIV (PLWH) have greater prevalence of HPV infections and increased risks of HPV-related cancers [1,4]. The initial acquisition of HPV is related to sexual activity and is transmitted from one individual to another through contact with infected mucus membranes, similarly to HIV [5]. Men who have sex with men (MSM) have been shown to have a higher incidence of both anal HPV infection and anal cancers, relative to men who have sex with women [6,7]. In HIV-infected women, the risk and burden of cervical cancer associated with HPV infection is increased relative to HIV-negative women [8]. However, the risk factors for acquisition of oral HPV in the oropharynx, oral HPV incidence in HIV infected individuals, as well as HPV viral dynamics among PLWH compared to HIV- individuals, are less well understood. In a study of patients seeking dental care, 32% of HIV infected patients had HPV detected in oral rinse samples compared to 16% of non-HIV infected patients [9], and more high-risk HPV subtypes were detected in the HIV group, and a lower $CD4^+$ T-cell count was linked to HPV detection. HPV infections are often eradicated by the host immune system over a period of 1–2 years [10,11]. However, in HIV-infected individuals, particularly those with immune dysfunction, the ability to clear the HPV virus is impaired [12,13]. This inability to clear HPV leads to both persistence of the HPV infection and an increased risk for progression to malignancy. Therefore, more work is needed to better understand the impact of HIV on HPV infection and persistence in the oropharynx.

In this study, we sought to further understand two questions: 1) What are the risk factors for acquisition of HPV in the oral cavity among PLWH, and 2) what are the dynamics of oral HPV persistence in PLWH compared with non-HIV infected individuals? By improving our understanding of oral HPV infection in this high-risk group, we hope to broaden our understanding of the nature and magnitude of the risk of HPV-associated disease risk and develop appropriate screening approaches for this vulnerable population.

2. Methods

2.1. Participants

Healthy volunteers (HIV-) and HIV infected patients (HIV+) were recruited in 2015–2017 from five institutions: Montefiore Medical Center/Albert Einstein College of Medicine (The Bronx, NY; HIV+ and HIV-), Emory University (Atlanta, GA; HIV-), Johns Hopkins University (Baltimore, MD; HIV+ and HIV-), University of Michigan (Ann Arbor, MI; HIV+ and HIV-), and University of Pittsburg (Pittsburgh, PA; HIV+). Participants from HIV+ and HIV- populations were drawn from convenience samples and not matched on demographic characteristics. To qualify, volunteers needed to be 18 years or older and willing to return for follow up intervals of 3–4 months over a period of 2 years. Participants were excluded from analysis from the HIV infected group if they did not have an HIV diagnosis documented in the medical record. Healthy volunteers required a self-reported confirmation of being HIV-. Others were excluded if they had a history of head and neck cancer or did not have at least one valid HPV test.

The primary site for this investigation was the University of Michigan (UM). The study was approved by the UM Institutional Review Board (IRBMED, HUM00103999) as well as the IRBs at each participating institution. A separate but coordinated study enrolling HIV- participants at UM using the same instruments and protocols was also approved by IRBMED (HUM00090326). Informed consent was obtained from all volunteers prior to enrollment in the study.

2.2. Data collection

Participants were followed every 3–4 months for up to two years after their baseline visit (maximum of 8 study visits). Participants were not excluded for missed follow up visits. All study participants completed a comprehensive questionnaire at baseline and an abbreviated questionnaire at all subsequent follow-up visits. The questionnaire covered topics related to demographic information; alcohol, cigarette, and other substance use; and sexual behavior, sexual history, and healthcare history. Although participants were asked to report their HPV vaccination status, the answers in many cases were not consistent with clinical age recommendations, suggesting that many participants may have misinterpreted the question. Accordingly, participant self-reported HPV vaccination status was not included in this analysis. The questionnaire was administered electronically via Qualtrics either on-site with study staff or offsite with access to remote assistance. Volunteers were free to skip or otherwise not answer any question.

2.3. Saliva sample collection, processing, and analysis

Approximately 2 mL of saliva/oral rinse were collected at each visit (baseline and every 3–4 months for 2 years) using Oragene RE-100 kits (DNAgenotek, Ottawa, Ontario, Canada) [14] or Scope-brand mouthwash (Proctor & Gamble, Cinncinnati,OH, USA) [15]. Participants used a sweetener or candy to stimulate saliva production if needed. The study coordinators reviewed the charts of HIV + participants to obtain and record T-cell subset counts, adherence to antiretroviral therapy (ART), overall health status, and other related questions at each visit.

To isolate DNA from the saliva and oral rinse specimens, the sample was heated to 50 °C for 60 min, and 1/25th volume of prepIT-L2P (DNA Genotek) was added. The sample was incubated for 10 min at 4 °C and centrifuged for 20 min at 4100 rpm. The supernatant was then added to an equal volume of 95% ethanol to precipitate the DNA. The DNA was pelleted, washed with 200 μL of 70% ethanol and dried. The DNA pellet was rehydrated with Tris-EDTA buffer and quantified with picogreen (Invitrogen P11496) or the QuBit Fluorometer (Invitrogen Q32850).

DNA samples were assayed using a previously described highly sensitive method [17]. Briefly, multiplex competitive PCR amplification of the heterogeneous E6 region was performed for 15 discrete high-risk (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68, 73), one potentially high-risk (90), and 2 low-risk (6, 11) HPV types, followed by probe-specific single base extension. Extension products were loaded onto a matrix silicon chip array and separated by size using matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectroscopy, allowing detection of any HPV types present in the sample. Samples were run in quadruplicate with appropriate controls.

2.4. Data management and statistical analysis

Study data were stored and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at UM with appropriate security protocols [16]. REDCap is a secure, Health Insurance Portability and Accountability Act (HIPAA)-compliant, web-based application designed to support data capture for research studies.

Demographic and behavioral characteristics of the HIV+ and HIV- populations were examined overall and compared by stratifying by sex. We tested for differences in the distributions of categorical variables between the HIV+ and HIV- populations using chi-square tests. HIV-related characteristics were assessed for the HIV + population. We determined oral HPV prevalence and prevalence ratios among valid tests at baseline using univariable and bivariable (adjusting for sex) log-binomial regression models for the HIV+ and HIV- populations separately. The level of significance was $\alpha = 0.05$ based on two-tailed tests.

Markov multistate transition modeling was used to estimate the incidence and clearance rate for oral HPV in the HIV+ and HIV- populations separately across all study visits. These models were continuous-time, finite-state stochastic processes that assume that the transition hazard rate depends on one's current state but not on one's history (i.e., it is assumed that previous infection did not increase the likelihood of future infection) [18]. Infection and clearance occur at any

time, but we could observe everyone's state only at certain points in time. As such, for a given rate of infection and clearance, we calculated the probability of each individual's observed trajectory for each genotype. For example, an individual who is positive for HPV 16 at one visit, HPV 16 and 18 at the next visit, and then only HPV 18 at the following visit is considered to have experienced an incident infection and a clearance, despite remaining HPV positive in all visits. By maximizing this probability as a function of the infection and clearance rates, we estimated best-fit rates. We determined hazard ratios for incidence and clearance based on HIV characteristic in univariable and bivariable (adjusting for sex) models. Persistence was defined as two consecutive visits with the same HPV genotype detected, regardless of the specific time between them. Data were analyzed in R 4.0 (R Foundation for Statistical Computing; Vienna, Austria), and the multistate transition models were implemented with the *msm* package [19].

3. Results

3.1. Demographic, behavioral, and HIV characteristics

We included 245 HIV+ and 198 HIV- participants in this analysis. The HIV+ and HIV- populations were significantly different in the distribution of most demographic and behavioral characteristics (Table S1). The HIV + population had a greater proportion of male, non-White participants with an educational attainment of high school or less, who had never been married or partnered, were current smokers of tobacco or marijuana, had had sex with both men and women, had fewer lifetime vaginal sex partners (but used condoms more frequently), and had more lifetime oral and anal sex partners (and used condoms more frequently) than the HIV- population. The HIV + group was also more likely to report ever being diagnosed with a sexually transmitted infection (STI) other than HIV or HPV.

Clinical characteristics of the HIV + population are given in Supplementary Table S2. The majority of HIV + participants had never been diagnosed with AIDS (59%), had $CD4^+$ T-cell counts greater than 500 cells/μL (67%), and had HIV viral loads below 200 copies/mL (89%). Almost all were receiving antiretroviral treatment (ART) (97%) with fewer than 20% documented with poor adherence. Only 13% had a previously documented opportunistic infection.

3.2. HPV prevalence

The HIV + population had a higher prevalence of any tested HPV genotype (23%) at baseline than the HIV- population (10%) ($p < 0.0001$, Table 1). There was a large difference in prevalence by sex between both groups; the HPV prevalence was higher in men in both populations (27% vs. 15%, $p = 0.03$ for HIV+; 16% vs. 5% for HIV-, $p = 0.01$). Prevalence estimates varied depending on the genotypes included. Notably, HIV + participants had a greater prevalence of high-risk genotypes, both those covered by currently available vaccines and those not covered by currently available vaccines (Table S3). The likelihood of coinfection (i.e., concurrent detection of more than one HPV genotype) was 38% in HIV + participants and 11% in HIV- participants, but the difference did not reach the level of significance due to the small absolute number of HIV- participants that were HPV+ ($p = 0.06$).

Among the HIV + population, HPV prevalence was significantly higher among men, those currently not using alcohol, and those with 6 or more lifetimes kissing or oral sex (giving or receiving) partners (Table 2). The latter two did not reach significance when adjusting for gender but were still positively associated. HPV prevalence was also higher among those ever diagnosed with AIDS (Table 3). HPV prevalence was also non-significantly higher among those with a lower educational attainment, those who always used condoms during oral or anal sex (possibly related to confounding with number of sexual partners or other sexual behaviors), those with 6 or more anal sex partners, and those reporting a prior STI diagnosis.

Among the HIV- population, HPV prevalence was significantly higher among men, those with a high school diploma or less (albeit not significant after adjusting for sex), and those with 6 or more vaginal sex partners. HPV prevalence was significantly lower among both HIV+ and HIV- women who had sex with men compared to those who had sex with both men and women. HPV prevalence did significantly differ between the recruitment sites, but we did not have the statistical power to account for recruitment site in multivariable models. Selected demographic and behavioral characteristics by recruitment site are included in the supplemental material (Tables S4 and S5).

3.3. HPV incidence and clearance

There was substantial loss-to-follow-up after the first visit (45% of

Table 1
Oral HPV prevalence (among valid tests at baseline) by HIV status and sex. The male and female columns may not add up to the total because of participants who indicated "other" sex or did not answer. The p-value is for the test of proportions between all HIV+ and all HIV- individuals, except for the number of genotypes, which is for a chi-square test. Genotype-specific prevalence is included in the supplementary material (Table S5).

	HIV + (N = 245)						HIV -(N = 198)						p-value
	All (N = 245)		Male (N = 155)		Female (N = 86)		All (N = 198)		Male (N = 83)		Female (N = 115)		
	% HPV+	N	% HPV+	N	% HPV+	N	% HPV+	N	% HPV+	N	% HPV+	N	
Any tested: 6, 11, 16, 18, 31, 33, 35 39, 45, 51, 52, 56, 58, 59, 66, 68, 73, 90	23%	56	27%	42	15%	13	10%	19	16%	13	5%	6	< **0.001**
Number of genotypes detected in same saliva sample													0.06
1 genotype	14%	35	17%	27	8%	7	9%	17	14%	12	4%	5	
2 or more genotypes	9%	21	10%	15	7%	6	1%	2	1%	1	1%	1	
Clinical test high-risk: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68	18%	44	23%	35	9%	8	7%	13	12%	10	3%	3	< **0.001**
IARC Group 1 and 2A: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68	16%	38	20%	31	8%	7	5%	9	8%	7	2%	2	< **0.001**
Gardasil 9 vaccine genotypes: 6, 11, 16, 18, 31, 33, 45, 52, 58	15%	37	19%	29	9%	8	6%	11	10%	8	3%	3	**0.001**
Gardasil 9 vaccine high-risk genotypes: 16, 18, 31, 33, 45, 52, 58	11%	28	15%	23	6%	5	4%	7	7%	6	1%	1	**0.002**
Non-vaccine high risk genotypes: 35, 39, 51, 56, 59, 66, 68	10%	25	13%	20	5%	4	4%	7	6%	5	2%	2	**0.007**
Gardasil vaccine genotypes: 6, 11, 16, 18	10%	25	12%	19	7%	6	5%	10	8%	7	3%	3	**0.05**
Genotypes 16, 18	7%	16	8%	13	3%	3	3%	6	6%	5	1%	1	0.09
Genital warts genotypes: 6, 11	5%	12	5%	8	5%	4	2%	4	2%	2	2%	2	0.11

Table 2
HPV prevalence and prevalence ratio (PR) for any tested genotype in the oral cavity (among valid tests at baseline) by participant characteristic. Bivariable models adjust for sex as well as the given variable. Bold values are associated with confidence intervals that do not contain 1. Abbreviations: MSM, men who have sex with men; MSW, men who have sex with women; MSMW, men who have sex with men and women; WSM, women who have sex with men; WSW, women who have sex with women; WSMW, women who have sex with men and women.

	HIV+ (N = 245)						HIV- (N = 101)					
	% HPV+	N HPV+/ N	Univariable		Bivariable		% HPV+	N HPV+	Univariable		Bivariable	
			PR	95% CI	PR	95% CI			PR	95% CI	PR	95% CI
Demographics												
Sex												
Male	27.1%	42/155	1.0	(ref)	–	–	15.7%	13/83	1.0	(ref)	–	–
Female	15.1%	13/86	**0.56**	**(0.31, 0.98)**	–	–	5.2%	6/115	**0.33**	**(0.13, 0.84)**	–	–
Age												
18-29	28.6%	4/14	1.0	(ref)	1.0	(ref)	7.1%	1/14	1.0	(ref)	1.0	(ref)
30-49	21.1%	19/90	0.74	(0.29, 1.85)	1.01	(0.35, 2.91)	10.5%	9/86	1.47	(0.20, 10.7)	1.46	(0.21, 10.3)
50+	23.4%	33/141	0.82	(0.33, 1.98)	1.14	(0.41, 3.17)	9.2%	9/98	1.29	(0.18, 9.39)	1.48	(0.21, 10.4)
Race												
White	19.4%	13/67	1.0	(ref)	1.0	(ref)	9.4%	9/96	1.0	(ref)	1.0	(ref)
Black	21.1%	22/204	1.09	(0.59, 2.01)	1.32	(0.71, 2.46)	4.5%	2/44	0.48	(0.11, 2.15)	0.45	(0.10, 1.09)
Hispanic	26.9%	7/26	1.39	(0.62, 3.09)	1.36	(0.59, 3.13)	25.0%	5/20	2.67	(0.12, 7.11)	2.27	(0.87, 5.91)
Educational attainment												
High school or less	26.2%	27/103	1.0	(ref)	1.0	(ref)	17.9%	7/39	1.0	(ref)	1.0	(ref)
Some college or AA degree	22.7%	17/75	0.86	(0.51, 1.46)	0.77	(0.45, 1.31)	7.0%	3/43	0.39	(0.10, 1.40)	0.52	(0.14, 1.90)
College or postgraduate degree	16.3%	8/49	0.62	(0.31, 1.27)	0.55	(0.27, 1.12)	6.5%	7/108	**0.36**	**(0.14, 0.96)**	0.51	(0.19, 1.35)
Recruitment site												
Albert Einstein College of Medicine	24.1%	20/83	1.60	(0.86, 2.96)	**1.88**	**(1.01, 3.50)**	15.7%	8/51	1.94	(0.77, 4.87)	1.78	(0.72, 4.42)
Emory University	–	–	–	–	–	–	5.7%	2/35	0.71	(0.16, 3.17)	0.76	(0.18, 3.32)
John Hopkins University	35.6%	16/45	**2.36**	**(1.27, 4.40)**	**2.87**	**(1.55, 5.31)**	7.7%	1/13	0.95	(0.13, 7.01)	0.67	(0.09, 4.94)
University of Michigan	15.1%	14/93	1.0	(ref)	1.0	(ref)	8.0%	8/99	1.0	(ref)	1.0	(ref)
University of Pittsburgh	25.0%	6/24	1.66	(0.71, 3.86)	1.81	(0.79. 4.15)	–	–	–	–	–	–
Marital status												
Married or living with partner	20.0%	15/75	0.83	(0.47, 1.49)	0.83	(0.46, 1.49)	7.3%	7/96	0.86	(0.29, 2.58)	0.93	(0.31, 2.77)
Never married/partnered	24.0%	23/96	1.0	(ref)	1.0	(ref)	8.4%	5/59	1.0	(ref)	1.0	(ref)
Separated/divorced/widowed	26.0%	13/50	1.08	(0.60, 1.95)	1.22	(0.68, 2.19)	14.3%	5/35	1.69	(0.52, 5.41)	1.79	(0.57, 5.64)
Substance use												
Alcohol use												
Never or former user	30.3%	30/99	1.0	(ref)	1.0	(ref)	7.5%	5/67	1.0	(ref)	1.0	(ref)
Current users	17.5%	21/120	**0.58**	**(0.35, 0.94)**	**0.53**	**(0.32, 0.86)**	9.1%	11/121	1.22	(0.44, 3.35)	1.41	(0.52, 3.84)
Tobacco use												
Never smoker	19.2%	14/73	1.0	(ref)	1.0	(ref)	4.8%	4/83	1.0	(ref)	1.0	(ref)
Former smoker	22.8%	13/57	1.19	(0.61, 2.33)	1.18	(0.61, 2.27)	9.9%	7/71	2.05	(0.62, 6.70)	2.09	(0.65, 6.77)
Current smoker	23.5%	20/85	1.23	(0.67, 2.25)	1.19	(0.65, 2.18)	15.6%	5/32	3.24	(0.93, 11.3)	2.45	(0.70, 8.56)
Marijuana use												
Never user	25.3%	19/75	1.0	(ref)	1.0	(ref)	4.0%	3/75	1.0	(ref)	1.0	(ref)
Former user	21.6%	18/83	0.86	(0.49, 1.50)	0.79	(0.45, 1.40)	8.9%	7/79	2.22	(0.59, 8.25)	2.50	(0.68, 9.21)
Current user	21.4%	12/56	0.85	(0.45, 1.60)	0.82	(0.43, 1.53)	16.0%	4/25	4.00	(0.96, 16.7)	3.74	(0.90, 15.6)
Sexual behavior												
Sexual partners												
MSM	27.7%	13/34	**6.22**	**(1,48, 26.0)**	–	–	0.0%	0/9	0.0	–	–	–
MSW	33.3%	10/20	**7.50**	**(1.77, 31.8)**	–	–	14.0%	7/43	**5.53**	**(1.20, 25.6)**	–	–
MSMW	25.5%	12/25	**5.74**	**(1.36, 24.2)**	–	–	15.4%	2/11	6.08	(0.94, 39.4)	–	–
WSM	4.4%	2/43	1.0	(ref)	–	–	2.5%	2/77	1.0	(ref)	–	–
WSMW	37.5%	6/10	**8.44**	**(1.89, 37.6)**	–	–	19.0%	4/17	**7.5**	**(1.48, 38.3)**	–	–

(*continued on next page*)

Table 2 (*continued*)

	HIV+ (N = 245)						HIV- (N = 101)					
	% HPV+	N HPV+/ N	Univariable		Bivariable		% HPV+	N HPV+	Univariable		Bivariable	
			PR	95% CI	PR	95% CI			PR	95% CI	PR	95% CI
Circumcised (male only)												
No	31.2%	20/64	1.0	(ref)	–	–	19.4%	6/31	1.0	(ref)	–	–
Yes	23.7%	18/76	0.76	(0.44, 1.30)	–	–	12.0%	6/50	0.62	(0.22, 1.75)	–	–
Circumcised partner												
Never	13.1%	8/61	1.0	(ref)	1.0	(ref)	6.2%	4/65	1.0	(ref)	1.0	(ref)
Ever	24.3%	25/103	1.85	(0.89, 3.84)	1.52	(0.70, 3.28)	5.3%	3/57	0.86	(0.20, 3.66)	0.81	(0.19, 3.46)
Lifetime number of kissing partners												
0-5	12.1%	7/58	1.0	(ref)	1.0	(ref)	7.0%	4/57	1.0	(ref)	1.0	(ref)
≥ 6	28.2%	29/103	**2.33**	**(1.09, 4.99)**	2.02	(0.94, 4.33)	9.2%	9/98	1.31	(0.42, 4.06)	1.25	(0.41, 3.82)
Lifetime number of vaginal sex partners												
0-5	23.9%	33/138	1.0	(ref)	1.0	(ref)	2.1%	2/97	1.0	(ref)	1.0	(ref)
≥ 6	19.4%	15/77	0.81	(0.47, 1.40)	0.95	(0.55, 1.66)	15.7%	14/89	**7.63**	**(1.78, 32.6)**	**7.84**	**(1.84, 33.4)**
Condom use during vaginal sex												
Rarely or never	14.3%	4/28	0.65	(0.23, 1.81)	0.64	(0.23, 1.77)	7.4%	5/68	1.14	(0.23, 5.55)	1.12	(0.23, 5.42)
Most to some of the time	21.6%	11/51	0.99	(0.49, 1.98)	1.02	(0.51, 2.03)	13.8%	9/65	2.15	(0.49, 9.35)	1.94	(0.45, 8.34)
All the time	21.8%	15/64	1.0	(ref)	1.0	(ref)	6.5%	2/31	1.0	(ref)	1.0	(ref)
Lifetime number of oral sex partners (performing)												
0-5	17.0%	17/100	1.0	(ref)	1.0	(ref)	7.0%	8/114	1.0	(ref)	1.0	(ref)
≥ 6	28.7%	33/115	**1.69**	**(1.00, 2.83)**	1.39	(0.80, 2.42)	11.4%	8/70	1.63	(0.64, 4.14)	1.44	(0.57, 3.63)
Lifetime number of oral sex partners (receiving)												
0-5	15.4%	15/97	1.0	(ref)	1.0	(ref)	6.3%	7/111	1.0	(ref)	1.0	(ref)
≥ 6	29.1%	34/117	**1.88**	**(1.09, 3.24)**	1.60	(0.91, 2.84)	12.3%	9/73	1.95	(0.76, 5.01)	1.59	(0.62, 4.07)
Condom use during oral sex												
Rarely or never	19.4%	21/108	0.64	(0.34, 1.22)	0.48	(0.26, 0.88)	9.9%	13/131	0.59	(0.15, 2.33)	0.47	(0.14, 1.59)
Most to some of the time	18.2%	6/33	0.60	(0.25, 1.46)	0.53	(0.23, 1.23)	16.7%	2/12	1.0	(ref)	1.0	(ref)
All the time	30.3%	10/33	1.0	(ref)	1.0	(ref)	0.0%	0/7	0.0	–		
Lifetime number of anal sex partners												
0-5	17.4%	16/92	1.0	(ref)	1.0	(ref)	6.6%	9/136	1.0	(ref)	1.0	(ref)
6+	27.2%	22/81	1.56	(0.88, 2.76)	1.06	(0.54, 2.08)	7.1%	1/14	1.08	(0.15, 7.91)	0.72	(0.09, 5.6) 0
Condom use during anal sex												
Rarely or never	17.4%	8/46	0.51	(0.24, 1.09)	0.47	(0.21, 1.04)	8.5%	3/35	0.90	(0.16, 4.95	1.08	(0.19, 6.09)
Most to some of the time	20.5%	8/39	0.60	(0.28, 1.27)	0.56	(0.27, 1.19)	9.5%	2/21	1.0	(ref)	1.0	(ref)
All the time	34.1%	14/41	1.0	(ref)	1.0	(ref)	0.0%	0/16	0.0	–		
Prior STI diagnosis												
No	19.6%	21/107	1.0	(ref)	1.0	(ref)	7.8%	12/153	1.0	(ref)	1.0	(ref)
Yes	25.4%	35/138	1.29	(0.80, 2.09)	1.27	(0.79, 2.04)	15.6%	7/45	1.98	(0.83, 4.74)	1.80	(0.77, 4.23)

the HIV+ and 35% of the HIV- participants). We have provided the characteristics of the study populations completing at least 2 visits in Table S6. Among the HIV + population, 134 individuals had ≥2 visits with valid HPV tests, with a mean number of completed visits of 2.9 and a median of 183 days between visits. Among the HIV- population, 128 individuals had a mean of 4.7 visits and a median of 112 days between visits. There were significantly ($p < 0.001$) more individuals with a persistent HPV dynamic between a pair of visits among the HIV+ (35 of 135; 26%) than among the HIV- group (5 of 123; 4%). We present alluvial plots illustrating the change in participant oral HPV status between adjacent visits in Fig. 1. Note that these plots denote any HPV infection, whereas the incidence and clearance results treat each genotype as independent. Visually, we see more persistence between visits among the HIV + population than among the HIV- population. Controlling for the potential effects of sex on incidence and clearance (which were not significant), the HPV clearance rate was significantly lower among the HIV + population (HR 0.20; 95% CI: 0.11, 0.36), but the increase in incidence in the HIV + population was not (HR 1.42; 95% CI: 0.83, 2.43). We estimated the mean time to clearance in the HIV + population was 473 days (95% CI: 336, 664), equating to about 53% (95% CI: 42%, 65%) of infections clearing within one year. For the HIV- population, the mean time to clearance was 97 days (95% CI: 62, 151), such that 97% of infections (95% CI: 91%, 99%) cleared within one year. The most common persistent genotypes among the HIV + individuals were 16, 56, 39, and 66. The persistent genotypes among the HIV- individuals were 16, 18, 35, 52, and 66. HPV 16, which is the most common genotype to cause head and neck cancers, was found in 4% (10/245) of those who were HIV+ and 1% (2/198) in those who were HIV- (Table S5).

The hazard ratios for oral HPV incidence by HIV characteristic were suggestive but did not always reach significance because of the lower numbers of individuals in certain categories (Table 4). Those diagnosed with AIDS had a non-significantly lower clearance rate and significantly higher incidence rate of oral HPV infection compared to those never diagnosed with AIDS. The clearance rate among those with AIDS was also lower, though this observation was not statistically significant.

Table 3
HPV prevalence and prevalence ratio (PR) for any tested genotype in the oral cavity (among valid tests at baseline) by HIV characteristic. Bivariable models adjust for sex as well as the given variable. Bold values are associated with confidence intervals that do not contain 1.

	Prevalence (N = 245)					
	% HPV+	N HPV+	Univariable		Bivariable	
			PR	95% CI	PR	95% CI
Diagnosed with AIDS						
No	17.1%	24/140	1.0	(ref)	1.0	(ref)
Yes	30.3%	30/99	**1.77**	**(1.10, 2.83)**	**1.67**	**(1.04, 2.68)**
CD4 count (cells/uL)						
<200	30.4%	7/23	1.48	(0.74, 2.93)	1.41	(0.72, 2.72)
200-499	27.8%	15/54	1.35	(0.80, 2.28)	1.28	(0.76, 2.17)
≥ 500	20.6%	34/165	1.0	(ref)	1.0	(ref)
HIV viral load (copies/mL)						
<200	21.9%	48/219	1.0	(ref)	1.0	(ref)
≥200	33.3%	8/24	1.52	(0.82, 2.82)	1.61	(0.89, 2.88)
Non-adherence in the past year						
No	21.8%	41/188	1.0	(ref)	1.0	(ref)
Yes	29.3%	12/41	1.34	(0.78, 2.32)	1.38	(0.81, 2.36)
Opportunistic infection						
No	21.7%	44/203	1.0	(ref)	1.0	(ref)
Yes	19.4%	6/31	0.89	(0.42, 1.92)	0.91	(0.43, 1.94)

Similarly, those with $CD4^+$ counts <200 cells/μL were found to have a higher incidence and no clearance events, although the number of individuals in this category was small and the differences compared to those with $CD4^+$ counts >200 cells/μL did not reach the threshold for significance. Out of these 10 individuals with at least two valid visits, 8 were HPV infected at some point during the study, and none cleared their infection during the study period, so that the clearance hazard ratio was not distinguishable from 0. A higher HIV viral load was associated with a significantly increased incidence rate and lower clearance rate that did not reach statistical significance. Non-significant increases in incidence and decreases in clearance were also observed with higher viral load and non-adherence to ART.

4. Discussion

In this multicenter study conducted at five large academic health centers in the U.S., we observed significant differences in prevalence of oral HPV infection among HIV + patients compared to HIV- healthy volunteers. Overall, the prevalence of HPV in oral saliva samples from HIV + individuals was approximately twice that of HIV- individuals. The increase in prevalence among those with HIV extended to high-risk types associated with increased cancer risk, including those high-risk HPV types not targeted by the 9-valent, recombinant HPV vaccine (i.e., HPV 35, 39, 51, 56, 59, 66, 68). Based on these data, this group of patients is likely at higher risk for the development of oropharyngeal cancer and may benefit from intensified cancer screening or surveillance.

Among HIV + individuals, immune dysfunction, reflected by a $CD4^+$ T-cell count <200 cells/μL or HIV viral load ≥200 copies/mL, was associated with higher prevalence, incidence, and persistence of oral HPV, albeit not always significantly so. Immune dysfunction, non-adherence to ART, and a history of AIDS were also consistently associated with longer time to clearance of oral HPV, even if not reaching significance. Of note, no clearance events were observed in the small number of participants in the HIV + group with $CD4^+$ <200 cells/μL.

Our findings are consistent with prior studies, which suggest that while the majority of oral HPV infections are cleared quickly (within 6–12 months) through immune system activation, mechanisms of immune system evasion and the lack of a robust immune response in HIV + individuals may allow some HPV infections to persist for more prolonged periods of time [9,13,20–22]. Here, the modeled mean time to clearance was 3–4 months for the HIV- population and about 16 months for the HIV + population. Immune modulation associated with HIV infection, which includes the depletion of $CD4^+$ T cells and lack of cytotoxic T-cell response to the oncogenes E6 and E7 in HPV infection, may lead to decreased clearance of oral HPV [23,24].

In addition to HIV status, we observed significantly higher prevalence of oral HPV among men vs. women, irrespective of HIV serostatus. Data from HIV- participants in the National Health and Nutrition Examination Survey (NHANES) has shown that men were more likely to have an oral HPV infection than women, independent of other risk factors, including number of sex partners and tobacco smoking [15, 25–27]. Reports describing HIV + individuals have also found a higher

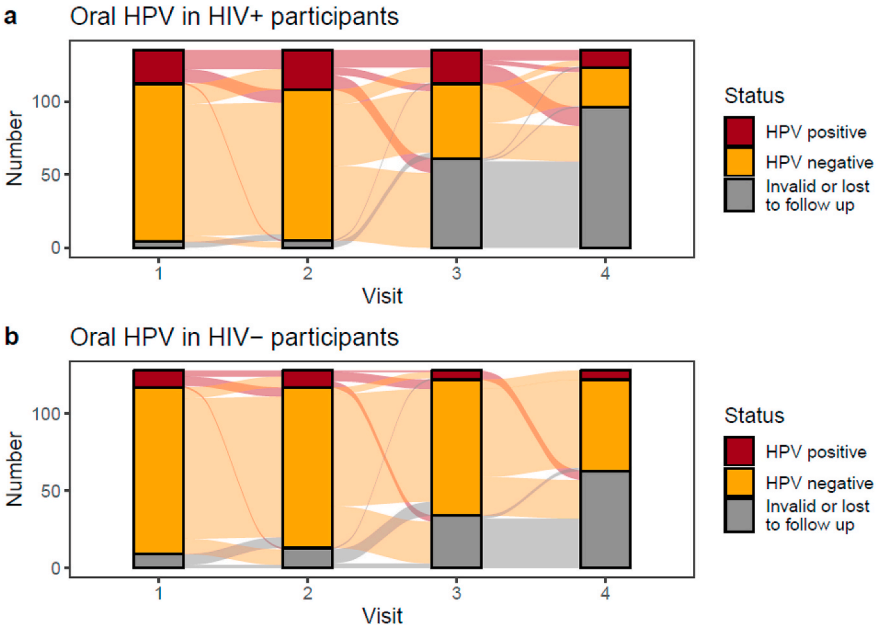

Fig. 1. Alluvial plots denote transitions in oral HPV infection status (any genotype) over the first four study visits in a) HIV+ and b) HIV- participants who had at least 2 valid HPV tests before loss to follow up or completion of 4th visit.

Table 4
Empirical HPV incidence and clearance rates and model-based incidence and clearance hazard ratios (HR) for any tested genotype in the oral cavity by HIV characteristic over the study period. Bivariable models adjust for sex as well as the given variable. Bold values are associated with confidence intervals that do not contain 1.

	N with longitudinal data	Incidence (per 100,000 person-days)	Univariable incidence		Bivariable incidence		Clearance (per 100,000 person-days)	Univariable clearance		Bivariable clearance	
			HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI
Diagnosed with AIDS											
No	84	3.4	1.0	(ref)	1.0	(ref)	187.9	1.0	(ref)	1.0	(ref)
Yes	46	7.4	**1.96**	**(1.04, 3.68)**	**1.98**	**(1.05, 3.70)**	144.3	0.64	(0.31, 1.33)	0.71	(0.33,1.54)
CD4 count (cells/uL)											
<200	10	10.0	1.66	(0.69, 3.99)	1.61	(0.67, 3.89)	0.0	0.0	–	0.0	–
200-499	21	5.8	1.32	(0.61, 2.87)	1.22	(0.56, 2.65)	183.0	1.08	(0.61, 2.87)	0.89	(0.38, 2.05)
≥ 500	101	4.5	1.0	(ref)	1.0	(ref)	170.3	1.0	(ref)	1.0	(ref)
HIV viral load (copies/mL)											
<200	121	4.5	1.0	(ref)	1.0	(ref)	172.3	1.0	(ref)	1.0	(ref)
≥200	11	12.2	**2.15**	**(1.02, 4.52)**	**2.15**	**(1.03, 4.51)**	44.8	0.17	(0.02, 1.27)	0.15	(0.02, 1.12)
Non-adherence in the past year											
No	107	4.6	1.0	(ref)	1.0	(ref)	174.3	1.0	(ref)	1.0	(ref)
Yes	20	8.6	1.54	(0.75, 3.16)	1.54	(0.75, 3.16)	76.7	0.35	(0.11, 1.17)	0.34	(0.10, 1.13)
Opportunistic infection											
No	119	4.9	1.0	(ref)	1.0	(ref)	161.8	1.0	(ref)	1.0	(ref)
Yes	11	7.8	1.58	(0.63, 4.01)	1.57	(0.62, 3.94)	142.2	1.17	(0.29, 4.72)	1.20	(0.29, 4.88)

prevalence of oral HPV in men vs. women [9,28] and among men who have sex with women (MSW) vs. MSM only [20,22,29,30], suggesting the importance of vaginal-to-oral transmission. It is also postulated that a significant number of women may have increased natural immunity from repeated cervicovaginal exposure to HPV leading to lower risk of oral HPV [26,27,31].

Our data support oral sexual transmission as a primary model for oral HPV acquisition [32–35], with increased odds of oral HPV among HIV+ and HIV- adults with ≥6 vs. <6 lifetime oral sex partners, although these findings did not remain significant after adjustment for sex. In addition, we observed an increased risk of oral HPV with ≥6 vs. <6 lifetime deep kissing partners among HIV + individuals before adjustment by gender. Women who had sex with men and women (WSMW) were significantly more likely to have oral HPV than women who had only had sex with men (WSM). There were no statistically significant differences among MSM, MSW, and MSMW.

Active tobacco use has previously been shown to be associated with oral HPV infection among HIV + individuals, with positive associations seen with higher cumulative pack years and number of packs each day [5,20,36]. However, an association with history of tobacco smoking was not confirmed in the current study, where the odds of oral HPV were not significantly higher for current or former tobacco users compared to never users among either HIV + or HIV- individuals. A previous study also found no relationship between smoking intensity or duration and detection of oral HPV in both HIV+ and HIV- individuals [28]. Although we did observe an independent association with alcohol for HPV-positive oropharyngeal cancer in a hospital-based case-control study of HIV- patients [37], we did not see an association between alcohol and risk of oral HPV among HIV+ (or HIV-) non-cancer patients in the separate study [9]. Here, we observed significantly lower odds of oral HPV with recent alcohol use among HIV + individuals. However, our result may be the result of confounding by study site (Table S3: The University of Michigan HIV + population had the highest current alcohol use and the lowest prevalence of oral HPV). We also could not exclude the possibility of confounding for other risk factors such as sexual activity and tobacco smoking.

There are several limitations to consider in the interpretation of our results. First, we used a convenience sample rather than a case-control study design, so that the HIV+ and HIV- groups differed in many relevant variables. Thus, because the sample sizes precluded concurrent adjustment for multiple covariates such as tobacco smoking, sexual activity, and immune status, our results may be confounded by unadjusted risk factors. Second, since our main analyses were cross-sectional (i.e., using baseline samples), the temporal relationship between potentially time-varying covariates and oral HPV and HIV infection is unclear. This notwithstanding, our conclusions were corroborated by the associations observed with immune status in HIV + individuals and risk of incident and persistent oral HPV infections (i.e., inverse association with clearance), which were assessed prospectively in a subset of participants that have also been shown in other prospective studies [20,38]. Lastly, we observed significant heterogeneity in oral HPV prevalence by study site among HIV + individuals, which may be associated with population risk differences that we were not able to adjust for.

This multicenter study provides additional information on potential clinical markers for high-risk oral HPV infection and persistence in HIV + populations. There is a growing public health interest in identifying risk factors for oral HPV and the potential implications for cancer screening [39–42]. Our findings suggest that HIV + individuals with poorly controlled infection may be a candidate group for intensified screening to detect HPV-associated oropharyngeal cancer. However, the low prevalence of high-risk oral HPV, low population risk of oropharyngeal cancer, and lack of a clearly defined precancerous phase, currently precludes the use of oral HPV testing for oropharyngeal cancer screening [9,43–45]. For oral HPV screening to eventually be effective in populations at higher risk of cancer, such as among PLWH [46,47], there is a need to further characterize the natural history of oral HPV and the overall risk of HPV-associated oropharyngeal cancer among this vulnerable group [43,45].

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Author statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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