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Risk Factors for Acquisition and Clearance of Oral Human Papillomavirus Infection Among HIV-Infected and HIV-Uninfected Adults

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Abstract and Introduction

Abstract

Human papillomavirus (HPV) causes the majority of oropharyngeal cancers in the United States, yet the risk factors for and natural history of oral HPV infection are largely unknown. In 2010â€“2011, a US-based longitudinal cohort study of 761 human immunodeficiency virus (HIV)-infected and 469 at-risk HIV-uninfected participants from the Multicenter AIDS Cohort Study and the Women's Interagency HIV Study was initiated. Semiannually collected oral rinses were evaluated for 37 HPV genotypes using the Roche LINEAR ARRAY HPV Genotyping Test (Roche Molecular Systems, Pleasanton, California), and factors associated with oral HPV incidence and clearance were explored using adjusted Wei-Lin-Weissfeld modeling. Through 2013, the 2-year cumulative incidence of any type of oral HPV infection was 34% in HIV-infected persons and 19% in HIV-uninfected persons. However, many of these infections cleared. Seven percent of incident infections and 35% of prevalent infections persisted for at least 2 years. After adjustment for other risk factors, HIV infection (adjusted hazard ratio = 2.3, 95% confidence interval: 1.7, 3.2), reduced current CD4 cell count, and increased numbers of oral sex and "rimming" partners increased the risk of incident oral HPV infection, whereas male sex, older age, and current smoking increased the risk of oral HPV persistence (each $P < 0.05$). This helps explain the consistent associations observed between these factors and prevalent oral HPV infection in previous cross-sectional studies.

Introduction

The incidence of oropharyngeal cancers caused by oral human papillomavirus (HPV) infection has increased over the last 20 years, and they now represent the majority of oropharyngeal cancers in the United States.[1,2] In case-control studies, oral HPV infection has been found to greatly increase the odds of oropharyngeal cancer.[3,4] Nevertheless, the natural history of oral HPV has not been well characterized.

Cross-sectional studies have observed that 5%â€“8% of adults worldwide have an oral HPV infection at any given time,[5,6] and prevalent oral HPV is more common among men, cigarette smokers, human immunodeficiency virus (HIV)-infected persons, and persons with a high number of sexual partners.[5,7,8] Preliminary longitudinal studies indicated that oral HPV infection was infrequent and had a high clearance rate.[9â€“13] However, these studies had short follow-up periods and/or limited sample sizes,[9â€“14] limiting their ability to adequately identify risk factors for oral HPV acquisition and clearance.

We sought to investigate the natural history of oral HPV infection in HIV-infected persons, since they are of particular interest due to their higher oral HPV prevalence[7,15] and incidence of oropharyngeal cancer.[16,17] We conducted a prospective cohort study to identify risk factors for oral HPV incidence and clearance in a multicenter US population of HIV-infected and at-risk HIV-uninfected adults.[7]

Methods

Study Population and Design

The Persistent Oral Human Papillomavirus Study (POPS) is an ongoing prospective study nested within 2 longitudinal studies of HIV infection. We included participants from the Chicago, Illinois; Washington, DC/Baltimore, Maryland; and Pittsburgh, Pennsylvania sites of the Multicenter AIDS Cohort Study (MACS) and participants from the Chicago, Bronx (New York City), and Brooklyn (New York City) sites of the Women's Interagency HIV Study (WIHS).[7,18,19] A convenience sample of HIV-infected persons and HIV-uninfected persons (who were at risk for HIV and were similar to HIV-infected persons in terms of demographic and behavioral characteristics) was enrolled in the POPS between October 2009 and March 2011, as previously reported.[7] Enrollment was stratified by study site, by HIV status, and by ever use of combination antiretroviral therapy (cART), also known as highly active antiretroviral therapy (HAART). We restricted the current analysis to POPS data collected between 2010 and 2013. POPS participants had similar demographic, behavioral, and biological characteristics as the MACS and WIHS participants, except that more of them were cART-naive.[7] This study's definition of cART was reported use of 3 or more antiretroviral medications.[20] The POPS protocol was approved by the executive committees and institutional review boards of all study sites. All of the participants provided written informed consent.

Participants were followed semiannually for up to 3 years, through March 2013. At each visit (approximately 6 months apart), exfoliated epithelial cells were collected by means of a 30-second oral rinse and gargle sample using Scope mouthwash (Procter & Gamble, Cincinnati, Ohio),[21,22] which has shown a strong reliability and a higher sensitivity than alternative methods.[22,23] Participants who preferred not to use Scope (<5% of participants) used saline instead to collect oral exfoliated cells, since both solutions have been shown to have strong DNA yields, DNA quality, and stability at room temperature.[21,22] Risk factor data were collected semiannually through computer-assisted self-interview in the MACS and through interviewer-administered questionnaires in the WIHS. The study's definition for the number of oral sex partners included all male or female partners that the participant had *performed* oral sex on (fellatio or cunnilingus). Recent behaviors were defined as those performed in the past 6 months.

Laboratory Analysis

Oral rinse samples were stored at 4Â°C for up to 2 weeks until processed.[24] DNA was purified from the oral rinse using a magnetic bead-based automated platform (QIAsymphony SP; QIAGEN, Germantown, Maryland), as previously described.[25] Purified DNA was evaluated for 37 different HPV DNA genotypes utilizing PGMY09/11 polymerase chain reaction primer pools and primers for Î²-globin, followed by reverse line blot hybridization to the Roche LINEAR ARRAY HPV Genotyping Test (Roche Molecular Systems, Pleasanton, California). HPV types were classified as either oncogenic (high-risk) or nononcogenic (low-risk) according to the criteria of the International Agency for Research on Cancer.[26â€“28] Oncogenic HPV types included types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, and 73, while nononcogenic types included types 6, 11, 26, 40, 42, 53â€“55, 61, 62, 64, 66, 67, 69â€–72, 81â€“84, 89 (CP6108), and IS39.

Statistical Analyses

Type-specific oral HPV infection was classified as prevalent if it was detected at baseline and as incident if it was first detected after a negative type-specific test at baseline. Clearance of type-specific HPV infection was analyzed on the basis of 2 definitions: 1) requiring either a single negative test or 2) requiring 2 consecutive negative tests. Infections that met either definition were considered to have been cleared at the time of the first negative test.

Participant characteristics were compared utilizing $Ï‡^2$ tests for categorical variables and Mann-Whitney tests for median values for continuous variables. Cumulative incidence and clearance curves were estimated through the Kaplan-Meier method and were utilized to explore the incidence and time to clearance of oral HPV. For the 15% of infections with missing intermittent visits, we assumed that the HPV results were the same at the missing intermittent visit as at the previous visit. Both prevalent infections and re-detected infections (e.g., +, â^', â^', +) were excluded from incident analyses. All other newly detected infections were classified as incident, although we performed sensitivity analyses comparing sexually abstinent and sexually active participants to examine whether some incidentally detected infections were acquired prior to the study and reactivated during the study. We also conducted sensitivity analyses requiring incident infections to have at least 2 negative tests prior to the first detection of oral HPV, and found the associations with risk factors to be similar.

Risk factors were explored using unadjusted and adjusted Wei-Lin-Weissfeld models,[29,30] stratifying by HIV status and/or sex. Variables that were significant ($P < 0.05$) in unadjusted models and variables considered relevant based on previous literature were included in adjusted Wei-Lin-Weissfeld models.[7,10] Covariates that were strongly correlated were considered in separate models but were also considered in combination to determine which variables to include in the final model. In a sensitivity analysis carried out to explore intermittently detected infections that were variably detected throughout the study (e.g., +, â^', +, â^', +), we categorized all infections with at least 3 follow-up visits into discrete patterns (persistent, intermittent, and cleared) as previously described.[9] Results were also considered after restricting the data to oncogenic types only and to HPV16 alone, since HPV16 is known to cause most HPV-positive oropharyngeal cancers.[31] All statistical tests were 2-sided, and results were considered significant at an Î± level of 0.05.

Results

Participant Characteristics

During this study, 6,065 oral rinse samples were collected from 1,230 participants who contributed 2 or more study visits. Oral samples that were Î²-globinâ€“negative ($n = 24$; 0.4%) were excluded from analysis. Median follow-up time was 24.4 months (interquartile range, 18.4â€“35.4).

Study participants included 550 (45%) men from the MACS (mostly men who had sex with men), and 680 (55%) women from the WIHS (mostly heterosexual women) (). Thus, most participants who reported performing oral sex had performed the act on a man (fellatio). However, approximately 5% of both the MACS and WIHS participants had recently performed oral sex on a woman (cunnilingus). When compared with women from the WIHS, men from the MACS were significantly more likely to be white, older,

never smokers, and current alcohol drinkers and to have had a greater number of recent oral sex and "rimming" (oral-anal contact) partners (each $P < 0.01$;).

Table 1.Â Baseline Characteristics of the Cohort by Sex and Human Immunodeficiency Virus Serostatus, Persistent Oral Papillomavirus Study, 2010â€“2013

Participant Characteristic	Overall (*n* = 1,230)		Sex and %		HIV Serostatus and %	
	No.	%	Male (MACS) (*n* = 550)	Female (WIHS) (*n* = 680)	HIV-Infected (*n* = 761)	HIV-Uninfected (*n* = 469)
Age, years[a]	Â	Â	Â	Â	Â	Â
Â Â Â <45	373	30	15[b]	43[b]	29	32
Â Â Â 45â€“55	499	41	41	41	45	34
Â Â Â >55	357	29	45	16	26	34
Race/ethnicity	Â	Â	Â	Â	Â	Â
Â Â Â White non-Hispanic	366	30	62[b]	4[b]	26[c]	35[c]
Â Â Â Black non-Hispanic	682	55	32	74	59	51
Â Â Â Hispanic, any race	157	13	5	19	13	13
Â Â Â Other race	24	2	1	3	2	2
Sex	Â	Â	Â	Â	Â	Â
Â Â Â Male (MACS)	550	45	100	0	43	47
Â Â Â Female (WIHS)	680	55	0	100	57	53
Study site	Â	Â	Â	Â	Â	Â
Â Â Â Baltimore, Maryland/Washington, DC	189	15	34	Â	14	17
Â Â Â Pittsburgh, Pennsylvania	172	14	31	Â	13	15
Â Â Â Chicago, Illinois	398	32	34	31	35	28
Â Â Â Bronx, New York	206	17	Â	30	16	18
Â Â Â Brooklyn, New York	265	22	Â	39	22	22
Cigarette smoking	Â	Â	Â	Â	Â	Â
Â Â Â Never smoker	381	31	41[b]	23[b]	31	32
Â Â Â Former smoker	363	30	31	29	29	30
Â Â Â Current smoker	476	39	28	48	40	37
Current alcohol consumption, drinks/day	Â	Â	Â	Â	Â	Â
Â Â Â 0 (none)	658	54	41[b]	64[b]	59[c]	46[c]
Â Â Â <2	468	38	46	32	35	43
Â Â Â â‰¥2	97	8	13	4	6.2	11
Lifetime no. of oral sex partners[d]	Â	Â	Â	Â	Â	Â
Â Â Â 0â€“4	463	39	13[b]	59[b]	40	39
Â Â Â 5â€“99	462	39	40	38	38	40
Â Â Â â‰¥100	266	22	47	3	22	21

No. of oral sex partners in last 6 months	Â	Â	Â	Â	Â	Â
Â Â Â 0	685	56	35[b]	73[b]	61[c]	49[c]
Â Â Â 1	283	23	26	21	21	26
Â Â Â 2â€“5	169	14	25	5	11	18
Â Â Â â‰¥6	77	6	14	0	6	7
Performed oral sex on a woman in last 6 months	Â	Â	Â	Â	Â	Â
Â Â Â No	1,173	95	94	95	97	93
Â Â Â Yes	62	5	6	5	3	7
No. of "rimming"[e] partners in last 6 months	Â	Â	Â	Â	Â	Â
Â Â Â 0	755	81	70[b]	93[b]	81	80
Â Â Â 1	101	11	15	6	10	13
Â Â Â â‰¥2	78	8	14	2	9	8
Ever having a tonsillectomy	Â	Â	Â	Â	Â	Â
Â Â Â No	891	75	59[b]	87[b]	75	75
Â Â Â Yes	278	23	39	11	23	24
Â Â Â Unsure	19	2	2	1	2	1
Frequency of tooth-brushing in last 6 months, times/day	Â	Â	Â	Â	Â	Â
Â Â Â â‰¥2	707	59	56	62	57	63
Â Â Â 1	368	31	35	28	31	29
Â Â Â <1	56	5	6	4	5	4
Â Â Â No teeth/dentures	65	5	3	7	6	5
cART use	Â	Â	Â	Â	Â	Â
Â Â Â Current use	604	79	87[b]	74[b]	79	Â
Â Â Â Former use	98	13	9	16	13	Â
Â Â Â Never use (cART-naive)	58	8	5	10	8	Â
Current CD4 cell count among HIV-infected persons, cells/ÂµL[f]	Â	Â	Â	Â	Â	Â
Â Â Â â‰¥500	424	56	60[b]	53[b]	56	Â
Â Â Â 200â€“499	262	35	34	35	35	Â
Â Â Â <200	72	10	6	12	10	Â
CD4 cell count nadir among HIV-infected persons, cells/ÂµL[g]	Â	Â	Â	Â	Â	Â
Â Â Â â‰¥500	130	17	17[b]	18[b]	17	Â
Â Â Â 200â€“499	409	55	55	54	55	Â
Â Â Â <200	210	28	28	28	28	Â
HIV RNA viral load, copies/mL	Â	Â	Â	Â	Â	Â
Â Â Â <50	485	64	75[b]	57[b]	64	Â

Â Â Â 50â€“20,000	192	25	18	31	25	Â
Â Â Â â‰¥20,000	77	10	8	12	10	Â
No. of study visits	Â	Â	Â	Â	Â	Â
Â Â Â 2â€“3	221	18	17	18	18	17
Â Â Â 4â€“5	555	44	39	49	44	46
Â Â Â 6â€“7	476	38	43	33	39	37

Abbreviations: AIDS, acquired immunodeficiency syndrome; cART, combination antiretroviral therapy; HIV, human immunodeficiency virus; IQR, interquartile range; MACS, Multicenter AIDS Cohort Study; WIHS, Women's Interagency HIV Study.
[a]Median ages: overallâ€”49.7 (IQR, 43.0â€“56.2); MACSâ€”53.7 (IQR, 48.3â€“60.0); WIHSâ€”46.4 (IQR, 40.1â€“52.4); HIV-infectedâ€”49.4 (IQR, 43.5â€“55.2); HIV-uninfectedâ€”50.4 (IQR, 42.2â€“58.4).
[b] $P < 0.05$ for difference between MACS and WIHS participants.
[c] $P < 0.05$ for difference between HIV-infected and HIV-uninfected participants.
[d]Median lifetime numbers of oral sex partners: overallâ€”10 (IQR, 3â€“61); MACSâ€”61 (IQR, 30â€“224); WIHSâ€”3 (IQR, 1â€“10); HIV-infectedâ€”10 (IQR, 3â€“61); HIV-uninfectedâ€”10 (IQR, 3â€“61).
[e]Oral-anal contact.
[f]Median current CD4 cell count: overallâ€”549 (IQR, 351â€“759); MACSâ€”575 (IQR, 389â€“759); WIHSâ€—520 (IQR, 316â€“752); HIV-infectedâ€—549 (IQR, 351â€“759); HIV-uninfectedâ€—922 (IQR, 751â€“1,192).
[g]Median CD4 cell count nadir: overallâ€—292 (IQR, 185â€“422); MACSâ€—275 (IQR, 179â€“421); WIHSâ€—312 (IQR, 188â€“422); HIV-infectedâ€—292 (IQR, 185â€“422).

Table 1.Â Baseline Characteristics of the Cohort by Sex and Human Immunodeficiency Virus Serostatus, Persistent Oral Papillomavirus Study, 2010â€“2013

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Age, years[a]	Â	Â	Â	Â	Â	Â
Â Â Â <45	373	30	15[b]	43[b]	29	32
Â Â Â 45â€“55	499	41	41	41	45	34
Â Â Â >55	357	29	45	16	26	34
Race/ethnicity	Â	Â	Â	Â	Â	Â
Â Â Â White non-Hispanic	366	30	62[b]	4[b]	26[c]	35[c]
Â Â Â Black non-Hispanic	682	55	32	74	59	51
Â Â Â Hispanic, any race	157	13	5	19	13	13
Â Â Â Other race	24	2	1	3	2	2
Sex	Â	Â	Â	Â	Â	Â
Â Â Â Male (MACS)	550	45	100	0	43	47
Â Â Â Female (WIHS)	680	55	0	100	57	53
Study site	Â	Â	Â	Â	Â	Â
Â Â Â Baltimore, Maryland/Washington, DC	189	15	34	Â	14	17
Â Â Â Pittsburgh, Pennsylvania	172	14	31	Â	13	15
Â Â Â Chicago, Illinois	398	32	34	31	35	28
Â Â Â Bronx, New York	206	17	Â	30	16	18

Â Â Â Brooklyn, New York	265	22	Â	39	22	22
Cigarette smoking	Â	Â	Â	Â	Â	Â
Â Â Â Never smoker	381	31	41[b]	23[b]	31	32
Â Â Â Former smoker	363	30	31	29	29	30
Â Â Â Current smoker	476	39	28	48	40	37
Current alcohol consumption, drinks/day	Â	Â	Â	Â	Â	Â
Â Â Â 0 (none)	658	54	41[b]	64[b]	59[c]	46[c]
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Lifetime no. of oral sex partners[d]	Â	Â	Â	Â	Â	Â
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Â Â Â â‰¥100	266	22	47	3	22	21
No. of oral sex partners in last 6 months	Â	Â	Â	Â	Â	Â
Â Â Â 0	685	56	35[b]	73[b]	61[c]	49[c]
Â Â Â 1	283	23	26	21	21	26
Â Â Â 2â€“5	169	14	25	5	11	18
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Performed oral sex on a woman in last 6 months	Â	Â	Â	Â	Â	Â
Â Â Â No	1,173	95	94	95	97	93
Â Â Â Yes	62	5	6	5	3	7
No. of "rimming"[e] partners in last 6 months	Â	Â	Â	Â	Â	Â
Â Â Â 0	755	81	70[b]	93[b]	81	80
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Ever having a tonsillectomy	Â	Â	Â	Â	Â	Â
Â Â Â No	891	75	59[b]	87[b]	75	75
Â Â Â Yes	278	23	39	11	23	24
Â Â Â Unsure	19	2	2	1	2	1
Frequency of tooth-brushing in last 6 months, times/day	Â	Â	Â	Â	Â	Â
Â Â Â â‰¥2	707	59	56	62	57	63
Â Â Â 1	368	31	35	28	31	29
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Â Â Â No teeth/dentures	65	5	3	7	6	5
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Â Â Â Current use	604	79	87[b]	74[b]	79	Â

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[g]Median CD4 cell count nadir: overallâ€—292 (IQR, 185â€–422); MACSâ€—275 (IQR, 179â€–421); WIHSâ€—312 (IQR, 188â€–422); HIV-infectedâ€—292 (IQR, 185â€–422).

This study population included 761 (62%) HIV-infected persons and 469 (38%) at-risk HIV-uninfected persons. While HIV-infected participants and HIV-uninfected participants had many similarities, HIV-infected participants were more likely to be black, to not currently drink alcohol, and to have a lower number of recent oral sex partners (each $P < 0.05$;).

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Performed oral sex on a woman in last 6 months	Â	Â	Â	Â	Â	Â
Â Â Â No	1,173	95	94	95	97	93
Â Â Â Yes	62	5	6	5	3	7

No. of "rimming"[e] partners in last 6 months	Â	Â	Â	Â	Â	Â
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Â Â Â Former use	98	13	9	16	13	Â
Â Â Â Never use (cART-naive)	58	8	5	10	8	Â
Current CD4 cell count among HIV-infected persons, cells/ÂµL[f]	Â	Â	Â	Â	Â	Â
Â Â Â â‰¥500	424	56	60[b]	53[b]	56	Â
Â Â Â 200â€“499	262	35	34	35	35	Â
Â Â Â <200	72	10	6	12	10	Â
CD4 cell count nadir among HIV-infected persons, cells/ÂµL[g]	Â	Â	Â	Â	Â	Â
Â Â Â â‰¥500	130	17	17[b]	18[b]	17	Â
Â Â Â 200â€“499	409	55	55	54	55	Â
Â Â Â <200	210	28	28	28	28	Â
HIV RNA viral load, copies/mL	Â	Â	Â	Â	Â	Â
Â Â Â <50	485	64	75[b]	57[b]	64	Â
Â Â Â 50â€“20,000	192	25	18	31	25	Â
Â Â Â â‰¥20,000	77	10	8	12	10	Â
No. of study visits	Â	Â	Â	Â	Â	Â
Â Â Â 2â€“3	221	18	17	18	18	17
Â Â Â 4â€“5	555	44	39	49	44	46
Â Â Â 6â€“7	476	38	43	33	39	37

Abbreviations: AIDS, acquired immunodeficiency syndrome; cART, combination antiretroviral therapy; HIV, human immunodeficiency virus; IQR, interquartile range; MACS, Multicenter AIDS Cohort Study; WIHS, Women's Interagency HIV Study.

[a]Median ages: overallâ€”49.7 (IQR, 43.0â€“56.2); MACSâ€”53.7 (IQR, 48.3â€“60.0); WIHSâ€”46.4 (IQR, 40.1â€“52.4); HIV-infectedâ€”49.4 (IQR, 43.5â€“55.2); HIV-uninfectedâ€”50.4 (IQR, 42.2â€–58.4).

[b] $P < 0.05$ for difference between MACS and WIHS participants.
[c] $P < 0.05$ for difference between HIV-infected and HIV-uninfected participants.
[d]Median lifetime numbers of oral sex partners: overallâ€”10 (IQR, 3â€“61); MACSâ€”61 (IQR, 30â€“224); WIHSâ€”3 (IQR, 1â€–10); HIV-infectedâ€”10 (IQR, 3â€–61); HIV-uninfectedâ€—10 (IQR, 3â€–61).
[e]Oral-anal contact.
[f]Median current CD4 cell count: overallâ€—549 (IQR, 351â€–759); MACSâ€—575 (IQR, 389â€–759); WIHSâ€—520 (IQR, 316â€–752); HIV-infectedâ€—549 (IQR, 351â€–759); HIV-uninfectedâ€—922 (IQR, 751â€–1,192).
[g]Median CD4 cell count nadir: overallâ€—292 (IQR, 185â€–422); MACSâ€—275 (IQR, 179â€–421); WIHSâ€—312 (IQR, 188â€–422); HIV-infectedâ€—292 (IQR, 185â€–422).

Prevalence and Incidence of Oral HPV Infection

Type-specific prevalent and incident oral HPV infections were common among both HIV-uninfected and HIV-infected participants in this cohort. The baseline prevalence of oral HPV was 20% in HIV-uninfected persons and 35% in HIV-infected persons. Twenty-nine percent of HIV-uninfected participants and 48% of HIV-infected participants had at least 1 prevalent or incident oral HPV infection during this study. In addition, 11% of HIV-uninfected persons and 29% of HIV-infected persons had multiple types of oral HPV infection detected at some point during this study.

In HIV-uninfected participants, there were 123 oral HPV infections detected throughout the study, with 55 being oncogenic types and 8 being HPV16. The incidence rate of any oral HPV infection in HIV-uninfected participants was 10.3 (95% confidence interval (CI): 8.5, 12.3) per 1,000 person-months (123 infections), while the incidence rates of any oncogenic oral HPV type and HPV16 were 4.6 (95% CI: 3.5, 6.0) per 1,000 person-months and 0.6 (95% CI: 0.3, 1.3) per 1,000 person-months, respectively. After 2 years of follow-up of HIV-uninfected participants, the cumulative incidence of any oral HPV infection, any oncogenic HPV type, and HPV16 was 19% (95% CI: 16, 23), 10% (95% CI: 7.5, 14), and 2.3% (95% CI: 1.1, 4.6), respectively.

Among HIV-infected persons, there were 454 oral HPV infections detected throughout the study, with 169 being oncogenic types and 23 being HPV16. The incidence rate of any oral HPV infection in HIV-infected persons was 24.1 (95% CI: 21.9, 26.3) per 1,000 person-months (454 infections), while the incidence rates of any oncogenic type and HPV16 were 9.0 (95% CI: 7.7, 10.4) per 1,000 person-months and 1.2 (95% CI: 0.8, 1.8) per 1,000 person-months, respectively. After 2 years of follow-up of HIV-uninfected participants, the cumulative incidence of any oral HPV infection, any oncogenic HPV type, and HPV16 was 34% (95% CI: 30, 37), 18% (95% CI: 15, 21), and 4.5% (95% CI: 2.9, 6.9), respectively.

Risk Factors for Incident Oral HPV Infection

The incidence rates of oral HPV infection were significantly higher among HIV-infected persons than among HIV-uninfected persons (incidence rate = 24.1 per 1,000 person-months vs. 10.3 per 1,000 person-months; $P < 0.001$) (Figure 1), and the risk of oral HPV infection increased as current CD4-positive T-lymphocyte (CD4 cell) count declined (P for trend < 0.001; Figure 1). Additional factors associated with risk of oral HPV infection in unadjusted analysis included younger age, several measures of sexual behavior, and never having had a tonsillectomy (see and Web Table 1 http://aje.oxfordjournals.org/content/181/1/40/suppl/DC2 (available at http://aje.oxfordjournals.org/); each P <0.05). In contrast, rates of oral HPV infection were similar for men and women (MACS vs. WIHS: incidence rate = 19.5 per 1,000 person-months vs. 17.9 per 1,000 person-months; P =0.75). Additionally, current cigarette smoking, marijuana use, and current cART use were not associated with risk of oral HPV infection (each $P > 0.05$).

Table 2.Â Risk Factors for Incident Oral Human Papillomavirus Infection by Human Immunodeficiency Virus Serostatus, Persistent Oral Papillomavirus Study, 2010â€“2013

Participant Characteristic[a]	HIV Serostatus											
	HIV-Infected						HIV-Uninfected					
	No. of Infections	Person-Months	HR	95% CI	aHR[b]	95% CI	No. of Infections	Person-Months	HR	95% CI	aHR[b]	95% CI
Age, years	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â <45	177	5,280	1	Referent	1	Referent	31	3,780	1	Referent	1	Referent
Â Â Â 45â€“54	180	8,653	0.67	0.41, 1.1	0.77	0.52, 1.1	52	4,058	1.6	0.83, 3.1	1.2	0.62, 2.4
Â Â Â â‰¥55	97	4,831	0.59	0.35, 1.0	0.59	0.38, 0.91	40	4,086	1.2	0.64, 2.4	1.1	0.49, 2.4

P for trend	Â	Â	0.03		0.01		Â	Â	0.61		0.84	
Sex	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â Female (WIHS)	211	10,356	1	Referent	1	Referent	1	5,858	1	Referent	1	Referent
Â Â Â Male (MACS)	243	8,445	1.1	0.73, 1.5	1.3	0.74, 2.2	75	6,075	1.4	0.85, 2.3	2.3	0.87, 6.3
Cigarette smoking	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â Never smoker	134	5,700	1	Referent	1	Referent	1	3,980	1	Referent	1	Referent
Â Â Â Former smoker	98	5,480	0.77	0.45, 1.3	0.75	0.39, 1.4	33	3,528	1.1	0.64, 2.1	1.1	0.64, 1.7
Â Â Â Current smoker	207	7,456	1.1	0.64, 1.9	0.86	0.42, 1.8	55	4,350	1.2	0.74, 2.1	1.0	0.56, 1.8
Current alcohol consumption, drinks/day	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0 (none)	270	10,982	1	Referent	1	Referent	1	5,369	1	Referent	1	Referent
Â Â Â <2	151	6,513	1.1	0.86, 1.3	0.98	0.78, 1.2	59	5,126	1.0	0.67, 1.5	0.94	0.61, 1.4
Â Â Â â‰¥2	22	1,168	1.2	0.59, 2.5	1.2	0.46, 3.0	12	1,387	0.8	0.39, 1.6	0.74	0.34, 1.6
Ever having a tonsillectomy	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â No	355	13,512	1	Referent	1	Referent	1	8,500	1	Referent	1	Referent
Â Â Â Yes	67	4,459	0.58	0.41, 0.81	0.62	0.44, 0.87	22	2,984	0.71	0.41, 1.3	0.74	0.41, 1.3
Â Â Â Unknown	10	301	1.1	0.49, 2.7	0.86	0.35, 2.1	2	122	1.5	0.53, 4.0	0.97	0.27, 3.5
No. of recent oral sex partners[c]	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0	267	11,502	1	Referent	1	Referent	49	5,501	1	Referent	1	Referent
Â Â Â 1	72	3,702	0.91	0.72, 1.2	0.84	0.66, 1.1	28	3,267	0.91	0.60, 1.4	0.84	0.60, 1.2
Â Â Â 2â€“5	64	2,126	1.4	0.99, 2.0	1.2	0.86, 1.7	30	2,359	1.6	0.97, 2.6	1.4	0.93, 2.1
Â Â Â â‰¥6	35	1,203	1.2	0.75, 2.0	1.1	0.62, 1.9	16	705	2.7	1.5, 4.6	2.3	1.1, 4.8
P for trend	Â	Â	0.93		0.44		Â	Â	<0.001		<0.001	
P for interaction[d]	0.05											
Recently performing oral sex on a woman[e]	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â No	433	18,222	1	Referent	1	Referent	1	11,131	1	Referent	1	Â

Â Â Â Yes	21	579	1.3	0.81, 2.1	1.0	0.54, 1.8	20	803	3.2	1.7, 6.1	3.6	1.8, 7.0
P for interaction[d]	0.03											
No. of recent "rimming"[f] partners[e]	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0	277	11,250	1	Referent	1	Referent	1	7,772	1	Referent	1	Â
Â Â Â 1	26	1,386	0.72	0.43, 1.2	0.72	0.42, 1.2	17	1,275	1.3	0.68, 2.5	1.7	0.83, 3.3
Â Â Â â‰¥2	48	1,294	1.3	0.81, 2.1	1.2	0.73, 1.9	18	766	2.7	1.5, 5.0	1.6	0.80, 3.1
P for trend	Â	Â	0.96		0.92		Â	Â	<0.001		0.02	
P for interaction[d]	0.04											
Lifetime no. of oral sex partners	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0â€“4	114	7,100	1	Referent	1	Referent	26	4,150	1	Referent	1	Â
Â Â Â 5â€“99	191	6,947	1.7	1.1, 2.7	2.2	1.2, 4.0	52	4,813	1.5	0.82, 2.7	1.3	0.70, 2.5
Â Â Â â‰¥100	125	4,290	1.8	1.3, 2.5	2.9	1.6, 5.2	34	2,610	1.8	1.0, 3.4	1.8	0.80, 4.3
P for trend	Â	Â	<0.001		0.01		Â	Â	0.04		0.46	
P for interaction[d]	0.76											
CD4 cell count, cells/ÂµL	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â >500	181	10,404	1	Referent	1	Referent	Â	Â	Â	Â	Â	Â
Â Â Â 200â€“499	159	6,594	1.4	1.1, 1.8	1.4	1.1, 1.7	Â	Â	Â	Â	Â	Â
Â Â Â â‰¤200	112	1,698	3.5	1.8, 6.5	3.5	1.7, 7.3	Â	Â	Â	Â	Â	Â
P for trend	Â	Â	0.007		0.01		Â	Â	Â	Â	Â	Â

Abbreviations: aHR, adjusted hazard ratio; AIDS, acquired immunodeficiency syndrome; CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio; MACS, Multicenter AIDS Cohort Study; WIHS, Women's Interagency HIV Study.

[a]All variables were time-updated except for ever having a tonsillectomy and lifetime number of oral sex partners, on which datawere collected only at the Persistent Oral Papillomavirus Study baseline visit.

[b]Adjusted for HIV status, current CD4 cell count, age, sex, cigarette smoking, alcohol drinking, study site, history of tonsillectomy, recent tooth-brushing, lifetime and recent numbers of oral sex partners, and recently performing oral sex on a woman.

[c]The associations for recent oral sex partners were not adjusted for number of recent rimming partners, because of collinearity of the 2 variables ($r = 0.60$). When rimming was included in the model, the associations between number of recent oral sex partners and oral HPV incidence were similar but attenuated.

[d]Tests for interaction examined the interaction between HIV-infected and HIV-uninfected persons in adjusted analyses; where the *P* value for interaction is not shown, it was greater than 0.10.

[e]Assocations for recently performing oral sex on a woman and number of recent rimming partners were adjusted for recent and lifetime numbers of oral sex partners, along with other cofactors.

[f]Oral-anal contact.

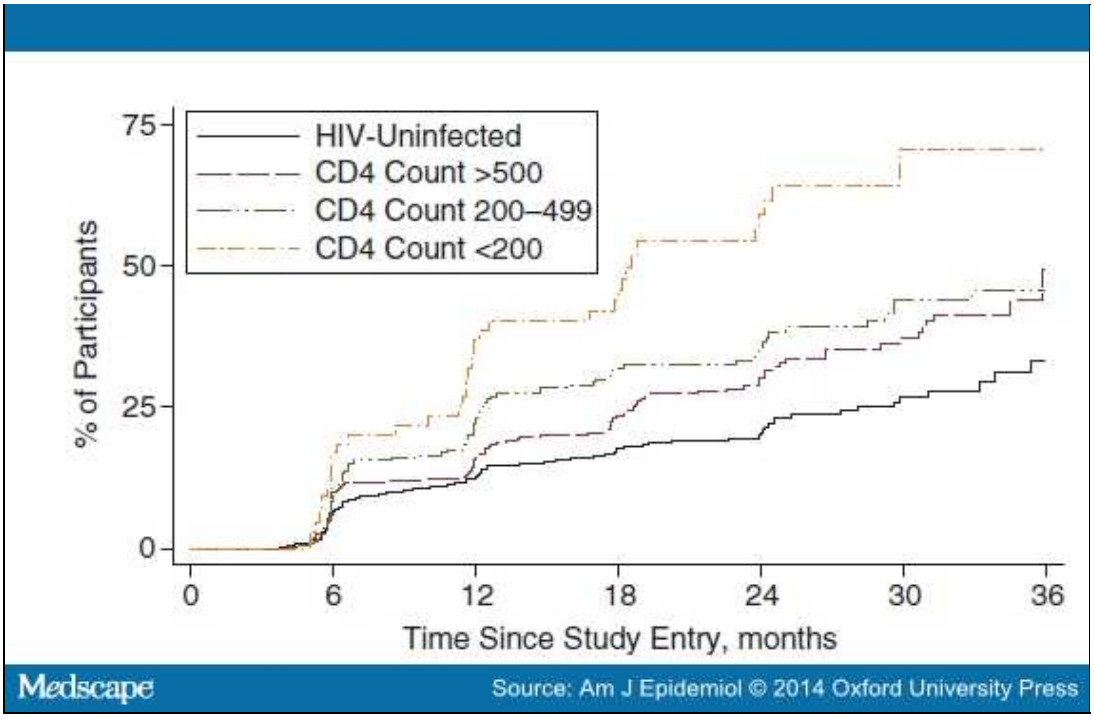

Figure 1.

Â

Cumulative incidence of any oral human papillomavirus (HPV) infection by human immunodeficiency virus (HIV) status and current CD4 cell count (cells/ÂµL) in the Persistent Oral Papillomavirus Study, 2010â€“2013. This cumulative-incidence graph represents the percentage of participants with at least 1 incident oral HPV infection detected during the follow-up period. All persons in CD4 cell count categories were HIV-infected. Participants were considered to have an incident oral HPV infection if they tested positive for a type-specific oral HPV infection that they had tested negative for at the baseline visit. When HIV status/CD4 cell count was utilized as a categorical variable, the *P* value for trend was less than 0.001. This graph presents the linear trend in oral HPV incidence in these groups as derived using Wei-Lin-Weissfeld modeling.

In adjusted analysis stratified by HIV status, number of oral sex partners remained an important risk factor for oral HPV infection (). Among HIV-uninfected persons, risk of oral HPV infection significantly increased with *recent* number of partners for performance of oral sex or "rimming" and with recent cunnilingus (each $P < 0.05$;). In contrast, among HIV-infected persons, risk significantly increased with *lifetime* number of oral sex partners but not with the risk factors above (for each recent behavior, *P*'s for interaction for HIV-infected persons vs. HIV-uninfected persons were 0.05 or less;). Notably, recent and lifetime numbers of oral sex partners significantly increased risk of oral HPV infection even after adjustment for other sexual behaviors (*P*'s for trend < 0.01; Web Table 2 http://aje.oxfordjournals.org/content/181/1/40/suppl/DC2).

Table 2.Â Risk Factors for Incident Oral Human Papillomavirus Infection by Human Immunodeficiency Virus Serostatus, Persistent Oral Papillomavirus Study, 2010â€“2013

Participant Characteristic[a]	HIV Serostatus											
	HIV-Infected						HIV-Uninfected					
	No. of Infections	Person-Months	HR	95% CI	aHR[b]	95% CI	No. of Infections	Person-Months	HR	95% CI	aHR[b]	95% CI
Age, years	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â <45	177	5,280	1	Referent	1	Referent	31	3,780	1	Referent	1	Referent
Â Â Â 45â€“54	180	8,653	0.67	0.41, 1.1	0.77	0.52, 1.1	52	4,058	1.6	0.83, 3.1	1.2	0.62, 2.4
Â Â Â â‰¥55	97	4,831	0.59	0.35, 1.0	0.59	0.38, 0.91	40	4,086	1.2	0.64, 2.4	1.1	0.49, 2.4

P for trend	Â	Â	0.03		0.01		Â	Â	0.61		0.84	
Sex	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â Female (WIHS)	211	10,356	1	Referent	1	Referent	1	5,858	1	Referent	1	Referent
Â Â Â Male (MACS)	243	8,445	1.1	0.73, 1.5	1.3	0.74, 2.2	75	6,075	1.4	0.85, 2.3	2.3	0.87, 6.3
Cigarette smoking	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â Never smoker	134	5,700	1	Referent	1	Referent	1	3,980	1	Referent	1	Referent
Â Â Â Former smoker	98	5,480	0.77	0.45, 1.3	0.75	0.39, 1.4	33	3,528	1.1	0.64, 2.1	1.1	0.64, 1.7
Â Â Â Current smoker	207	7,456	1.1	0.64, 1.9	0.86	0.42, 1.8	55	4,350	1.2	0.74, 2.1	1.0	0.56, 1.8
Current alcohol consumption, drinks/day	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0 (none)	270	10,982	1	Referent	1	Referent	1	5,369	1	Referent	1	Referent
Â Â Â <2	151	6,513	1.1	0.86, 1.3	0.98	0.78, 1.2	59	5,126	1.0	0.67, 1.5	0.94	0.61, 1.4
Â Â Â â‰¥2	22	1,168	1.2	0.59, 2.5	1.2	0.46, 3.0	12	1,387	0.8	0.39, 1.6	0.74	0.34, 1.6
Ever having a tonsillectomy	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â No	355	13,512	1	Referent	1	Referent	1	8,500	1	Referent	1	Referent
Â Â Â Yes	67	4,459	0.58	0.41, 0.81	0.62	0.44, 0.87	22	2,984	0.71	0.41, 1.3	0.74	0.41, 1.3
Â Â Â Unknown	10	301	1.1	0.49, 2.7	0.86	0.35, 2.1	2	122	1.5	0.53, 4.0	0.97	0.27, 3.5
No. of recent oral sex partners[c]	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0	267	11,502	1	Referent	1	Referent	49	5,501	1	Referent	1	Referent
Â Â Â 1	72	3,702	0.91	0.72, 1.2	0.84	0.66, 1.1	28	3,267	0.91	0.60, 1.4	0.84	0.60, 1.2
Â Â Â 2â€“5	64	2,126	1.4	0.99, 2.0	1.2	0.86, 1.7	30	2,359	1.6	0.97, 2.6	1.4	0.93, 2.1
Â Â Â â‰¥6	35	1,203	1.2	0.75, 2.0	1.1	0.62, 1.9	16	705	2.7	1.5, 4.6	2.3	1.1, 4.8
P for trend	Â	Â	0.93		0.44		Â	Â	<0.001		<0.001	
P for interaction[d]	0.05											
Recently performing oral sex on a woman[e]	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â No	433	18,222	1	Referent	1	Referent	1	11,131	1	Referent	1	Â

Â Â Â Yes	21	579	1.3	0.81, 2.1	1.0	0.54, 1.8	20	803	3.2	1.7, 6.1	3.6	1.8, 7.0
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No. of recent "rimming"[f] partners[e]	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
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Â Â Â â‰¥2	48	1,294	1.3	0.81, 2.1	1.2	0.73, 1.9	18	766	2.7	1.5, 5.0	1.6	0.80, 3.1
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P for interaction[d]	0.04											
Lifetime no. of oral sex partners	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0â€“4	114	7,100	1	Referent	1	Referent	26	4,150	1	Referent	1	Â
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Â Â Â â‰¥100	125	4,290	1.8	1.3, 2.5	2.9	1.6, 5.2	34	2,610	1.8	1.0, 3.4	1.8	0.80, 4.3
P for trend	Â	Â	<0.001		0.01		Â	Â	0.04		0.46	
P for interaction[d]	0.76											
CD4 cell count, cells/ÂµL	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â >500	181	10,404	1	Referent	1	Referent	Â	Â	Â	Â	Â	Â
Â Â Â 200â€“499	159	6,594	1.4	1.1, 1.8	1.4	1.1, 1.7	Â	Â	Â	Â	Â	Â
Â Â Â â‰¤200	112	1,698	3.5	1.8, 6.5	3.5	1.7, 7.3	Â	Â	Â	Â	Â	Â
P for trend	Â	Â	0.007		0.01		Â	Â	Â	Â	Â	Â

Abbreviations: aHR, adjusted hazard ratio; AIDS, acquired immunodeficiency syndrome; CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio; MACS, Multicenter AIDS Cohort Study; WIHS, Women's Interagency HIV Study.
[a]All variables were time-updated except for ever having a tonsillectomy and lifetime number of oral sex partners, on which datawere collected only at the Persistent Oral Papillomavirus Study baseline visit.
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[c]The associations for recent oral sex partners were not adjusted for number of recent rimming partners, because of collinearity of the 2 variables ($r = 0.60$). When rimming was included in the model, the associations between number of recent oral sex partners and oral HPV incidence were similar but attenuated.
[d]Tests for interaction examined the interaction between HIV-infected and HIV-uninfected persons in adjusted analyses; where the *P* value for interaction is not shown, it was greater than 0.10.
[e]Assocations for recently performing oral sex on a woman and number of recent rimming partners were adjusted for recent and lifetime numbers of oral sex partners, along with other cofactors.
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	HIV Serostatus	

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	No. of Infections	Person-Months	HR	95% CI	aHR[b]	95% CI	No. of Infections	Person-Months	HR	95% CI	aHR[b]	95% CI
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Â Â Â â‰¥55	97	4,831	0.59	0.35, 1.0	0.59	0.38, 0.91	40	4,086	1.2	0.64, 2.4	1.1	0.49, 2.4
P for trend	Â	Â	0.03		0.01		Â	Â	0.61		0.84	
Sex	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
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Cigarette smoking	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â Never smoker	134	5,700	1	Referent	1	Referent	1	3,980	1	Referent	1	Referent
Â Â Â Former smoker	98	5,480	0.77	0.45, 1.3	0.75	0.39, 1.4	33	3,528	1.1	0.64, 2.1	1.1	0.64, 1.7
Â Â Â Current smoker	207	7,456	1.1	0.64, 1.9	0.86	0.42, 1.8	55	4,350	1.2	0.74, 2.1	1.0	0.56, 1.8
Current alcohol consumption, drinks/day	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0 (none)	270	10,982	1	Referent	1	Referent	1	5,369	1	Referent	1	Referent
Â Â Â <2	151	6,513	1.1	0.86, 1.3	0.98	0.78, 1.2	59	5,126	1.0	0.67, 1.5	0.94	0.61, 1.4
Â Â Â â‰¥2	22	1,168	1.2	0.59, 2.5	1.2	0.46, 3.0	12	1,387	0.8	0.39, 1.6	0.74	0.34, 1.6
Ever having a tonsillectomy	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â No	355	13,512	1	Referent	1	Referent	1	8,500	1	Referent	1	Referent
Â Â Â Yes	67	4,459	0.58	0.41, 0.81	0.62	0.44, 0.87	22	2,984	0.71	0.41, 1.3	0.74	0.41, 1.3
Â Â Â Unknown	10	301	1.1	0.49, 2.7	0.86	0.35, 2.1	2	122	1.5	0.53, 4.0	0.97	0.27, 3.5
No. of recent oral sex partners[c]	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0	267	11,502	1	Referent	1	Referent	49	5,501	1	Referent	1	Referent
Â Â Â 1	72	3,702	0.91	0.72, 1.2	0.84	0.66, 1.1	28	3,267	0.91	0.60, 1.4	0.84	0.60, 1.2
Â Â Â 2â€“5	64	2,126	1.4	0.99,	1.2	0.86,	30	2,359	1.6	0.97,	1.4	0.93,

				2.0		1.7				2.6		2.1
Â Â Â â‰¥6	35	1,203	1.2	0.75, 2.0	1.1	0.62, 1.9	16	705	2.7	1.5, 4.6	2.3	1.1, 4.8
P for trend	Â	Â	0.93		0.44		Â	Â	<0.001		<0.001	
P for interaction[d]	0.05											
Recently performing oral sex on a woman[e]	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â No	433	18,222	1	Referent	1	Referent	1	11,131	1	Referent	1	Â
Â Â Â Yes	21	579	1.3	0.81, 2.1	1.0	0.54, 1.8	20	803	3.2	1.7, 6.1	3.6	1.8, 7.0
P for interaction[d]	0.03											
No. of recent "rimming"[f] partners[e]	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0	277	11,250	1	Referent	1	Referent	1	7,772	1	Referent	1	Â
Â Â Â 1	26	1,386	0.72	0.43, 1.2	0.72	0.42, 1.2	17	1,275	1.3	0.68, 2.5	1.7	0.83, 3.3
Â Â Â â‰¥2	48	1,294	1.3	0.81, 2.1	1.2	0.73, 1.9	18	766	2.7	1.5, 5.0	1.6	0.80, 3.1
P for trend	Â	Â	0.96		0.92		Â	Â	<0.001		0.02	
P for interaction[d]	0.04											
Lifetime no. of oral sex partners	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0â€“4	114	7,100	1	Referent	1	Referent	26	4,150	1	Referent	1	Â
Â Â Â 5â€“99	191	6,947	1.7	1.1, 2.7	2.2	1.2, 4.0	52	4,813	1.5	0.82, 2.7	1.3	0.70, 2.5
Â Â Â â‰¥100	125	4,290	1.8	1.3, 2.5	2.9	1.6, 5.2	34	2,610	1.8	1.0, 3.4	1.8	0.80, 4.3
P for trend	Â	Â	<0.001		0.01		Â	Â	0.04		0.46	
P for interaction[d]	0.76											
CD4 cell count, cells/ÂµL	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â >500	181	10,404	1	Referent	1	Referent	Â	Â	Â	Â	Â	Â
Â Â Â 200â€“499	159	6,594	1.4	1.1, 1.8	1.4	1.1, 1.7	Â	Â	Â	Â	Â	Â
Â Â Â â‰¤200	112	1,698	3.5	1.8, 6.5	3.5	1.7, 7.3	Â	Â	Â	Â	Â	Â
P for trend	Â	Â	0.007		0.01		Â	Â	Â	Â	Â	Â

Abbreviations: aHR, adjusted hazard ratio; AIDS, acquired immunodeficiency syndrome; CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio; MACS, Multicenter AIDS Cohort Study; WIHS, Women's Interagency HIV Study.

[a]All variables were time-updated except for ever having a tonsillectomy and lifetime number of oral sex partners, on which datawere collected only at the Persistent Oral Papillomavirus Study baseline visit.

[b]Adjusted for HIV status, current CD4 cell count, age, sex, cigarette smoking, alcohol drinking, study site, history of tonsillectomy, recent tooth-brushing, lifetime and recent numbers of oral sex partners, and recently performing oral sex on a woman.

[c]The associations for recent oral sex partners were not adjusted for number of recent rimming partners, because of collinearity of the

2 variables (r = 0.60). When rimming was included in the model, the associations between number of recent oral sex partners and oral HPV incidence were similar but attenuated.
[d]Tests for interaction examined the interaction between HIV-infected and HIV-uninfected persons in adjusted analyses; where the P value for interaction is not shown, it was greater than 0.10.
[e]Assocations for recently performing oral sex on a woman and number of recent rimming partners were adjusted for recent and lifetime numbers of oral sex partners, along with other cofactors.
[f]Oral-anal contact.

Table 2.Â Risk Factors for Incident Oral Human Papillomavirus Infection by Human Immunodeficiency Virus Serostatus, Persistent Oral Papillomavirus Study, 2010â€“2013

Participant Characteristic[a]	HIV Serostatus											
	HIV-Infected						HIV-Uninfected					
	No. of Infections	Person-Months	HR	95% CI	aHR[b]	95% CI	No. of Infections	Person-Months	HR	95% CI	aHR[b]	95% CI
Age, years	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â <45	177	5,280	1	Referent	1	Referent	31	3,780	1	Referent	1	Referent
Â Â Â 45â€“54	180	8,653	0.67	0.41, 1.1	0.77	0.52, 1.1	52	4,058	1.6	0.83, 3.1	1.2	0.62, 2.4
Â Â Â â‰¥55	97	4,831	0.59	0.35, 1.0	0.59	0.38, 0.91	40	4,086	1.2	0.64, 2.4	1.1	0.49, 2.4
P for trend	Â	Â	0.03		0.01		Â	Â	0.61		0.84	
Sex	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â Female (WIHS)	211	10,356	1	Referent	1	Referent	1	5,858	1	Referent	1	Referent
Â Â Â Male (MACS)	243	8,445	1.1	0.73, 1.5	1.3	0.74, 2.2	75	6,075	1.4	0.85, 2.3	2.3	0.87, 6.3
Cigarette smoking	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â Never smoker	134	5,700	1	Referent	1	Referent	1	3,980	1	Referent	1	Referent
Â Â Â Former smoker	98	5,480	0.77	0.45, 1.3	0.75	0.39, 1.4	33	3,528	1.1	0.64, 2.1	1.1	0.64, 1.7
Â Â Â Current smoker	207	7,456	1.1	0.64, 1.9	0.86	0.42, 1.8	55	4,350	1.2	0.74, 2.1	1.0	0.56, 1.8
Current alcohol consumption, drinks/day	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0 (none)	270	10,982	1	Referent	1	Referent	1	5,369	1	Referent	1	Referent
Â Â Â <2	151	6,513	1.1	0.86, 1.3	0.98	0.78, 1.2	59	5,126	1.0	0.67, 1.5	0.94	0.61, 1.4
Â Â Â â‰¥2	22	1,168	1.2	0.59, 2.5	1.2	0.46, 3.0	12	1,387	0.8	0.39, 1.6	0.74	0.34, 1.6
Ever having a tonsillectomy	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â No	355	13,512	1	Referent	1	Referent	1	8,500	1	Referent	1	Referent
				0.41,		0.44,				0.41,		0.41,

Â Â Â Yes	67	4,459	0.58	0.81, 0.62	0.87		22	2,984	0.71	1.3	0.74	1.3
Â Â Â Unknown	10	301	1.1	0.49, 2.7	0.86	0.35, 2.1	2	122	1.5	0.53, 4.0	0.97	0.27, 3.5
No. of recent oral sex partners[c]	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0	267	11,502	1	Referent	1	Referent	49	5,501	1	Referent	1	Referent
Â Â Â 1	72	3,702	0.91	0.72, 1.2	0.84	0.66, 1.1	28	3,267	0.91	0.60, 1.4	0.84	0.60, 1.2
Â Â Â 2â€“5	64	2,126	1.4	0.99, 2.0	1.2	0.86, 1.7	30	2,359	1.6	0.97, 2.6	1.4	0.93, 2.1
Â Â Â â‰¥6	35	1,203	1.2	0.75, 2.0	1.1	0.62, 1.9	16	705	2.7	1.5, 4.6	2.3	1.1, 4.8
P for trend	Â	Â	0.93		0.44		Â	Â	<0.001		<0.001	
P for interaction[d]	0.05											
Recently performing oral sex on a woman[e]	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â No	433	18,222	1	Referent	1	Referent	1	11,131	1	Referent	1	Â
Â Â Â Yes	21	579	1.3	0.81, 2.1	1.0	0.54, 1.8	20	803	3.2	1.7, 6.1	3.6	1.8, 7.0
P for interaction[d]	0.03											
No. of recent "rimming"[f] partners[e]	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0	277	11,250	1	Referent	1	Referent	1	7,772	1	Referent	1	Â
Â Â Â 1	26	1,386	0.72	0.43, 1.2	0.72	0.42, 1.2	17	1,275	1.3	0.68, 2.5	1.7	0.83, 3.3
Â Â Â â‰¥2	48	1,294	1.3	0.81, 2.1	1.2	0.73, 1.9	18	766	2.7	1.5, 5.0	1.6	0.80, 3.1
P for trend	Â	Â	0.96		0.92		Â	Â	<0.001		0.02	
P for interaction[d]	0.04											
Lifetime no. of oral sex partners	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0â€“4	114	7,100	1	Referent	1	Referent	26	4,150	1	Referent	1	Â
Â Â Â 5â€“99	191	6,947	1.7	1.1, 2.7	2.2	1.2, 4.0	52	4,813	1.5	0.82, 2.7	1.3	0.70, 2.5
Â Â Â â‰¥100	125	4,290	1.8	1.3, 2.5	2.9	1.6, 5.2	34	2,610	1.8	1.0, 3.4	1.8	0.80, 4.3
P for trend	Â	Â	<0.001		0.01		Â	Â	0.04		0.46	
P for interaction[d]	0.76											
CD4 cell count, cells/ÂµL	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â >500	181	10,404	1	Referent	1	Referent	Â	Â	Â	Â	Â	Â

Â Â Â 200â€“499	159	6,594	1.4	1.1, 1.8	1.4	1.1, 1.7	Â	Â	Â	Â	Â	Â
Â Â Â â‰¤200	112	1,698	3.5	1.8, 6.5	3.5	1.7, 7.3	Â	Â	Â	Â	Â	Â
P for trend	Â	Â	0.007		0.01		Â	Â	Â	Â	Â	Â

Abbreviations: aHR, adjusted hazard ratio; AIDS, acquired immunodeficiency syndrome; CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio; MACS, Multicenter AIDS Cohort Study; WIHS, Women's Interagency HIV Study.
[a]All variables were time-updated except for ever having a tonsillectomy and lifetime number of oral sex partners, on which datawere collected only at the Persistent Oral Papillomavirus Study baseline visit.
[b]Adjusted for HIV status, current CD4 cell count, age, sex, cigarette smoking, alcohol drinking, study site, history of tonsillectomy, recent tooth-brushing, lifetime and recent numbers of oral sex partners, and recently performing oral sex on a woman.
[c]The associations for recent oral sex partners were not adjusted for number of recent rimming partners, because of collinearity of the 2 variables (*r* = 0.60). When rimming was included in the model, the associations between number of recent oral sex partners and oral HPV incidence were similar but attenuated.
[d]Tests for interaction examined the interaction between HIV-infected and HIV-uninfected persons in adjusted analyses; where the *P* value for interaction is not shown, it was greater than 0.10.
[e]Assocations for recently performing oral sex on a woman and number of recent rimming partners were adjusted for recent and lifetime numbers of oral sex partners, along with other cofactors.
[f]Oral-anal contact.

HIV infection was significantly associated with increased risk of oral HPV infection (adjusted hazard ratio = 2.3, 95% CI: 1.7, 3.2). Among HIV-infected persons, low current CD4 cell count remained a strong risk factor for oral HPV infection in adjusted analysis (*P* for trend < 0.001; , , and Web Table 3 http://aje.oxfordjournals.org/content/181/1/40/suppl/DC2). Low current CD4 cell count increased risk of oral HPV infection (*P* for trend = 0.01) even after adjustment for correlated measures such as CD4 cell count nadir and HIV viral load. In contrast, low CD4 cell count nadir and high HIV viral load did not independently increase risk of oral HPV infection (*P*'s for trend > 0.10). Risk of oral HPV infection was also higher among persons without a history of tonsillectomy and declined with increasing age among HIV-infected persons (*P* for trend < 0.01; and).

Table 2.Â Risk Factors for Incident Oral Human Papillomavirus Infection by Human Immunodeficiency Virus Serostatus, Persistent Oral Papillomavirus Study, 2010â€“2013

Participant Characteristic[a]	HIV Serostatus											
	HIV-Infected						HIV-Uninfected					
	No. of Infections	Person-Months	HR	95% CI	aHR[b]	95% CI	No. of Infections	Person-Months	HR	95% CI	aHR[b]	95% CI
Age, years	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â <45	177	5,280	1	Referent	1	Referent	31	3,780	1	Referent	1	Referent
Â Â Â 45â€“54	180	8,653	0.67	0.41, 1.1	0.77	0.52, 1.1	52	4,058	1.6	0.83, 3.1	1.2	0.62, 2.4
Â Â Â â‰¥55	97	4,831	0.59	0.35, 1.0	0.59	0.38, 0.91	40	4,086	1.2	0.64, 2.4	1.1	0.49, 2.4
P for trend	Â	Â	0.03		0.01		Â	Â	0.61		0.84	
Sex	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â Female (WIHS)	211	10,356	1	Referent	1	Referent	1	5,858	1	Referent	1	Referent
Â Â Â Male (MACS)	243	8,445	1.1	0.73, 1.5	1.3	0.74, 2.2	75	6,075	1.4	0.85, 2.3	2.3	0.87, 6.3
Cigarette smoking	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â Never smoker	134	5,700	1	Referent	1	Referent	1	3,980	1	Referent	1	Referent

Â Â Â Former smoker	98	5,480	0.77	0.45, 1.3	0.75	0.39, 1.4	33	3,528	1.1	0.64, 2.1	1.1	0.64, 1.7
Â Â Â Current smoker	207	7,456	1.1	0.64, 1.9	0.86	0.42, 1.8	55	4,350	1.2	0.74, 2.1	1.0	0.56, 1.8
Current alcohol consumption, drinks/day	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0 (none)	270	10,982	1	Referent	1	Referent	1	5,369	1	Referent	1	Referent
Â Â Â <2	151	6,513	1.1	0.86, 1.3	0.98	0.78, 1.2	59	5,126	1.0	0.67, 1.5	0.94	0.61, 1.4
Â Â Â â‰¥2	22	1,168	1.2	0.59, 2.5	1.2	0.46, 3.0	12	1,387	0.8	0.39, 1.6	0.74	0.34, 1.6
Ever having a tonsillectomy	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â No	355	13,512	1	Referent	1	Referent	1	8,500	1	Referent	1	Referent
Â Â Â Yes	67	4,459	0.58	0.41, 0.81	0.62	0.44, 0.87	22	2,984	0.71	0.41, 1.3	0.74	0.41, 1.3
Â Â Â Unknown	10	301	1.1	0.49, 2.7	0.86	0.35, 2.1	2	122	1.5	0.53, 4.0	0.97	0.27, 3.5
No. of recent oral sex partners[c]	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0	267	11,502	1	Referent	1	Referent	49	5,501	1	Referent	1	Referent
Â Â Â 1	72	3,702	0.91	0.72, 1.2	0.84	0.66, 1.1	28	3,267	0.91	0.60, 1.4	0.84	0.60, 1.2
Â Â Â 2â€“5	64	2,126	1.4	0.99, 2.0	1.2	0.86, 1.7	30	2,359	1.6	0.97, 2.6	1.4	0.93, 2.1
Â Â Â â‰¥6	35	1,203	1.2	0.75, 2.0	1.1	0.62, 1.9	16	705	2.7	1.5, 4.6	2.3	1.1, 4.8
P for trend	Â	Â	0.93		0.44		Â	Â	<0.001		<0.001	
P for interaction[d]	0.05											
Recently performing oral sex on a woman[e]	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â No	433	18,222	1	Referent	1	Referent	1	11,131	1	Referent	1	Â
Â Â Â Yes	21	579	1.3	0.81, 2.1	1.0	0.54, 1.8	20	803	3.2	1.7, 6.1	3.6	1.8, 7.0
P for interaction[d]	0.03											
No. of recent "rimming"[f] partners[e]	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0	277	11,250	1	Referent	1	Referent	1	7,772	1	Referent	1	Â
Â Â Â 1	26	1,386	0.72	0.43, 1.2	0.72	0.42, 1.2	17	1,275	1.3	0.68, 2.5	1.7	0.83, 3.3
Â Â Â â‰¥2	48	1,294	1.3	0.81,	1.2	0.73,	18	766	2.7	1.5, 5.0	1.6	0.80,

				2.1		1.9						3.1
P for trend	Â	Â	0.96		0.92		Â	Â	<0.001		0.02	
P for interaction[d]	0.04											
Lifetime no. of oral sex partners	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0â€“4	114	7,100	1	Referent	1	Referent	26	4,150	1	Referent	1	Â
Â Â Â 5â€“99	191	6,947	1.7	1.1, 2.7	2.2	1.2, 4.0	52	4,813	1.5	0.82, 2.7	1.3	0.70, 2.5
Â Â Â â‰¥100	125	4,290	1.8	1.3, 2.5	2.9	1.6, 5.2	34	2,610	1.8	1.0, 3.4	1.8	0.80, 4.3
P for trend	Â	Â	<0.001		0.01		Â	Â	0.04		0.46	
P for interaction[d]	0.76											
CD4 cell count, cells/ÂµL	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â >500	181	10,404	1	Referent	1	Referent	Â	Â	Â	Â	Â	Â
Â Â Â 200â€“499	159	6,594	1.4	1.1, 1.8	1.4	1.1, 1.7	Â	Â	Â	Â	Â	Â
Â Â Â â‰¤200	112	1,698	3.5	1.8, 6.5	3.5	1.7, 7.3	Â	Â	Â	Â	Â	Â
P for trend	Â	Â	0.007		0.01		Â	Â	Â	Â	Â	Â

Abbreviations: aHR, adjusted hazard ratio; AIDS, acquired immunodeficiency syndrome; CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio; MACS, Multicenter AIDS Cohort Study; WIHS, Women's Interagency HIV Study.
[a]All variables were time-updated except for ever having a tonsillectomy and lifetime number of oral sex partners, on which datawere collected only at the Persistent Oral Papillomavirus Study baseline visit.
[b]Adjusted for HIV status, current CD4 cell count, age, sex, cigarette smoking, alcohol drinking, study site, history of tonsillectomy, recent tooth-brushing, lifetime and recent numbers of oral sex partners, and recently performing oral sex on a woman.
[c]The associations for recent oral sex partners were not adjusted for number of recent rimming partners, because of collinearity of the 2 variables ($r = 0.60$). When rimming was included in the model, the associations between number of recent oral sex partners and oral HPV incidence were similar but attenuated.
[d]Tests for interaction examined the interaction between HIV-infected and HIV-uninfected persons in adjusted analyses; where the *P* value for interaction is not shown, it was greater than 0.10.
[e]Assocations for recently performing oral sex on a woman and number of recent rimming partners were adjusted for recent and lifetime numbers of oral sex partners, along with other cofactors.
[f]Oral-anal contact.

Table 3.Â Risk Factors Related to Oral Human Papillomavirus Incidence by Sex and Human Immunodeficiency Virus Serostatus, Persistent Oral Papillomavirus Study, 2010â€“2013

Participant Characteristic	HIV Serostatus and Sex							
	HIV-Infected				HIV-Uninfected			
	Male (MACS)		Female (WIHS)		Male (MACS)		Female (WIHS)	
	aHR[a]	95% CI	aHR[a]	95% CI	aHR[a]	95% CI	aHR[a]	95% CI
Age, years	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â <45	1	Referent	1	Referent	1	Referent	1	Referent
Â Â Â 45â€“54	0.71	0.41, 1.2	0.86	0.56, 1.3	0.73	0.27, 2.0	1.4	0.68, 2.9
Â Â Â â‰¥55	0.50	0.27, 0.93	0.79	0.49, 1.3	0.71	0.26, 2.0	1.5	0.64, 3.8
P for trend	0.02		0.20		0.52		0.62	

Cigarette smoking	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â Never smoker	1	Referent	1	Referent	1	Referent	1	Referent
Â Â Â Former smoker	0.84	0.56, 1.2	0.74	0.22, 2.5	0.88	0.52, 1.5	2.0	0.58, 7.0
Â Â Â Current smoker	0.74	0.45, 1.2	0.98	0.30, 3.2	0.88	0.44, 1.8	1.5	0.43, 5.2
Ever having a tonsillectomy	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â No	1	Referent	1	Referent	1	Referent	1	Referent
Â Â Â Yes	0.48	0.31, 0.72	0.84	0.47, 1.5	0.7	0.38, 1.3	0.85	0.21, 3.4
Â Â Â Unknown	1.1	0.41, 2.7	0.79	0.49, 1.3	1.1	0.41, 3.1	Â	Â
Current alcohol consumption, drinks/day	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0 (none)	1	Referent	1	Referent	1	Referent	1	Referent
Â Â Â <2	0.8	0.58, 1.1	1.1	0.83, 3.8	0.74	0.46, 1.2	1.1	0.63, 1.9
Â Â Â â‰¥2	0.47	0.25, 0.87	3.3	2.0, 5.6	0.54	0.20, 1.4	1.1	0.43, 2.7
No. of recent oral sex partners	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0	1	Referent	1	Referent	1	Referent	1	Referent
Â Â Â 1	0.67	0.47, 0.95	1.1	0.85, 1.5	1	0.60, 2.8	0.82	0.50, 1.4
Â Â Â 2â€“5	1.1	0.80, 1.6	1.7	1.0, 2.8	1.7	0.95, 3.0	1.4	0.88, 2.3
Â Â Â â‰¥6	1.1	0.63, 1.8	Â	Â	3.0	1.3, 6.7	Â	Â
P for trend	0.64		0.44		<0.001		0.97	
Recently performing oral sex on a woman	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â No	1	Referent	1	Referent	1	Referent	1	Referent
Â Â Â Yes	1.3	0.52, 3.2	0.86	0.40, 1.8	2.8	1.1, 7.2	4.2	1.8, 10.2
Lifetime no. of oral sex partners	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0â€“4	1	Referent	1	Referent	1	Referent	1	Referent
Â Â Â 5â€“99	1.8	0.85, 3.8	2.0	0.96, 4.0	0.80	0.26, 2.5	1.6	0.75, 3.3
Â Â Â â‰¥100	2.3	1.2, 4.4	3.0	1.5, 6.0	1.2	0.33, 4.2	1.0	0.34, 3.5
P for trend	0.004		0.01		0.60		0.26	
No. of recent "rimming"[b] partners[c]	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0	1	Referent	1	Referent	1	Referent	1	Referent
Â Â Â 1	0.68	0.36, 1.3	1.0	0.36, 3.0	1.1	0.45, 2.5	4.6	1.9, 11.3
Â Â Â â‰¥2	1.4	0.82, 2.3	2.1	0.89, 5.0	1.8	0.84, 3.7	Â	Â
CD4 cell count, cells/ÂµL	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â >500	1	Referent	1	Referent	Â	Â	Â	Â
Â Â Â 200â€“499	1.4	1.0, 1.9	1.3	0.93, 1.8	Â	Â	Â	Â
Â Â Â â‰¤200	1.9	1.1, 3.3	4.6	1.9, 11.3	Â	Â	Â	Â
P for trend	0.03		0.04		Â	Â	Â	Â

Abbreviations: aHR, adjusted hazard ratio; AIDS, acquired immunodeficiency syndrome; CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio; MACS, Multicenter AIDS Cohort Study; WIHS, Women's Interagency HIV Study.
[a]Adjusted for HIV status, current CD4 cell count, age, cigarette smoking, alcohol drinking, study site, history of tonsillectomy, recent tooth-brushing, lifetime and recent numbers of oral sex partners, and recently performing oral sex on a woman.

[b]Oral-anal contact.
[c]Results for rimming were adjusted for number of recent oral sex partners and other risk factors. However, results for the other risk factors were not adjusted for number of recent rimming partners.

Table 2.Â Risk Factors for Incident Oral Human Papillomavirus Infection by Human Immunodeficiency Virus Serostatus, Persistent Oral Papillomavirus Study, 2010â€“2013

Participant Characteristic[a]	HIV Serostatus											
	HIV-Infected						HIV-Uninfected					
	No. of Infections	Person-Months	HR	95% CI	aHR[b]	95% CI	No. of Infections	Person-Months	HR	95% CI	aHR[b]	95% CI
Age, years	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â <45	177	5,280	1	Referent	1	Referent	31	3,780	1	Referent	1	Referent
Â Â Â 45â€“54	180	8,653	0.67	0.41, 1.1	0.77	0.52, 1.1	52	4,058	1.6	0.83, 3.1	1.2	0.62, 2.4
Â Â Â â‰¥55	97	4,831	0.59	0.35, 1.0	0.59	0.38, 0.91	40	4,086	1.2	0.64, 2.4	1.1	0.49, 2.4
P for trend	Â	Â	0.03		0.01		Â	Â	0.61		0.84	
Sex	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â Female (WIHS)	211	10,356	1	Referent	1	Referent	1	5,858	1	Referent	1	Referent
Â Â Â Male (MACS)	243	8,445	1.1	0.73, 1.5	1.3	0.74, 2.2	75	6,075	1.4	0.85, 2.3	2.3	0.87, 6.3
Cigarette smoking	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â Never smoker	134	5,700	1	Referent	1	Referent	1	3,980	1	Referent	1	Referent
Â Â Â Former smoker	98	5,480	0.77	0.45, 1.3	0.75	0.39, 1.4	33	3,528	1.1	0.64, 2.1	1.1	0.64, 1.7
Â Â Â Current smoker	207	7,456	1.1	0.64, 1.9	0.86	0.42, 1.8	55	4,350	1.2	0.74, 2.1	1.0	0.56, 1.8
Current alcohol consumption, drinks/day	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0 (none)	270	10,982	1	Referent	1	Referent	1	5,369	1	Referent	1	Referent
Â Â Â <2	151	6,513	1.1	0.86, 1.3	0.98	0.78, 1.2	59	5,126	1.0	0.67, 1.5	0.94	0.61, 1.4
Â Â Â â‰¥2	22	1,168	1.2	0.59, 2.5	1.2	0.46, 3.0	12	1,387	0.8	0.39, 1.6	0.74	0.34, 1.6
Ever having a tonsillectomy	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â No	355	13,512	1	Referent	1	Referent	1	8,500	1	Referent	1	Referent
Â Â Â Yes	67	4,459	0.58	0.41, 0.81	0.62	0.44, 0.87	22	2,984	0.71	0.41, 1.3	0.74	0.41, 1.3
Â Â Â Unknown	10	301	1.1	0.49, 2.7	0.86	0.35, 2.1	2	122	1.5	0.53, 4.0	0.97	0.27, 3.5

No. of recent oral sex partners[c]	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0	267	11,502	1	Referent	1	Referent	49	5,501	1	Referent	1	Referent
Â Â Â 1	72	3,702	0.91	0.72, 1.2	0.84	0.66, 1.1	28	3,267	0.91	0.60, 1.4	0.84	0.60, 1.2
Â Â Â 2â€“5	64	2,126	1.4	0.99, 2.0	1.2	0.86, 1.7	30	2,359	1.6	0.97, 2.6	1.4	0.93, 2.1
Â Â Â â‰¥6	35	1,203	1.2	0.75, 2.0	1.1	0.62, 1.9	16	705	2.7	1.5, 4.6	2.3	1.1, 4.8
P for trend	Â	Â	0.93		0.44		Â	Â	<0.001		<0.001	
P for interaction[d]	0.05											
Recently performing oral sex on a woman[e]	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â No	433	18,222	1	Referent	1	Referent	1	11,131	1	Referent	1	Â
Â Â Â Yes	21	579	1.3	0.81, 2.1	1.0	0.54, 1.8	20	803	3.2	1.7, 6.1	3.6	1.8, 7.0
P for interaction[d]	0.03											
No. of recent "rimming"[f] partners[e]	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0	277	11,250	1	Referent	1	Referent	1	7,772	1	Referent	1	Â
Â Â Â 1	26	1,386	0.72	0.43, 1.2	0.72	0.42, 1.2	17	1,275	1.3	0.68, 2.5	1.7	0.83, 3.3
Â Â Â â‰¥2	48	1,294	1.3	0.81, 2.1	1.2	0.73, 1.9	18	766	2.7	1.5, 5.0	1.6	0.80, 3.1
P for trend	Â	Â	0.96		0.92		Â	Â	<0.001		0.02	
P for interaction[d]	0.04											
Lifetime no. of oral sex partners	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0â€“4	114	7,100	1	Referent	1	Referent	26	4,150	1	Referent	1	Â
Â Â Â 5â€“99	191	6,947	1.7	1.1, 2.7	2.2	1.2, 4.0	52	4,813	1.5	0.82, 2.7	1.3	0.70, 2.5
Â Â Â â‰¥100	125	4,290	1.8	1.3, 2.5	2.9	1.6, 5.2	34	2,610	1.8	1.0, 3.4	1.8	0.80, 4.3
P for trend	Â	Â	<0.001		0.01		Â	Â	0.04		0.46	
P for interaction[d]	0.76											
CD4 cell count, cells/ÂµL	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â >500	181	10,404	1	Referent	1	Referent	Â	Â	Â	Â	Â	Â
Â Â Â 200â€“499	159	6,594	1.4	1.1, 1.8	1.4	1.1, 1.7	Â	Â	Â	Â	Â	Â
Â Â Â â‰¤200	112	1,698	3.5	1.8, 6.5	3.5	1.7, 7.3	Â	Â	Â	Â	Â	Â
P for trend	Â	Â	0.007		0.01		Â	Â	Â	Â	Â	Â

Abbreviations: aHR, adjusted hazard ratio; AIDS, acquired immunodeficiency syndrome; CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio; MACS, Multicenter AIDS Cohort Study; WIHS, Women's Interagency HIV Study.
[a]All variables were time-updated except for ever having a tonsillectomy and lifetime number of oral sex partners, on which datawere collected only at the Persistent Oral Papillomavirus Study baseline visit.
[b]Adjusted for HIV status, current CD4 cell count, age, sex, cigarette smoking, alcohol drinking, study site, history of tonsillectomy, recent tooth-brushing, lifetime and recent numbers of oral sex partners, and recently performing oral sex on a woman.
[c]The associations for recent oral sex partners were not adjusted for number of recent rimming partners, because of collinearity of the 2 variables (*r* = 0.60). When rimming was included in the model, the associations between number of recent oral sex partners and oral HPV incidence were similar but attenuated.
[d]Tests for interaction examined the interaction between HIV-infected and HIV-uninfected persons in adjusted analyses; where the *P* value for interaction is not shown, it was greater than 0.10.
[e]Assocations for recently performing oral sex on a woman and number of recent rimming partners were adjusted for recent and lifetime numbers of oral sex partners, along with other cofactors.
[f]Oral-anal contact.

Table 3.Â Risk Factors Related to Oral Human Papillomavirus Incidence by Sex and Human Immunodeficiency Virus Serostatus, Persistent Oral Papillomavirus Study, 2010â€“2013

Participant Characteristic	HIV Serostatus and Sex							
	HIV-Infected				HIV-Uninfected			
	Male (MACS)		Female (WIHS)		Male (MACS)		Female (WIHS)	
	aHR[a]	95% CI	aHR[a]	95% CI	aHR[a]	95% CI	aHR[a]	95% CI
Age, years	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â <45	1	Referent	1	Referent	1	Referent	1	Referent
Â Â Â 45â€“54	0.71	0.41, 1.2	0.86	0.56, 1.3	0.73	0.27, 2.0	1.4	0.68, 2.9
Â Â Â â‰¥55	0.50	0.27, 0.93	0.79	0.49, 1.3	0.71	0.26, 2.0	1.5	0.64, 3.8
P for trend	0.02		0.20		0.52		0.62	
Cigarette smoking	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â Never smoker	1	Referent	1	Referent	1	Referent	1	Referent
Â Â Â Former smoker	0.84	0.56, 1.2	0.74	0.22, 2.5	0.88	0.52, 1.5	2.0	0.58, 7.0
Â Â Â Current smoker	0.74	0.45, 1.2	0.98	0.30, 3.2	0.88	0.44, 1.8	1.5	0.43, 5.2
Ever having a tonsillectomy	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â No	1	Referent	1	Referent	1	Referent	1	Referent
Â Â Â Yes	0.48	0.31, 0.72	0.84	0.47, 1.5	0.7	0.38, 1.3	0.85	0.21, 3.4
Â Â Â Unknown	1.1	0.41, 2.7	0.79	0.49, 1.3	1.1	0.41, 3.1	Â	Â
Current alcohol consumption, drinks/day	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0 (none)	1	Referent	1	Referent	1	Referent	1	Referent
Â Â Â <2	0.8	0.58, 1.1	1.1	0.83, 3.8	0.74	0.46, 1.2	1.1	0.63, 1.9
Â Â Â â‰¥2	0.47	0.25, 0.87	3.3	2.0, 5.6	0.54	0.20, 1.4	1.1	0.43, 2.7
No. of recent oral sex partners	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0	1	Referent	1	Referent	1	Referent	1	Referent
Â Â Â 1	0.67	0.47, 0.95	1.1	0.85, 1.5	1	0.60, 2.8	0.82	0.50, 1.4
Â Â Â 2â€“5	1.1	0.80, 1.6	1.7	1.0, 2.8	1.7	0.95, 3.0	1.4	0.88, 2.3
Â Â Â â‰¥6	1.1	0.63, 1.8	Â	Â	3.0	1.3, 6.7	Â	Â

P for trend	0.64		0.44		<0.001		0.97	
Recently performing oral sex on a woman	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â No	1	Referent	1	Referent	1	Referent	1	Referent
Â Â Â Yes	1.3	0.52, 3.2	0.86	0.40, 1.8	2.8	1.1, 7.2	4.2	1.8, 10.2
Lifetime no. of oral sex partners	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0â€“4	1	Referent	1	Referent	1	Referent	1	Referent
Â Â Â 5â€“99	1.8	0.85, 3.8	2.0	0.96, 4.0	0.80	0.26, 2.5	1.6	0.75, 3.3
Â Â Â â‰¥100	2.3	1.2, 4.4	3.0	1.5, 6.0	1.2	0.33, 4.2	1.0	0.34, 3.5
P for trend	0.004		0.01		0.60		0.26	
No. of recent "rimming"[b] partners[c]	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0	1	Referent	1	Referent	1	Referent	1	Referent
Â Â Â 1	0.68	0.36, 1.3	1.0	0.36, 3.0	1.1	0.45, 2.5	4.6	1.9, 11.3
Â Â Â â‰¥2	1.4	0.82, 2.3	2.1	0.89, 5.0	1.8	0.84, 3.7	Â	Â
CD4 cell count, cells/ÂµL	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â >500	1	Referent	1	Referent	Â	Â	Â	Â
Â Â Â 200â€“499	1.4	1.0, 1.9	1.3	0.93, 1.8	Â	Â	Â	Â
Â Â Â â‰¤200	1.9	1.1, 3.3	4.6	1.9, 11.3	Â	Â	Â	Â
P for trend	0.03		0.04		Â	Â	Â	Â

Abbreviations: aHR, adjusted hazard ratio; AIDS, acquired immunodeficiency syndrome; CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio; MACS, Multicenter AIDS Cohort Study; WIHS, Women's Interagency HIV Study.
[a]Adjusted for HIV status, current CD4 cell count, age, cigarette smoking, alcohol drinking, study site, history of tonsillectomy, recent tooth-brushing, lifetime and recent numbers of oral sex partners, and recently performing oral sex on a woman.
[b]Oral-anal contact.
[c]Results for rimming were adjusted for number of recent oral sex partners and other risk factors. However, results for the other risk factors were not adjusted for number of recent rimming partners.

When analysis was conducted by sex, risk factors for oral HPV infection were similar among men and women, with the exception that heavy alcohol drinking increased risk among women and decreased risk among men (*P* for interaction < 0.001;). Analyses restricted to oncogenic or HPV16 infections revealed risk factors similar to those for all oral HPV infections (all *P*'s for interaction > 0.05; Web Table 4 http://aje.oxfordjournals.org/content/181/1/40/suppl/DC2).

Table 3.Â Risk Factors Related to Oral Human Papillomavirus Incidence by Sex and Human Immunodeficiency Virus Serostatus, Persistent Oral Papillomavirus Study, 2010â€“2013

Participant Characteristic	HIV Serostatus and Sex							
	HIV-Infected				HIV-Uninfected			
	Male (MACS)		Female (WIHS)		Male (MACS)		Female (WIHS)	
	aHR[a]	95% CI	aHR[a]	95% CI	aHR[a]	95% CI	aHR[a]	95% CI
Age, years	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â <45	1	Referent	1	Referent	1	Referent	1	Referent
Â Â Â 45â€“54	0.71	0.41, 1.2	0.86	0.56, 1.3	0.73	0.27, 2.0	1.4	0.68, 2.9
Â Â Â â‰¥55	0.50	0.27, 0.93	0.79	0.49, 1.3	0.71	0.26, 2.0	1.5	0.64, 3.8
P for trend	0.02		0.20		0.52		0.62	

Cigarette smoking	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â Never smoker	1	Referent	1	Referent	1	Referent	1	Referent
Â Â Â Former smoker	0.84	0.56, 1.2	0.74	0.22, 2.5	0.88	0.52, 1.5	2.0	0.58, 7.0
Â Â Â Current smoker	0.74	0.45, 1.2	0.98	0.30, 3.2	0.88	0.44, 1.8	1.5	0.43, 5.2
Ever having a tonsillectomy	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â No	1	Referent	1	Referent	1	Referent	1	Referent
Â Â Â Yes	0.48	0.31, 0.72	0.84	0.47, 1.5	0.7	0.38, 1.3	0.85	0.21, 3.4
Â Â Â Unknown	1.1	0.41, 2.7	0.79	0.49, 1.3	1.1	0.41, 3.1	Â	Â
Current alcohol consumption, drinks/day	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0 (none)	1	Referent	1	Referent	1	Referent	1	Referent
Â Â Â <2	0.8	0.58, 1.1	1.1	0.83, 3.8	0.74	0.46, 1.2	1.1	0.63, 1.9
Â Â Â â‰¥2	0.47	0.25, 0.87	3.3	2.0, 5.6	0.54	0.20, 1.4	1.1	0.43, 2.7
No. of recent oral sex partners	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0	1	Referent	1	Referent	1	Referent	1	Referent
Â Â Â 1	0.67	0.47, 0.95	1.1	0.85, 1.5	1	0.60, 2.8	0.82	0.50, 1.4
Â Â Â 2â€“5	1.1	0.80, 1.6	1.7	1.0, 2.8	1.7	0.95, 3.0	1.4	0.88, 2.3
Â Â Â â‰¥6	1.1	0.63, 1.8	Â	Â	3.0	1.3, 6.7	Â	Â
P for trend	0.64		0.44		<0.001		0.97	
Recently performing oral sex on a woman	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â No	1	Referent	1	Referent	1	Referent	1	Referent
Â Â Â Yes	1.3	0.52, 3.2	0.86	0.40, 1.8	2.8	1.1, 7.2	4.2	1.8, 10.2
Lifetime no. of oral sex partners	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0â€“4	1	Referent	1	Referent	1	Referent	1	Referent
Â Â Â 5â€“99	1.8	0.85, 3.8	2.0	0.96, 4.0	0.80	0.26, 2.5	1.6	0.75, 3.3
Â Â Â â‰¥100	2.3	1.2, 4.4	3.0	1.5, 6.0	1.2	0.33, 4.2	1.0	0.34, 3.5
P for trend	0.004		0.01		0.60		0.26	
No. of recent "rimming"[b] partners[c]	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0	1	Referent	1	Referent	1	Referent	1	Referent
Â Â Â 1	0.68	0.36, 1.3	1.0	0.36, 3.0	1.1	0.45, 2.5	4.6	1.9, 11.3
Â Â Â â‰¥2	1.4	0.82, 2.3	2.1	0.89, 5.0	1.8	0.84, 3.7	Â	Â
CD4 cell count, cells/ÂµL	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â >500	1	Referent	1	Referent	Â	Â	Â	Â
Â Â Â 200â€“499	1.4	1.0, 1.9	1.3	0.93, 1.8	Â	Â	Â	Â
Â Â Â â‰¤200	1.9	1.1, 3.3	4.6	1.9, 11.3	Â	Â	Â	Â
P for trend	0.03		0.04		Â	Â	Â	Â

Abbreviations: aHR, adjusted hazard ratio; AIDS, acquired immunodeficiency syndrome; CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio; MACS, Multicenter AIDS Cohort Study; WIHS, Women's Interagency HIV Study.
[a]Adjusted for HIV status, current CD4 cell count, age, cigarette smoking, alcohol drinking, study site, history of tonsillectomy, recent tooth-brushing, lifetime and recent numbers of oral sex partners, and recently performing oral sex on a woman.

[b]Oral-anal contact.
[c]Results for rimming were adjusted for number of recent oral sex partners and other risk factors. However, results for the other risk factors were not adjusted for number of recent rimming partners.

Risk of oral HPV infection increased with number of lifetime oral sex partners (but not number of recent oral sex partners) in HIV-infected persons, consistent with a hypothesis of reactivation of infection. Therefore, we compared risk factors for oral HPV infection among persons who were sexually abstinent during the study (*n* = 231; 19% of all participants) and persons who were sexually active during the study. Incidence rates were similar in the 2 groups (15.6 per 1,000 person-months vs. 19.4 per 1,000 person-months; *P* = 0.26). HIV infection, low current CD4 cell count, and lifetime number of oral sex partners significantly increased risk of oral HPV in the sexually abstinent group.

Clearance of Oral HPV

The majority of incident oral HPV infections cleared within the first year in both HIV-infected and HIV-uninfected persons. Indeed, when type-specific HPV clearance was defined by a single negative test, 83% (95% CI: 78, 86) of incident infections cleared within a year (Figure 2A). Clearance at 1 year was similar in HIV-uninfected and HIV-infected participants (80% vs. 83%; *P* = 0.80). Estimates of 1-year clearance rates were similar for oncogenic (81%), nononcogenic (83%), and HPV16 (83%) infections. In contrast, prevalent infections were significantly less likely to clear than incident infections (hazard ratio = 2.9, 95% CI: 2.4, 3.6), with an estimated 1-year clearance rate for prevalent infections of 51% (95% CI: 47, 55; Figure 2B). While many infections cleared quickly, it is notable that 23% (95% CI: 21, 26) of infections persisted for at least 2 years, including 7% (95% CI: 5, 10) of incident infections and 35% (95% CI: 31, 39) of prevalent infections.

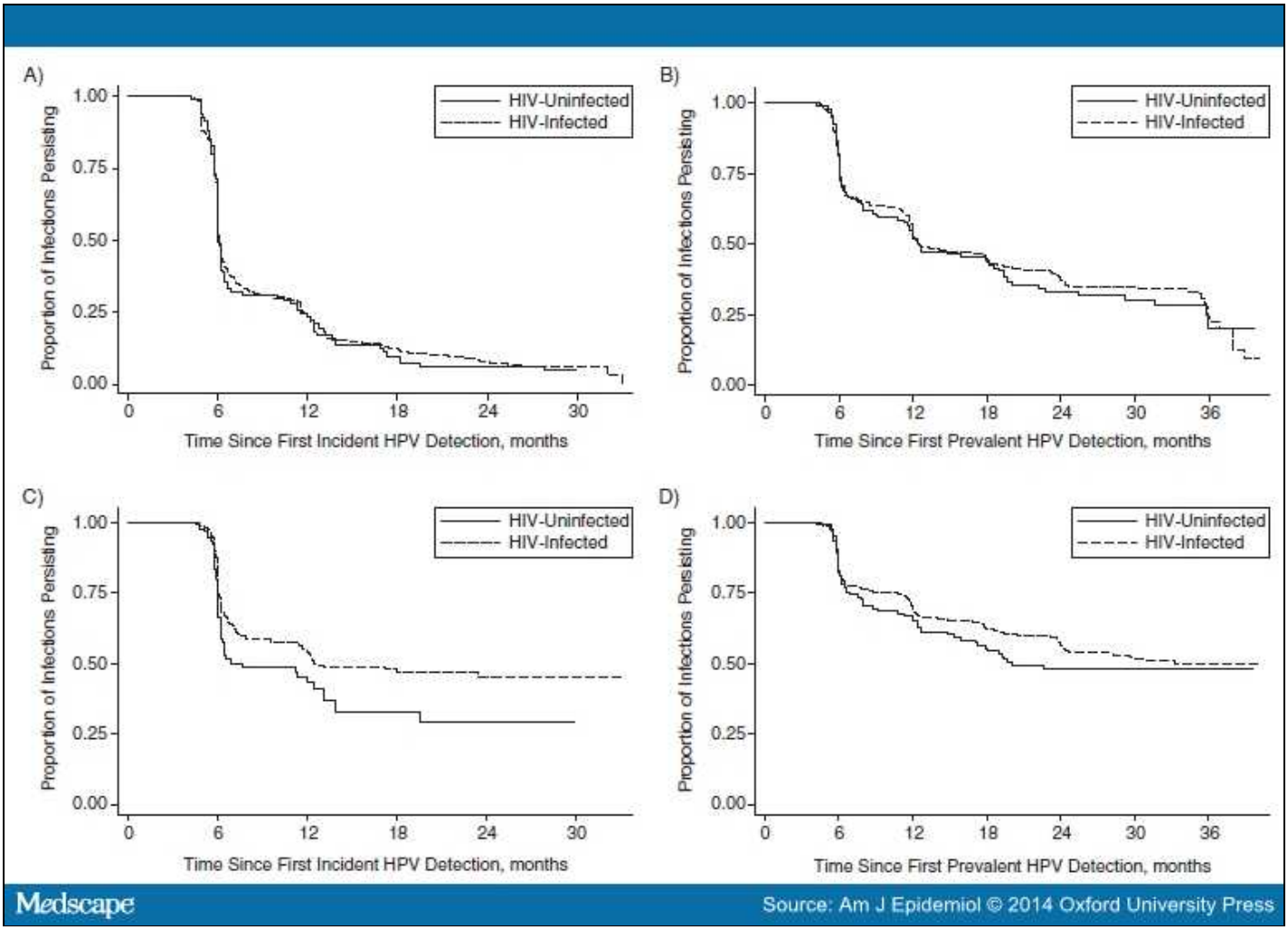

Figure 2.

Â

Clearance of incident (parts A and C) and prevalent (parts B and D) oral human papillomavirus (HPV) infection among human immunodeficiency virus (HIV)-infected and HIV-uninfected persons in the Persistent Oral Papillomavirus Study, 2010â€“2013. Parts A

and B show results obtained when a single negative test was required for the definition of clearance; parts C and D show results obtained when 2 consecutive negative tests were required for an infection to be considered cleared. Numbers of persistent and total infections at 12 months were A) 92/464, B) 221/625, C) 121/461, and D) 363/589. When rates of oral HPV clearance in HIV-infected persons and HIV-uninfected persons were compared using unadjusted Wei-Lin-Weissfeld modeling, the hazard ratios were A) 0.96 (95% confidence interval (CI): 0.70, 1.3), B) 0.94 (95% CI: 0.72, 1.2), C) 0.68 (95% CI: 0.49, 0.95), and D) 0.85 (95% CI: 0.62, 1.2).

When type-specific clearance was defined by 2 consecutive negative tests rather than 1 negative test, 1-year clearance rates for oral HPV infection were appreciably lower for both incident (53% vs. 83%) and prevalent (35% vs. 51%) infections (Figure 2C and 2D). Indeed, 23% of the type-specific HPV infections were intermittently detected during this study.

Risk Factors for Oral HPV Clearance

Male sex, current cigarette smoking, older age, and prevalent (vs. incident) infection significantly reduced rates of clearance of oral HPV infection in unadjusted analysis (each $P < 0.05$; and Web Table 1 http://aje.oxfordjournals.org/content/181/1/40/suppl/DC2). Estimated 1-year clearance rates for oral HPV infection were 59% among men as compared with 70% among women ($P = 0.002$). HIV status, current and nadir CD4 cell count, current HIV viral load, marijuana use, cART use, and alcohol drinking were not significant factors for oral HPV clearance (all P's > 0.05; and Web Table 1 http://aje.oxfordjournals.org/content/181/1/40/suppl/DC2).

Table 4.Â Risk Factors Related to Clearance of Oral Human Papillomavirus Infection by Human Immunodeficiency Virus Serostatus, Persistent Oral Papillomavirus Study, 2010â€“2013

Participant Characteristic[a]	HIV Serostatus[b]											
	HIV-Infected						HIV-Uninfected					
	No. of Cleared Infections	Total No. of Infections With Follow-up	HR	95% CI	aHR[c]	95% CI	No. of Cleared Infections	Total No. of Infections With Follow-up	HR	95% CI	aHR[c]	95% CI
Age, years	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â <45	214	286	1	Referent	1	Referent	49	54	1	Referent	1	Referent
Â Â Â 45â€“54	263	347	0.77	0.55, 1.1	0.87	0.67, 1.1	74	103	0.59	0.41, 0.84	0.60	0.43, 0.85
Â Â Â â‰¥55	153	227	0.61	0.43, 0.88	0.82	0.61, 1.1	49	73	0.45	0.31, 0.63	0.52	0.35, 0.77
P for trend	Â	Â	0.003		0.18		Â	Â	<0.001		0.001	
Sex	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â Female (WIHS)	332	444	1	Referent	1	Referent	76	94	1	Referent	1	Referent
Â Â Â Male (MACS)	298	416	0.72	0.57, 0.92	0.68	0.51, 0.90	96	136	0.75	0.56, 1.0	0.79	0.57, 1.1
Type of infection	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â Prevalent	315	490	1	Referent	1	Referent	1	136	1	Referent	1	Referent
Â Â Â Incident	315	370	2.6	2.1, 3.2	2.5	2.1, 3.0	86	94	2.2	1.6, 3.2	2.2	1.5, 3.3
Cigarette smoking[d]	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â Never smoker	167	206	1	Referent	1	Referent	1	59	1	Referent	1	Referent
Â Â Â Former smoker	147	200	0.80	0.53, 1.2	0.72	0.48, 1.1	43	53	0.92	0.63, 1.3	0.78	0.54, 1.1

Â Â Â Current smoker	305	441	0.86	0.57, 1.3	0.67[e]	0.41, 1.1	85	118	0.89	0.62, 1.3	0.75[e]	0.49, 1.1
Ever having a tonsillectomy	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â No	468	623	1	Referent	1	Referent	129	163	1	Referent	1	Referent
Â Â Â Yes	115	166	0.72	0.56, 0.92	0.83	0.64, 1.1	36	47	0.79	0.56, 1.1	1.0	0.69, 1.4
Â Â Â Unknown	20	23	0.86	0.63, 1.2	1.00	0.72, 1.4	2	5	0.36	0.15, 0.82	0.42	0.30, 0.60
CD4 cell count, cells/ÂµL[d]	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â >500	279	368	1	Referent	1	Referent	Â	Â	Â	Â	Â	Â
Â Â Â 200â€“499	218	314	0.96	0.81, 1.1	0.98	0.83, 1.2	Â	Â	Â	Â	Â	Â
Â Â Â â‰¤200	130	175	1.3	0.79, 2.2	1.1	0.74, 1.7	Â	Â	Â	Â	Â	Â
P for trend	Â	Â	0.52		0.94		Â	Â	Â	Â	Â	Â

Abbreviations: aHR, adjusted hazard ratio; AIDS, acquired immunodeficiency syndrome; CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio; MACS, Multicenter AIDS Cohort Study; WIHS, Women's Interagency HIV Study.
[a]All variables were time-updated except for ever having a tonsillectomy, for which data were collected only at the Persistent Oral Papillomavirus Study baseline visit.
[b]There were no significant interactions between oral HPV clearance and these risk factors by HIV status.
[c]Adjusted for current CD4 cell count, age, sex, type of infection, cigarette smoking, and history of tonsillectomy.
[d]Effect modification by sex/cohort (*P* for interaction < 0.10; Web Table 5).
[e]When HIV-infected and HIV-uninfected persons were combined, oral HPV clearance was significantly lower among current smokers (*P* < 0.05; Web Table 3).

Table 4.Â Risk Factors Related to Clearance of Oral Human Papillomavirus Infection by Human Immunodeficiency Virus Serostatus, Persistent Oral Papillomavirus Study, 2010â€“2013

Participant Characteristic[a]	HIV Serostatus[b]											
	HIV-Infected						HIV-Uninfected					
	No. of Cleared Infections	Total No. of Infections With Follow-up	HR	95% CI	aHR[c]	95% CI	No. of Cleared Infections	Total No. of Infections With Follow-up	HR	95% CI	aHR[c]	95% CI
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Â Â Â 45â€“54	263	347	0.77	0.55, 1.1	0.87	0.67, 1.1	74	103	0.59	0.41, 0.84	0.60	0.43, 0.85
Â Â Â â‰¥55	153	227	0.61	0.43, 0.88	0.82	0.61, 1.1	49	73	0.45	0.31, 0.63	0.52	0.35, 0.77
P for trend	Â	Â	0.003		0.18		Â	Â	<0.001		0.001	
Sex	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â Female (WIHS)	332	444	1	Referent	1	Referent	76	94	1	Referent	1	Referent

Â Â Â Male (MACS)	298	416	0.72	0.57, 0.92	0.68	0.51, 0.90	96	136	0.75	0.56, 1.0	0.79	0.57, 1.1
Type of infection	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â Prevalent	315	490	1	Referent	1	Referent	1	136	1	Referent	1	Referent
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Cigarette smoking[d]	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â Never smoker	167	206	1	Referent	1	Referent	1	59	1	Referent	1	Referent
Â Â Â Former smoker	147	200	0.80	0.53, 1.2	0.72	0.48, 1.1	43	53	0.92	0.63, 1.3	0.78	0.54, 1.1
Â Â Â Current smoker	305	441	0.86	0.57, 1.3	0.67[e]	0.41, 1.1	85	118	0.89	0.62, 1.3	0.75[e]	0.49, 1.1
Ever having a tonsillectomy	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â No	468	623	1	Referent	1	Referent	129	163	1	Referent	1	Referent
Â Â Â Yes	115	166	0.72	0.56, 0.92	0.83	0.64, 1.1	36	47	0.79	0.56, 1.1	1.0	0.69, 1.4
Â Â Â Unknown	20	23	0.86	0.63, 1.2	1.00	0.72, 1.4	2	5	0.36	0.15, 0.82	0.42	0.30, 0.60
CD4 cell count, cells/ÂµL[d]	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â >500	279	368	1	Referent	1	Referent	Â	Â	Â	Â	Â	Â
Â Â Â 200â€“499	218	314	0.96	0.81, 1.1	0.98	0.83, 1.2	Â	Â	Â	Â	Â	Â
Â Â Â â‰¤200	130	175	1.3	0.79, 2.2	1.1	0.74, 1.7	Â	Â	Â	Â	Â	Â
P for trend	Â	Â	0.52		0.94		Â	Â	Â	Â	Â	Â

Abbreviations: aHR, adjusted hazard ratio; AIDS, acquired immunodeficiency syndrome; CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio; MACS, Multicenter AIDS Cohort Study; WIHS, Women's Interagency HIV Study.
[a]All variables were time-updated except for ever having a tonsillectomy, for which data were collected only at the Persistent Oral Papillomavirus Study baseline visit.
[b]There were no significant interactions between oral HPV clearance and these risk factors by HIV status.
[c]Adjusted for current CD4 cell count, age, sex, type of infection, cigarette smoking, and history of tonsillectomy.
[d]Effect modification by sex/cohort (*P* for interaction < 0.10; Web Table 5).
[e]When HIV-infected and HIV-uninfected persons were combined, oral HPV clearance was significantly lower among current smokers (*P* < 0.05; Web Table 3).

Male sex, current cigarette smoking, older age, and prevalent (vs. incident) infection each independently reduced oral HPV clearance in adjusted analyses (each *P* < 0.05; and). Results were similar in analyses stratified by HIV status () and sex (Web Table 5 http://aje.oxfordjournals.org/content/181/1/40/suppl/DC2). However, cigarette smoking reduced clearance rates only among women, and clearance rates declined with decreased current CD4 cell count only among men (both *P*'s for interaction < 0.10; Web Table 5 http://aje.oxfordjournals.org/content/181/1/40/suppl/DC2). Analyses restricted to only oncogenic types or only HPV16 infections revealed similar results, with the exception that clearance rates for oral HPV16 infections declined more sharply with increasing age (*P* for interaction = 0.02; Web Table 4 http://aje.oxfordjournals.org/content/181/1/40/suppl/DC2).

Table 3.Â Risk Factors Related to Oral Human Papillomavirus Incidence by Sex and Human Immunodeficiency Virus Serostatus, Persistent Oral Papillomavirus Study, 2010â€“2013

Participant Characteristic	HIV Serostatus and Sex							
	HIV-Infected				HIV-Uninfected			
	Male (MACS)		Female (WIHS)		Male (MACS)		Female (WIHS)	
	aHR[a]	95% CI	aHR[a]	95% CI	aHR[a]	95% CI	aHR[a]	95% CI
Age, years	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â <45	1	Referent	1	Referent	1	Referent	1	Referent
Â Â Â 45â€“54	0.71	0.41, 1.2	0.86	0.56, 1.3	0.73	0.27, 2.0	1.4	0.68, 2.9
Â Â Â â‰¥55	0.50	0.27, 0.93	0.79	0.49, 1.3	0.71	0.26, 2.0	1.5	0.64, 3.8
P for trend	0.02		0.20		0.52		0.62	
Cigarette smoking	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â Never smoker	1	Referent	1	Referent	1	Referent	1	Referent
Â Â Â Former smoker	0.84	0.56, 1.2	0.74	0.22, 2.5	0.88	0.52, 1.5	2.0	0.58, 7.0
Â Â Â Current smoker	0.74	0.45, 1.2	0.98	0.30, 3.2	0.88	0.44, 1.8	1.5	0.43, 5.2
Ever having a tonsillectomy	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â No	1	Referent	1	Referent	1	Referent	1	Referent
Â Â Â Yes	0.48	0.31, 0.72	0.84	0.47, 1.5	0.7	0.38, 1.3	0.85	0.21, 3.4
Â Â Â Unknown	1.1	0.41, 2.7	0.79	0.49, 1.3	1.1	0.41, 3.1	Â	Â
Current alcohol consumption, drinks/day	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0 (none)	1	Referent	1	Referent	1	Referent	1	Referent
Â Â Â <2	0.8	0.58, 1.1	1.1	0.83, 3.8	0.74	0.46, 1.2	1.1	0.63, 1.9
Â Â Â â‰¥2	0.47	0.25, 0.87	3.3	2.0, 5.6	0.54	0.20, 1.4	1.1	0.43, 2.7
No. of recent oral sex partners	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0	1	Referent	1	Referent	1	Referent	1	Referent
Â Â Â 1	0.67	0.47, 0.95	1.1	0.85, 1.5	1	0.60, 2.8	0.82	0.50, 1.4
Â Â Â 2â€“5	1.1	0.80, 1.6	1.7	1.0, 2.8	1.7	0.95, 3.0	1.4	0.88, 2.3
Â Â Â â‰¥6	1.1	0.63, 1.8	Â	Â	3.0	1.3, 6.7	Â	Â
P for trend	0.64		0.44		<0.001		0.97	
Recently performing oral sex on a woman	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â No	1	Referent	1	Referent	1	Referent	1	Referent
Â Â Â Yes	1.3	0.52, 3.2	0.86	0.40, 1.8	2.8	1.1, 7.2	4.2	1.8, 10.2
Lifetime no. of oral sex partners	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0â€“4	1	Referent	1	Referent	1	Referent	1	Referent
Â Â Â 5â€“99	1.8	0.85, 3.8	2.0	0.96, 4.0	0.80	0.26, 2.5	1.6	0.75, 3.3
Â Â Â â‰¥100	2.3	1.2, 4.4	3.0	1.5, 6.0	1.2	0.33, 4.2	1.0	0.34, 3.5
P for trend	0.004		0.01		0.60		0.26	
No. of recent "rimming"[b] partners[c]	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â 0	1	Referent	1	Referent	1	Referent	1	Referent

Â Â Â 1	0.68	0.36, 1.3	1.0	0.36, 3.0	1.1	0.45, 2.5	4.6	1.9, 11.3
Â Â Â â‰¥2	1.4	0.82, 2.3	2.1	0.89, 5.0	1.8	0.84, 3.7	Â	Â
CD4 cell count, cells/ÂµL	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â >500	1	Referent	1	Referent	Â	Â	Â	Â
Â Â Â 200â€“499	1.4	1.0, 1.9	1.3	0.93, 1.8	Â	Â	Â	Â
Â Â Â â‰¤200	1.9	1.1, 3.3	4.6	1.9, 11.3	Â	Â	Â	Â
P for trend	0.03		0.04		Â	Â	Â	Â

Abbreviations: aHR, adjusted hazard ratio; AIDS, acquired immunodeficiency syndrome; CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio; MACS, Multicenter AIDS Cohort Study; WIHS, Women's Interagency HIV Study.
[a]Adjusted for HIV status, current CD4 cell count, age, cigarette smoking, alcohol drinking, study site, history of tonsillectomy, recent tooth-brushing, lifetime and recent numbers of oral sex partners, and recently performing oral sex on a woman.
[b]Oral-anal contact.
[c]Results for rimming were adjusted for number of recent oral sex partners and other risk factors. However, results for the other risk factors were not adjusted for number of recent rimming partners.

Table 4.Â Risk Factors Related to Clearance of Oral Human Papillomavirus Infection by Human Immunodeficiency Virus Serostatus, Persistent Oral Papillomavirus Study, 2010â€“2013

Participant Characteristic[a]	HIV Serostatus[b]											
	HIV-Infected						HIV-Uninfected					
	No. of Cleared Infections	Total No. of Infections With Follow-up	HR	95% CI	aHR[c]	95% CI	No. of Cleared Infections	Total No. of Infections With Follow-up	HR	95% CI	aHR[c]	95% CI
Age, years	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
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Â Â Â 45â€“54	263	347	0.77	0.55, 1.1	0.87	0.67, 1.1	74	103	0.59	0.41, 0.84	0.60	0.43, 0.85
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P for trend	Â	Â	0.003		0.18		Â	Â	<0.001		0.001	
Sex	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â Female (WIHS)	332	444	1	Referent	1	Referent	76	94	1	Referent	1	Referent
Â Â Â Male (MACS)	298	416	0.72	0.57, 0.92	0.68	0.51, 0.90	96	136	0.75	0.56, 1.0	0.79	0.57, 1.1
Type of infection	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â Prevalent	315	490	1	Referent	1	Referent	1	136	1	Referent	1	Referent
Â Â Â Incident	315	370	2.6	2.1, 3.2	2.5	2.1, 3.0	86	94	2.2	1.6, 3.2	2.2	1.5, 3.3
Cigarette smoking[d]	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â Never smoker	167	206	1	Referent	1	Referent	1	59	1	Referent	1	Referent

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Â Â Â â‰¤200	130	175	1.3	0.79, 2.2	1.1	0.74, 1.7	Â	Â	Â	Â	Â	Â
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Cigarette smoking[d]	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â Never smoker	167	206	1	Referent	1	Referent	1	59	1	Referent	1	Referent
Â Â Â Former smoker	147	200	0.80	0.53, 1.2	0.72	0.48, 1.1	43	53	0.92	0.63, 1.3	0.78	0.54, 1.1
Â Â Â Current smoker	305	441	0.86	0.57, 1.3	0.67[e]	0.41, 1.1	85	118	0.89	0.62, 1.3	0.75[e]	0.49, 1.1
Ever having a tonsillectomy	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â No	468	623	1	Referent	1	Referent	129	163	1	Referent	1	Referent
Â Â Â Yes	115	166	0.72	0.56, 0.92	0.83	0.64, 1.1	36	47	0.79	0.56, 1.1	1.0	0.69, 1.4
Â Â Â Unknown	20	23	0.86	0.63, 1.2	1.00	0.72, 1.4	2	5	0.36	0.15, 0.82	0.42	0.30, 0.60
CD4 cell count, cells/ÂµL[d]	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â	Â
Â Â Â >500	279	368	1	Referent	1	Referent	Â	Â	Â	Â	Â	Â
Â Â Â 200â€“499	218	314	0.96	0.81, 1.1	0.98	0.83, 1.2	Â	Â	Â	Â	Â	Â
Â Â Â â‰¤200	130	175	1.3	0.79, 2.2	1.1	0.74, 1.7	Â	Â	Â	Â	Â	Â
P for trend	Â	Â	0.52		0.94		Â	Â	Â	Â	Â	Â

Abbreviations: aHR, adjusted hazard ratio; AIDS, acquired immunodeficiency syndrome; CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio; MACS, Multicenter AIDS Cohort Study; WIHS, Women's Interagency HIV Study.
[a]All variables were time-updated except for ever having a tonsillectomy, for which data were collected only at the Persistent Oral Papillomavirus Study baseline visit.
[b]There were no significant interactions between oral HPV clearance and these risk factors by HIV status.
[c]Adjusted for current CD4 cell count, age, sex, type of infection, cigarette smoking, and history of tonsillectomy.
[d]Effect modification by sex/cohort (*P* for interaction < 0.10; Web Table 5).
[e]When HIV-infected and HIV-uninfected persons were combined, oral HPV clearance was significantly lower among current smokers (*P* < 0.05; Web Table 3).

Risk factors for clearance were similar when 2 consecutive negative tests were utilized to define clearance rather than 1 negative test (Web Tables 3 and 6 http://aje.oxfordjournals.org/content/181/1/40/suppl/DC2), with the exception that when a 2-negative-test definition of clearance was used, there was significantly lower clearance of oral HPV infection among HIV-infected persons than among HIV-uninfected persons (adjusted hazard ratio = 0.75, 95% CI: 0.60, 0.95).

Discussion

In this study of the natural history of oral HPV infection among HIV-infected and at-risk HIV-uninfected persons, sexual behavior, HIV infection, and severity of immunosuppression significantly increased the risk of oral HPV infection. In contrast, male sex, older age, and current cigarette smoking increased the risk of persistence. Our data therefore help explain the consistent associations observed between all of these factors and prevalent oral HPV infection in previous cross-sectional studies among HIV-infected[7,15,16,23] and HIV-uninfected[5,7,15,23,32] persons.

The vast majority of incident oral HPV infections in this analysis cleared within 2 years of follow-up (93%). Thus, clearance of oral HPV infections is quite similar to that of anogenital HPV infections among HIV-infected[33,34] and HIV-uninfected[35] persons, where only a small minority of incident infections (approximately 10%) persist to 2 years. While persistence of anogenital infection is an accepted surrogate for subsequent risk of anogenital dysplasia,[3,36] it remains to be determined whether persistent oral HPV infection could be used to identify persons at risk for oropharyngeal cancer.

Surprisingly, we found that the higher prevalence of oral HPV infection among immunosuppressed HIV-infected persons[7,15,23] is probably explained more by an increased risk of incident infection than by reduced clearance. This suggests that immunosuppression may act primarily on the earliest stage of the oral HPV carcinogenesis process. Indeed, in a recent study, Tugizov et al.[37] reported that the HIV proteins tat and gp120 disrupt the tight junctions in oral mucosal epithelium, a factor which may facilitate infection upon exposure. The lack of a major impact of immunosuppression on oral HPV clearance is counter to most previous studies of cervical HPV clearance[38,39] but is similar to the findings of 1 study involving cervical HPV[34] and 1 study involving oral HPV.[9]

To our knowledge, this is one of the first studies to have found that both performance of oral sex and "rimming" are associated with increased risk of oral HPV acquisition. While this provides some of the first prospective support for the sexual transmission of oral HPV infection, because of strong correlations between these and other sexual behaviors we cannot exclude the possibility of a role for additional factors, such as autoinoculation of anogenital HPV infections.[13,40] Our results are consistent with observed associations between sexual behaviors and oral HPV prevalence in several other studies,[5,7] although 1 recent study of primarily heterosexual men did not find an association between oral HPV incidence and oral sex.[10]

This study suggests that while some infections are newly acquired through sex, other incidentally detected oral HPV infections may be acquired through autoinoculation or may be reactivated latent infections, analogous to what has been observed in cervical HPV studies.[34,41,42] We observed a substantial number of incident infections among persons who reported not having had any form of sex during the study. In these sexually abstinent individuals, there was a strong association between oral HPV incidence and immunosuppression. Thus, the increased risk of oral HPV infection among immunosuppressed persons may be partially explained by reactivation or reacquisition of previously acquired infection due to poor immune surveillance.[43]

Several factors were associated with reduced clearance of oral HPV infection, including cigarette smoking, older age, and male sex. Higher persistence rates among men are of particular interest given their higher incidence rates of HPV-positive oropharyngeal cancer.[44] Reduced oral HPV clearance among men is consistent with a more vigorous immune response to infectious agents among women compared with men, potentially from hormonal differences.[45] In addition, the higher risk of oral HPV infection we observed among persons reporting cunnilingus (i.e., performing oral sex on a woman) is consistent with a hypothesis of higher rates of transmission with cunnilingus than with fellatio.[9,16] This could also contribute to the higher oropharyngeal cancer incidence among men.[1]

Our results also suggest that the higher oral HPV prevalence among cigarette smokers[5,7,32] may be due to a reduced ability to clear oral HPV infection rather than an increased likelihood of acquiring/reactivating oral HPV. This association was observed only among women, which is consistent with the results of another large oral HPV prevalence study.[5] In addition, the present study may help explain oral HPV's bimodal distribution with age,[5] as we observed older persons to have lower incidence but reduced clearance of oral HPV infections, particularly HPV16 infections. Finally, this study found that persons with a history of tonsillectomy may have a reduced risk of oral HPV infection. To our knowledge, this has not been previously observed and thus needs further replication, but it may suggest increased susceptibility of tonsillar epithelium to infection.

This study had several important strengths. To our knowledge, it was one of the first large and long-term longitudinal studies with male and female participants to provide information on the clearance of incident oral HPV infections with high follow-up rates and detailed information on risk factors. Previous longitudinal studies have had little follow-up time and/or limited numbers of participants and infections.[9â€“14] In addition, our population was valuable for gaining a better understanding of the natural history of oral HPV infection, given that oropharyngeal cancers often arise in middle age and HIV-infected persons are at increased risk for this cancer.[16]

However, the study also had limitations. This study population was enrolled through a convenience sample, although participants were representative of those in the larger MACS and WIHS cohorts. In addition, this was a high-risk study population, so the findings may have reduced generalizability to other populations, although the study had the advantage of comparing HIV-infected persons with

at-risk HIV-uninfected persons. Data on many of the covariates, such as sexual behavior, were self-reported via computer-assisted self-interview or interviewer-administered questionnaire and could have been misreported. In addition, the times to clearance for oral HPV should be interpreted with caution; our 6-month sampling interval may have underestimated incidence and clearance rates, given the fact that HPV infections are commonly transient. On the other hand, infections were commonly re-detected, so it is possible that a single negative test *overestimates* the actual clearance rate.

The results of this longitudinal study suggest that the risk of oral HPV infection is increased by oral sex and with immunosuppression, while the risk of oral HPV persistence is increased by older age, male sex, and cigarette smoking. As is the case for anogenital infections,[33â€“35] oral HPV infections appear to be often transient, but a subset of infections persists to at least 2 years. The risk of these long-term persistent oral HPV infections' progressing to oropharyngeal cancer is unknown. Additional research will be necessary to better understand these long-term persistent infections, as well as the biological underpinnings of associations with sex, age, and smoking.

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Abbreviations
AIDS; acquired immunodeficiency syndrome; cART; combination antiretroviral therapy; CI; confidence interval; HIV; human immunodeficiency virus; HPV; human papillomavirus; MACS; Multicenter AIDS Cohort Study; POPS; Persistent Oral Human Papillomavirus Study; WIHS; Women's Interagency HIV Study.

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