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The association of medication use with clearance or persistence of oral HPV infection

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Abstract

Purpose—Persistent oral human papillomavirus (HPV) infection increases risk for oropharyngeal carcinoma, and people living with HIV have higher rates of oral HPV infection and related cancers. Some prescription medications have immunomodulatory effects, but the impact of medication use on oral HPV natural history is unknown.

Methods—Scope® oral rinse-and-gargle samples were collected semi-annually from 1,666 participants and tested for 37 types of oral HPV DNA using PCR; 594 HPV-infected participants

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with 1,358 type-specific oral HPV infections were identified. Data were collected on recent (past 6 months) use of medications. The relationship between medication use and oral HPV clearance was evaluated using Wei-Lin-Weissfeld regression, adjusting for biologic sex, prevalent vs. incident infection, age, HIV status and CD4+ T-cell count.

Results—Out of 11 medications examined, oral HPV clearance was significantly reduced in participants reporting recent use of antipsychotics (HR=0.75, 95% CI=0.57–0.99), anxiolytics/sedatives (HR=0.78, 95% CI=0.63–0.96) and antidepressants (HR=0.82, 95% CI=0.67–0.999). Among antipsychotics users, effect modification by HIV status was observed, with reduced clearance in HIV-infected (HR=0.67, 95%: CI 0.49–0.91), but not HIV-uninfected participants (p-interaction=0.009). After adjusted analysis, antipsychotic use remained significantly associated with reduced oral HPV clearance overall (aHR=0.75, 95% CI=0.57–0.99), and when restricted to only HIV-infected participants (aHR=0.66, 95% CI=0.48–0.90). After adjustment, anxiolytic/sedative use and antidepressant use were no longer significantly associated with reduced oral HPV clearance.

Conclusions—Some medications were associated with decreased oral HPV clearance, most notably antipsychotic medications. These medications are prescribed for conditions that may have immunomodulating effects, so characteristics of underlying illness may have partially contributed to reduced oral HPV clearance.

Keywords

oral HPV; prescription medication; clearance; antipsychotic; HIV; immunomodulatory

Background and rationale

Persistent oncogenic oral human papillomavirus (HPV) infection is the presumed precursor for HPV-related oropharyngeal squamous cell carcinoma (OPSCC), but risk factors for oral HPV persistence are poorly understood [1]. Several commonly prescribed medication types have immunomodulatory effects, either as part of their primary therapeutic activity or as a side effect, including: antidepressants [2], antipsychotics [3], sedatives/anxiolytics [4], anti-asthmatics [5], antihypertensives [6], cholesterol-lowering medications[7], hormonal treatments [8], erectile dysfunction drugs [9], and diabetes medications [10]. It is therefore possible that these medications may impact oral HPV natural history, although this question has not been previously investigated.

People living with HIV (PLWH) have 2–3 times higher oral HPV prevalence than HIV-uninfected individuals, and are commonly taking multiple medications, in addition to antiretroviral therapy (ART) [11]. In a cross-sectional study of PLWH in the Southern U.S., 93% were receiving at least one non-ART medication, including antihypertensives (43%), lipid-lowering agents (34%) and antidepressants/antipsychotics/anxiolytics (34%), and the median number of medications per patient was 8 (IQR: 6–11) [12]. Indeed, as people are living longer with HIV, the diagnosis and treatment of age-related chronic conditions is increasing [13]. HIV-related immunosuppression, such as lower CD4+ T cell counts, may facilitate oral HPV persistence by attenuating immune responses to HPV [14]. However, it is unclear whether immunomodulatory medications may also play a role. Given the high

prevalence of polypharmacy and oral HPV infection among PLWH, we conducted a study to investigate whether medication use may impact oral HPV natural history among individuals with and without HIV.

Methods

Study design and study population

From 2010 to 2014, 1,666 participants were enrolled in the "Persistence of Oral Papillomavirus Study" (POPS), a longitudinal study of oral HPV natural history. POPS was nested within two ongoing observational studies of men and women with or at risk for HIV: the Multicenter AIDS Cohort Study (MACS) and the Women's Interagency HIV Study (WIHS) [15,16]. POPS participants were enrolled at 6 study locations: Baltimore/DC (MACS), Los Angeles (MACS), Pittsburgh (MACS), Brooklyn (WIHS), Bronx (WIHS), and Chicago (sites for MACS and WIHS). Each study center's Institutional Review Board approved the study. All participants provided written informed consent.

Data collection

At each semi-annual POPS visit, a 30-second Scope® oral rinse-and-gargle sample was collected to obtain oral exfoliated cells which was tested for 37 types of HPV DNA. A blood sample was also obtained, from which HIV status and CD4+ T cell count were determined. At each visit, participants completed a structured interviewer-administered questionnaire about their medication use in the past 6 months [17]. Data were collected on recent medication use, which was then grouped into the following 11 medication types: antiasthmatics (steroidal and non-steroidal), antidepressants, antihypertensives, antipsychotics (used to treat schizophrenia, bipolar disorder and related psychotic disorders), anxiolytics/sedatives (used to treat anxiety, sleeping disorders, epilepsy, alcohol withdrawal, muscle spasms and other conditions), cholesterol-lowering medications, diabetes medications, hormones (including hormone replacement therapy or hormones used to treat thyroid disorders, but excluding birth control hormones), non-steroidal anti-inflammatory drugs (NSAIDs), and erectile dysfunction medications (men only). For analysis, anxiolytics and sedatives were combined into a single medication group. Other types of medications, such as HIV-related medication, were not explored as part of this analysis.

Oral HPV detection and genotyping

Oral rinse samples were tested for 37 types of HPV DNA using a polymerase chain reaction (PCR) assay, followed by reverse line-blot hybridization (Roche Molecular Systems, Pleasanton, CA) [18]. Each sample was evaluated for the presence of high-risk/oncogenic types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66) and low-risk/non-oncogenic types (6, 11, 26, 38, 40, 42, 53, 54, 55, 61, 62, 64, 67, 68, 69, 70, 71, 72, 73, 81, 83, 84, 89, IS39), classified according to criteria from the International Agency for Research on Cancer [19–21]. Prevalent oral HPV infection was defined as any type-specific oral HPV infection detected at study enrollment. Incident infection was defined as any newly detected HPV type-specific infection that was preceded by at least one visit where that HPV type was not detected.

Clearance was defined as two consecutive HPV-negative oral rinses, with time of clearance as the visit of the first negative oral rinse sample. A secondary less conservative definition of clearance was considered, requiring only one HPV-negative oral rinse sample, but as results were similar with both clearance definitions, these results are not shown.

Statistical analyses

The units of analysis were type-specific oral HPV infections. Some participants were infected with multiple HPV types at the same visit. The effect of each medication type on oral HPV clearance was modeled using Wei-Lin-Weissfeld regression models, accounting for within-participant clustering of HPV infections [22]. First, the effect of each medication was considered in separate univariable models. Then, concomitant use of medication pairs were modeled for each of the medications that were commonly used in this study, to assess whether use of both medications together was associated with time to clearance, as compared to using none or only one of the medications. For medications associated with clearance, the number of total medications concurrently used was evaluated to determine whether a greater number of medications used increased strength of association with clearance. The final multivariable model adjusted for biologic sex, prevalent vs. incident HPV infection, age (<45, 45–54, ≥55 years), HIV status, and CD4+ T cell count (≥500, <500 cells/μL). Analyses were performed using Stata 12 [23]. Statistical significance was defined by a two-sided p-value <0.05.

Results

Participant characteristics

Of 1,666 participants, 594 HPV-infected participants with 1,358 type-specific oral HPV infections were identified. Half of participants (54%) were men, 55% were of Black race, and the median age was 50 years (Table 1). The study included 168 (28%) HIV-uninfected individuals and 426 (72%) people living with HIV (PLWH), most (81%) of whom were on current antiretroviral therapy (ART) and had CD4+ T cell count ≥500 cells/μL (50%).

At time of first oral HPV detection, most participants (84%) reported using at least 1 medication, not counting ART, or prescription erectile dysfunction medications (which were used by 17% of men). Among 594 HPV-infected study participants, the most commonly used prescription drugs were anti-hypertensives (39% of participants), NSAIDs (39%), cholesterol-lowering drugs (27%), antidepressants (25%) and anxiolytics/sedatives (21%) (Figure 1).

Concurrent use of two or more medications was reported by 34% of participants. The most commonly used medication classification pairs were: cholesterol-lowering and hypertension medications (15% of all study participants), hypertension and diabetes medications (9%), cholesterol-lowering and diabetes medications (7%) and antipsychotics and antidepressants (7%) (Figure 2).

Effect of medication use on time to oral HPV clearance

Oral HPV clearance was evaluated over 18,465 person-months of follow-up. Median time to clearance of oral HPV infection was 6.3 months (IQR: 5.9–12.1). In unadjusted analyses, reduced oral HPV clearance was significantly associated with recent use of 3 of the 11 medication classes evaluated: antipsychotics (HR=0.75, 95% CI=0.57–0.99), anxiolytics/sedatives (HR=0.78, 95% CI=0.63–0.96) and antidepressants (HR=0.82, 95% CI=0.67–0.99) (Table 2). Use of erectile dysfunction medications was marginally associated with reduced oral HPV clearance (HR=0.77, 95% CI=0.58–1.01). No other medication class was significantly associated with oral HPV clearance.

Among users of antipsychotics, there appeared to be effect modification by HIV status (p-interaction=0.009), with reduced clearance in PLWH (HR=0.67, 95% CI=0.49–0.91), but not HIV-uninfected participants (HR=1.38, 95% CI=0.88–2.17) (Table 2). Although statistically significant, the numbers of HIV-uninfected participants reporting use of antipsychotics at time of oral HPV detection was small (13 infections among 10 people), which limits interpretation of this possible interaction by HIV status. Use of anxiolytics/sedatives and antidepressants were more common among HIV-uninfected than PLWH in this study, and the associations of these medications did not differ by HIV status (p-interaction=0.99 and 0.81, respectively).

After adjusting for the effects of biologic sex, prevalent vs. incident oral HPV infection, age, HIV status and CD4+ T cell count measured at the visit of oral HPV detection, antipsychotic use remained significantly associated with reduced oral HPV clearance (aHR=0.75, 95% CI=0.57–0.99) overall and when restricted to only HIV-infected participants (aHR=0.66, 95% CI=0.48–0.90), but not among HIV-uninfected participants (aHR=1.62, 95%CI=0.96–2.73, p=interaction=0.009). After adjustment, anxiolytics/sedatives (aHR=0.89, 95% CI=0.73–1.07), antidepressants (aHR=0.89, 95% CI=0.71–1.11) and erectile dysfunction medications (aHR=0.78, 95% CI=0.59–1.05) were no longer statistically significantly associated with oral HPV clearance. We were underpowered to explore risk factors separately for oncogenic and non-oncogenic oral HPV infection; when explored, with not statistically significant, all 3 medication classes associated with reduced overall oral HPV clearance (antipsychotic medications, antidepressants and anxiolytics/sedatives) remained associated with both reduced oncogenic and non-oncogenic oral HPV infection clearance

Concomitant medication use

Of the participants using antipsychotics, 67% also reported use of antidepressants and 29% also reported use of anxiolytics/sedatives at time of oral HPV detection. When evaluating concurrent use of these 3 medication classes in unadjusted analyses, participants who reported recent use of all 3 medications had the greatest reduction in clearance (HR=0.57, 95% CI=0.35–0.94), followed by participants who used any 2 of these medications (HR=0.73, 95% CI=0.55–0.96) or only 1 of these three medications (HR=0.83, 95% CI=0.69–1.00), as compared to participants who used none of these medications (p-trend=0.002) (Figure 3). After adjustment for other risk factors, concomitant use of antipsychotics, antidepressants, and anxiolytics/sedatives remained marginally associated with reduced clearance, with increasing number of psychotropic medications used being

associated with significantly higher likelihood of decreased clearance (p-trend=0.04), and no interaction by HIV in this association. Concomitant use of other types of medications (i.e. commonly paired medications) was not significantly associated with oral HPV clearance.

Discussion

While most medications did not affect oral HPV clearance, use of antipsychotics, antidepressants and anxiolytics/sedatives were observed to decrease oral HPV clearance with stronger effects when used concomitantly. The mechanisms by which these medications reduce oral HPV clearance remain unclear, but may be due to immunomodulatory effects of the medication or the underlying illness being treated by the medication. However, other immunomodulatory medications examined (i.e. steroidal antiasthmatics) did not affect oral HPV clearance, suggesting the possibility of other explanatory factors.

The immunomodulatory effects of antipsychotics, which are used for treatment of schizophrenia or bipolar disorder, have been consistently reported, and may explain the reduced oral HPV clearance observed among users of these medications [3]. It is also possible that reduced oral HPV clearance was associated with immune dysregulation, which is known to be associated with psychotic diagnoses such as schizophrenia and bipolar disorder [24], or by biological or behavioral factors unique to individuals with these disorders. This study assessed medication use only, and we were unable to confirm diagnoses or the specific disorders that these medications were used to treat.

In this study, recent use of antidepressants and benzodiazepines (a major class of anxiolytic/sedative medications) also appeared to reduce oral HPV clearance, although the effect was not as strong as that observed with use of antipsychotics. It is possible the immunomodulatory effects of these medications, or the inflammatory response from conditions treated with these medications, such as depression [25–29,2], or anxiety and stress-related disorders[30,4] may influence oral HPV clearance, although associations were not statistically significant in adjusted analysis.

This study had several strengths and limitations. Strengths of this study included the large population size, longitudinal follow-up and centralized testing of oral HPV infection. In addition, detailed information on medication use was collected prospectively on validated survey instruments administered by experienced research staff who participants knew well. Medication use was self-reported and we cannot exclude the possibility of misreporting/misclassification and heterogeneity in medications within classes. Data on dose, frequency, and adherence of medication use were not available. Our analysis does not take into consideration differences in drug formulations or specific medications within each drug class.

Conclusion

In summary, we found significantly reduced oral HPV clearance in participants using antipsychotic medication with potential differential effects by HIV status although these results should be interpreted with caution as the numbers were limited and mechanisms of action are unclear.

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Oral rinse samples were processed and tested in the laboratory of Dr. Maura Gillison at The Ohio State University. Data were collected by the Multicenter AIDS Cohort Study (MACS). MACS (Principal Investigators): Johns Hopkins University Bloomberg School of Public Health (Joseph Margolick), U01-AI35042; Northwestern University (Steven Wolinsky), U01-AI35039; University of California, Los Angeles (Roger Detels), U01-AI35040; University of Pittsburgh (Charles Rinaldo), U01-AI35041; the Center for Analysis and Management of MACS, Johns Hopkins University Bloomberg School of Public Health (Lisa Jacobson), UM1-AI35043. The MACS is funded primarily by the National Institute of Allergy and Infectious Diseases (NIAID), with additional co-funding from the National Cancer Institute (NCI), the National Institute on Drug Abuse (NIDA), and the National Institute of Mental Health (NIMH). The MACS website is located at http://aidscohortstudy.org/. Data in this manuscript were also collected by the Women's Interagency HIV Study (WIHS). WIHS (Principal Investigators): U01-AI-103408; Bronx WIHS (Kathryn Anastos), U01-AI-035004; Brooklyn WIHS (Howard Minkoff and Deborah Gustafson), U01-AI-031834; Chicago WIHS (Mardge Cohen and Audrey French), U01-AI-034989; WIHS Data Management and Analysis Center (Stephen Gange and Elizabeth Golub), U01-AI-042590. The WIHS is funded primarily by the National Institute of Allergy and Infectious Diseases (NIAID), with additional co-funding from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the National Cancer Institute (NCI), the National Institute on Drug Abuse (NIDA), and the National Institute on Mental Health (NIMH).

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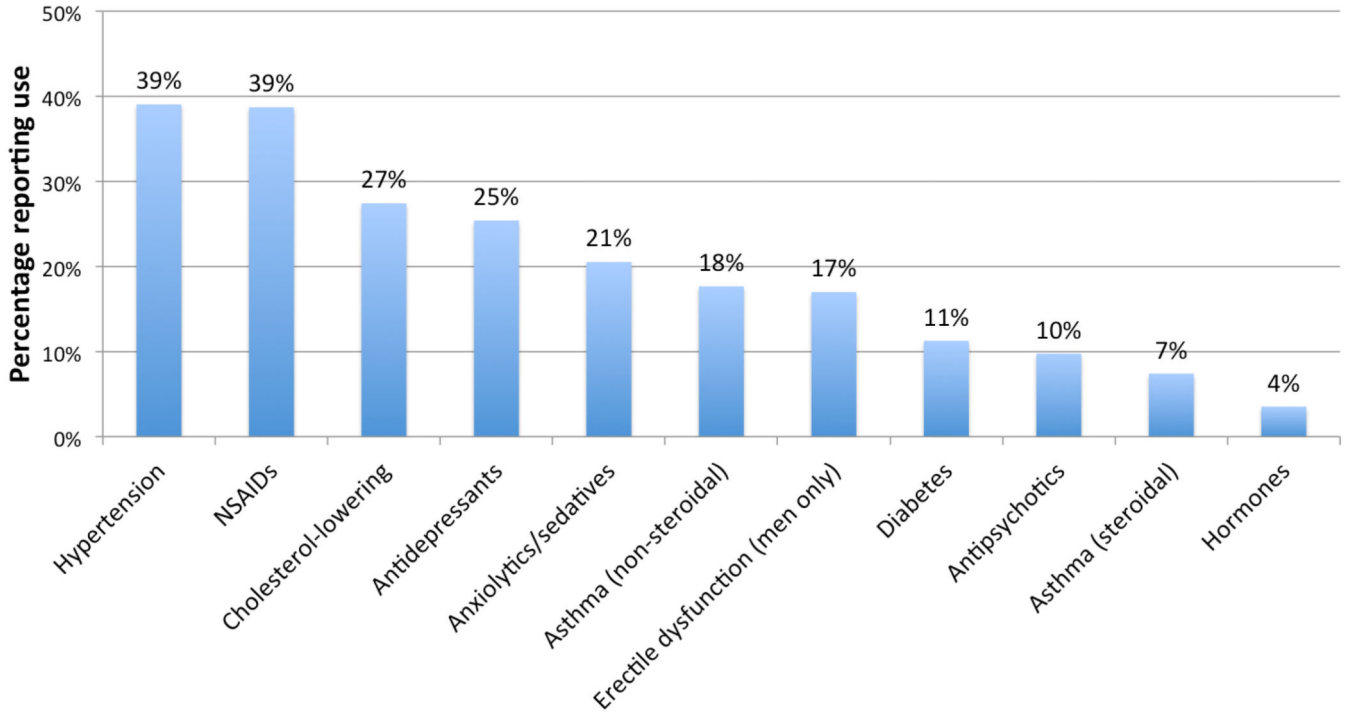

Figure 1. Prevalence of medication use at time of first oral HPV detectiona

[a] Medication use is shown for men (n=320) and women (n=274) together, with the exception of erectile dysfunction medications, which were assessed in men only.

NSAID = non-steroidal anti-inflammatory drugs

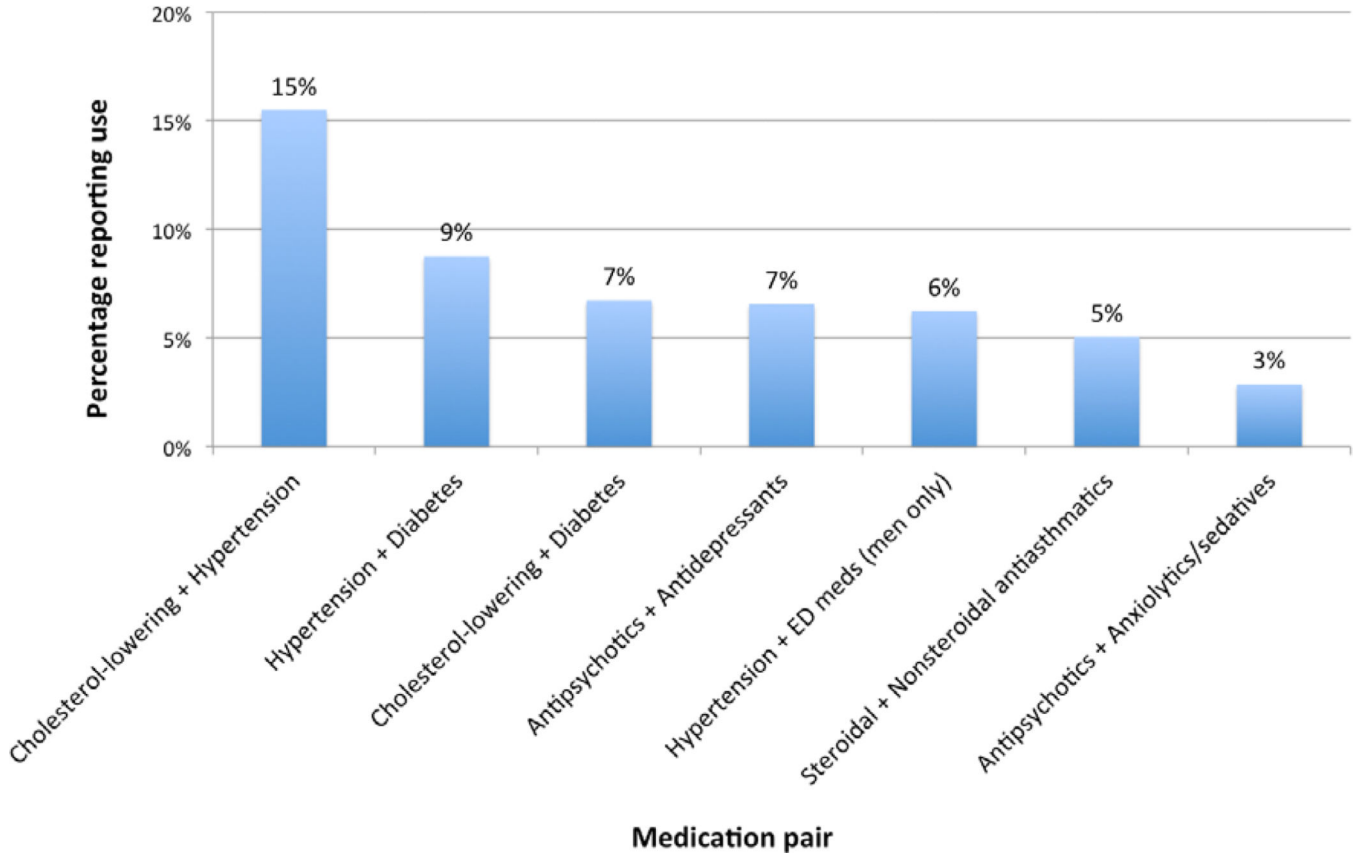

Figure 2. Prevalence of concomitant medication use at time of oral HPV detectiona

[a] Medication use is shown for men (n=320) and women (n=274) together, with the exception of erectile dysfunction medications, which were assessed in men only.

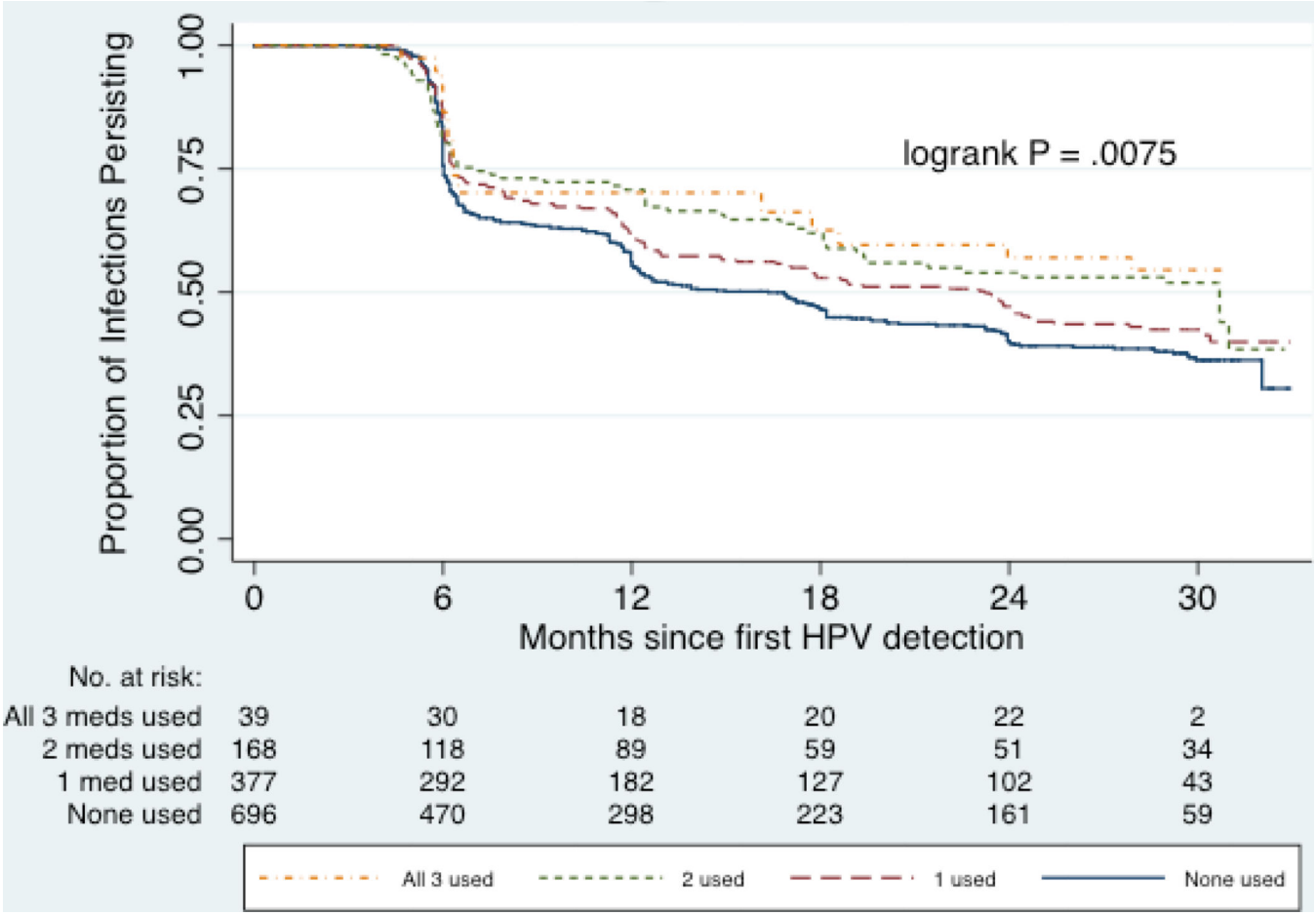

Figure 3.

Time to oral HPV clearance among 594 participants with 1,358 oral HPV infections, by use of antipsychotics, antidepressants and/or anxiolytics/sedatives

Table 1

Participant characteristics at time of first oral HPV detection

Participant characteristic[a]	No.	%
Sex		
Women (WIHS)	274	46%
Men (MACS)	320	54%
Infection type[b]		
Incident only	189	32%
Any Prevalent (with or without incident)	405	68%
Age (year)		
<45	162	27%
45–54	258	43%
≥55	174	29%
Race/Ethnicity		
White, non-Hispanic	186	31%
Black, non-Hispanic	328	55%
Hispanic (any race)	80	14%
Study site[c]		
Baltimore, Maryland	88	15%
Bronx, New York	93	16%
Brooklyn, New York	84	14%
Chicago, Illinois	202	34%
Los Angeles, California	24	4%
Pittsburgh, Pennsylvania	103	17%
HIV status		
Uninfected	168	28%
Infected	426	72%
AMONG HIV INFECTED		
Current CD4+ T cell count (cells/μL)		
≥500	212	50%
<500	214	50%
Current HIV RNA viral load (copies/mL)		
<200	286	68%
200–19,999	78	19%
≥20,000	57	14%
Current ART use		
No	83	20%
Yes	343	81%

[a] All participant characteristics are from the time of oral HPV detection

[b] Prevalent infection was defined as oral HPV detected at POPS enrollment. Incident infection was defined as newly detected oral HPV preceded by at least one HPV-negative oral rinse. Some participants had prevalent infection, followed by incident infection of another HPV type that was included in the analysis.

[c]Baltimore, Los Angeles and Pittsburgh study sites enrolled men only (MACS). Bronx and Brooklyn study sites enrolled women only (WIHS). Chicago study site enrolled both men and women.

Table 2

Unadjusted associations of recent medication use with time to oral HPV clearance among 594 participants with 1,358 oral HPV infections

Medication type used since last visit[a]	No. of cleared infections	Person-months of observation	HR (95% CI)
Antipsychotics[b]			
HIV-uninfected (n=299)			
No	122	3,968	Ref
Yes	13	273	1.38 (0.88–2.17)
HIV-infected (n=1,059)			
No	466	14,998	Ref
Yes	46	2,298	**0.67 (0.49–0.91)**
Anxiolytics/sedatives			
No	512	16,123	Ref
Yes	135	5,415	**0.78 (0.63–0.96)**
Antidepressants			
No	466	14,415	Ref
Yes	181	7,123	**0.82 (0.67–0.99)**
Asthma (steroidal) medications			
No	572	19,288	Ref
Yes	75	2,250	1.20 (0.89–1.63)
Asthma (non-steroidal) medications			
No	489	16,349	Ref
Yes	158	5,189	1.06 (0.87–1.28)
Cholesterol-lowering medications			
No	469	15,742	Ref
Yes	178	5,796	1.03 (0.86–1.25)
Diabetes medications			
No	567	19,231	Ref
Yes	80	2,307	1.19 (0.92–1.53)
Hormones			
No	618	20,665	Ref
Yes	29	872	1.10 (0.72–1.69)
Hypertension medications			
No	397	13,246	Ref
Yes	250	8,292	1.02 (0.86–1.22)
NSAIDs			
No	419	11,760	Ref
Yes	203	6,673	0.90 (0.76–1.07)
Erectile dysfunction medications (men only)			
No	296	9,952	Ref

Medication type used since last visit[a]	No. of cleared infections	Person-months of observation	HR (95% CI)
Yes	56	2,419	0.77 (0.58–1.01)

[a] All medication use variables were time-updated (i.e. medication use reported at each visit was applied to the WLW model, and was allowed to change if the participant started/stopped medication use). If a participant missed a visit, the last reported medication use status was used in the analysis.

Statistically significant values are listed in bold. Statistical significance was defined as two-sided p-value <0.05.

[b] Antipsychotic medication use was associated with reduced clearance in HIV-infected participants only (p-interaction=0.009)