Natural History of Anal vs Oral HPV Infection in HIV-Infected Men and Women

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Background. Human immunodeficiency virus (HIV)–infected individuals are at greater risk for human papillomavirus (HPV)–associated anal than oropharyngeal cancers. The prevalence of anal vs oral HPV infections is higher in this population, but whether this is explained by higher incidence or persistence is unknown.

Methods. Oral rinse and anal swab samples were collected semiannually from 404 HIV-infected adults in Baltimore, Maryland. Samples were tested for 37 HPV types using PGMY09/11 primers and reverse line-blot hybridization. Risk factors for HPV persistence were explored using adjusted Wei-Lin-Weissfeld models.

Results. The prevalence (84% vs 28%), incidence (145 vs 31 per 1000 person-months), and 12-month persistence (54% vs 29%) were higher for anal vs oral HPV infections, respectively (each P < .001). Heterosexual men had lower incidence of anal HPV than men who have sex with men and women, but a higher incidence of oral HPV infection (test of interaction P < 0.001). In adjusted analyses, risk factors for HPV persistence included prevalent vs incident (adjusted hazard ratio [aHR] = 4.0; 95% confidence interval [CI], 3.5–4.8) and anal vs oral HPV infections (aHR = 1.5; 95% CI, 1.2–1.9).

Conclusions. The higher incidence and persistence of anal vs oral HPV infections likely contributes to the higher burden of anal as compared to oral HPV-associated cancers in HIV-infected individuals.

Keywords. oral HPV; anal HPV; HIV; natural history; persistence; risk factors; incidence; variably detected.

Individuals infected with human immunodeficiency virus (HIV) are at elevated risk for all human papillomavirus (HPV)–associated cancers, including cervical, anal, and oropharyngeal cancers [1–3]. However, the standardized incidence ratios for these cancers among HIV-infected individuals compared to the general population vary considerably by anatomic site. For example, HIV-infected individuals have a >25-fold greater risk of anal cancer relative to the general population, but the risk for oropharyngeal cancer is only 2- to 6-fold greater [4, 5].

The underlying reasons for the different magnitudes of risk for HPV-associated cancers among HIV-infected individuals are unclear. In the case of cervical cancer, the elevated risk among immunosuppressed populations has been attributed to both higher incidence [6, 7] and higher persistence rates [6] of cervical HPV infection. Immunosuppression may also increase risk of disease progression [8, 9]. Cross-sectional studies have consistently shown the prevalence of anal HPV to exceed that of oral HPV among HIV-infected individuals [10–12]. To investigate the possible contribution of differences in incidence and persistence rates to the differing anal-oral HPV prevalence and cancer rates in HIV-infected individuals, a prospective study was performed to compare the natural histories of anal and oral HPV infections among HIV-infected individuals.

METHODS

Study Population and Data Collection
A convenience sample of 404 HIV-infected men and women was recruited from a clinic (the Moore clinic)
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dedicated to the care of HIV-infected individuals at the Johns Hopkins Hospital (JHH) in Baltimore, Maryland, in 2006. The study was approved by the Institutional Review Board at JHH, and written informed consent was collected from all participants.

Participants were followed semiannually for up to 2 and a half years. Baseline demographic and behavioral information was collected by use of an audio computer-assisted self-interview that obtained information regarding demographics, sexual history, and drug use. Measurement of current CD4 T-cell count (Beckton Dickinson BD TriTest) and HIV RNA level (Roche AMPLICOR HIV-1 Monitor Test, version 1.5) at baseline was performed unless the information was available in the medical record from within 6 weeks of that study visit. Nadir CD4 T-cell count and current antiretroviral therapy (ART, also known as HAART [highly active antiretroviral therapy] or effective ART) were abstracted from the medical record. ART was defined as the use of 3 or more antiretroviral medications, which includes a protease inhibitor, a nonnucleoside reverse transcriptase inhibitor, and one of the nucleoside reverse transcriptase inhibitors abacavir or tenofovir, an integrase inhibitor, or an entry inhibitor [13].

**Specimen Collection, Processing, and DNA Purification**

At each visit, exfoliated oral epithelial cells were collected by use of an oral rinse and gargle with 10 mL of Scope mouthwash [14]. A physician collected anal samples by use of a saline-moistened Dacron swab inserted 6 cm into the anal canal and removed in a circular motion against the anal wall. The swab was placed in 1 mL of Sample Transport Medium (Digene Diagnostics, Silver Spring, MD) [11].

Strict procedures were used to prevent specimen contamination as described in Koshiol et al [15], including placement of a negative control per 7 experimental samples in the polymerase chain reaction (PCR) plate. DNA was isolated from anal swab and oral rinse samples by centrifugation, resuspension in phosphate-buffered saline, and purification by use of a modified method for the Puregene DNA purification kit (Genta Systems, Minneapolis, MN). Purified DNA was evaluated for the presence of 37 HPV types by use of PGYM09/11 PCR primer pools and reverse line-blot hybridization (Roche Molecular Systems) [14, 16]. Samples that were β-globin and HPV negative were considered inevaluable. Line blots were independently interpreted by 2 technicians and discrepancies resolved by the principal investigator (M.L.G.).

**Statistical Analyses**

Associations between baseline characteristics and HPV infection (or number of visits) were evaluated using χ² tests for categorical data and t tests for continuous variables. Baseline and follow-up HPV DNA prevalence and 95% confidence intervals (CIs) were calculated for HPV16, overall HPV (all 37 types), any oncogenic types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, and 73), and any nononcogenic types (6, 11, 26, 40, 42, 53, 54, 55, 61, 62, 64, 66, 67, 69, 70, 71, 72, 81, 82, 83, 84, 89, and IS39) [17–19]. HPV infection status was evaluated both by person and by type-specific infection. In analyses by individual, a participant was considered infected if 1 or more of the 37 evaluated HPV types were detected at each visit. In analyses by infection, presence of each of the 37 type-specific HPV infections was evaluated for each individual at each visit (point prevalence). Type-specific HPV infections were categorized as prevalent if positive at baseline and incident if first detected thereafter. A type-specific infection was only considered to be incident once, even if variably detected throughout the study (for example: −/+−/+). Incidence rates were summarized as the number of type-specific infections in the population per 1000 person-months. Newly detected anal and oral HPV infections were compared with hazard ratios (HRs) calculated using the Wei-Lin-Weissfeld (WLW) method [7, 20], which consists of a Cox proportional hazard model with generalized estimating equation (GEE) with an exchangeable correlation structure and robust variance to adjust for the correlation between multiple HPV infections detected within a single person [7, 21].

For prevalent and incident infections, the proportion of infections that persisted to 6, 12, 18, and 24 months (since infection) were summarized and compared for anal and oral HPV infections using prevalence ratios (PRs) from log-binomial regression with GEE. Two definitions of type-specific HPV clearance were considered: type-specific detection followed by a single negative test or followed by 2 consecutive negative tests. All infections defined as persistent required at least 2 HPV-positive visits. Redetected infections that were initially defined as cleared by either definition were not included in these analyses.

The number of lifetime sexual partners was defined for women as the number of vaginal partners and for men was defined as the sum of the reported number of vaginal and anal sex partners. Men were categorized based on self-reported sexual preference as either heterosexual men preferring only sex with women, or as men who have sex with men (MSM). All women were grouped together, as only 10 women reported their sexual preference as lesbian or bisexual. Tobacco exposure included use of cigarettes, pipes, cigars, chewing tobacco, or snuff, and was described as never, former, and current use at baseline. Hard drug use was defined as ever using heroin, cocaine, or crack. Recent or current behaviors were considered as those performed within 6 months before this study.

Risk factors for prevalent HPV at baseline were explored using log-binomial regression with GEE. Unadjusted prevalence ratios (PRs) and adjusted prevalence ratios (aPRs) and their 95% CIs were reported. Risk factors significantly associated with anal or oral prevalence (P < .05) along with factors shown to be relevant based on previous literature were included in the final adjusted models. The combined model considered
both anal and oral HPV infections as outcomes, and an interaction term with each risk factor and the site of infection was evaluated. Trends were evaluated using continuous values for ordinal or continuous risk factors, when available.

Patterns of HPV infection were also described in an analysis restricted to those participants with at least 2 follow-up visits after their first detection of HPV. HPV patterns for each infection were defined as persistent (if positive for all the visits following the initial positive visit), cleared (if negative for at least the final 2 visits), or intermittent (if varying between positive and negative throughout the visits).

Time-to-event outcomes (HPV clearance and persistence) were summarized using Kaplan-Meier curves, where infections were either censored at the first negative visit or only after 2 consecutive negative visits. The inverses for each association were then calculated and reported as HPV persistence. Risk factors for anal and oral HPV persistence were explored using the WLW method. Unadjusted hazard ratios (HRs) and adjusted hazard ratios (aHRs) were reported along with their 95% CIs. For the primary persistence analyses, we carried forward the previous visit’s HPV results for missing intermittent visits if they were subsequently positive in the next detected visit (example: +/-/+). All statistical tests were 2 sided and considered significant at an α level of .05. Stata software version 11.0 (StataCorp) was used for statistical analyses.

RESULTS

Baseline Characteristics
The study population was primarily African American (82%), and the median age was 46 years (Table 1). Participants included 153 women (39%), 168 heterosexual men (43%), and 69 MSM (18%). A majority (76%) reported ever performing oral sex, whereas approximately a third (36%) had ever had receptive anal sex. Among the 404 individuals enrolled, the median length of follow-up was 18.2 months (interquartile range [IQR] = 6.2–24.0), with a maximum of 31.6 months. Characteristics of participants who were lost to follow-up were similar to those who remained for the full duration of the study (6 visits). In addition, participants contributing 4 or more visits were also similar to those with 3 or fewer visits, with the exception of a higher prevalence of ever use of ART (P = .04) among those with 4 or more visits.

Anal and Oral HPV Prevalence
A total of 1137 anal swab samples were collected from the 404 individuals over the study period, and 99.1% were evaluable for detection of HPV infection. Prevalent anal HPV infections were common at baseline (84% [95% CI, 80%–88%]; Table 1), as were multiple concurrent infections (71%; median, 4 [IQR = 1–7] HPV types per person). Baseline prevalence was highest for anal HPV types 16 (20.3%), 61 (20.0%), and 55 (19.5%). Younger age, sexual orientation, a high number of lifetime anal sex partners, and lower current CD4 T-cell count were associated with prevalent anal HPV infection (all P < .05; Table 2).

There were 1292 oral rinse samples collected from the 404 individuals throughout the study and 99.1% were evaluable. Prevalent oral HPV infection at baseline was significantly less common than anal HPV infection (28% vs 84%, P < .001; Table 1), and 11% of individuals had multiple concurrent oral HPV infections. Baseline prevalence was highest for oral HPV types 55 (4.3%), 83 (4.1%), and 72 (3.8%). There were no risk factors independently associated with prevalent oral HPV infection. After adjustment for risk factors such as sexual behavior and current CD4 T-cell count, prevalent anal HPV infection was 10-fold more common (aPR = 9.8 [95% CI, 7.8–12.2]) than prevalent oral HPV infection.

Anal and Oral HPV Incidence
Given the higher prevalence of anal vs oral HPV infections, we compared incidence rates at the 2 anatomic sites. The incidence of anal infection was significantly higher than for oral infection (145 vs 31 infections per 1000 person-months; aHR = 4.7 [95% CI, 3.6–6.2]; Table 3) particularly among oncogenic types (oncogenic vs nononcogenic, test for interaction P = .01). The anal HPV incidence was higher than oral HPV incidence among women (184 vs 22 per 1000 person-months), MSM (165 vs 31 per 1000 person-months), and heterosexual men (96 vs 38 per 1000 person-months, all P < .001). Of note, heterosexual men had the highest incidence of oral, but the lowest incidence of anal, HPV infections (test for interaction P < .001). Poisson regression with GEE was utilized to compare the incidence rates of anal and oral HPV infection, and the incidence rate ratios between anal and oral HPV were similar to the reported WLW hazard ratios in Table 3 (data not shown).

We explored baseline factors associated with incident infections at both anatomic sites (Table 2). The incidence of anal HPV infection was similar among individuals who did and did not report recent oral sex (161 vs 140 per 1000 person-months, trend test P = .54), whereas the incidence of oral HPV was similar among those who did and did not report recent oral sex (36 vs 27 per 1000 person months, trend test P = .15).

Anal and Oral HPV Persistence
Given the observed higher prevalence and incidence of anal vs oral HPV infections, we also compared persistence of infections at the 2 anatomic sites. When first considering HPV persistence, we noted that many anal and oral HPV infections had a pattern of intermittent detection during the study (eg, +/-/+). To further investigate patterns of infections, we performed an analysis restricted to the 1426 HPV infections among the 207 individuals with at least 2 follow-up visits following their first detection of HPV. Individuals in this analysis had a
median follow-up of 24.0 months (IQR = 18.6–24.5). In this analysis, 38% of all anal and oral infections were persistent (positive for all the visits following the initial positive visit), 26% were intermittent (varied between positive and negative throughout the visits), and 37% were cleared (negative for at least 2 consecutive visits and not positive for any subsequent visits; Figure 1).

Given these patterns of infection, we considered both a single negative and 2 consecutive negative definitions for

Table 1. Baseline Characteristics of the 404 Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
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<td></td>
</tr>
<tr>
<td>Median age at baseline (IQR)</td>
<td>46.4 (42.1–51.0)</td>
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<tr>
<td><strong>Sexual orientation</strong></td>
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<td></td>
</tr>
<tr>
<td>MSM</td>
<td>69</td>
<td>18</td>
</tr>
<tr>
<td>Heterosexual men</td>
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<td>43</td>
</tr>
<tr>
<td>Female</td>
<td>153</td>
<td>39</td>
</tr>
<tr>
<td><strong>Race/ethnicity</strong></td>
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<tr>
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<td>82</td>
</tr>
<tr>
<td>White non-Hispanic</td>
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<td>11</td>
</tr>
<tr>
<td>Hispanic, Native American, Asian</td>
<td>21</td>
<td>5.4</td>
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<td><strong>Other</strong></td>
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<td>1.8</td>
</tr>
<tr>
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<td></td>
</tr>
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<td>46</td>
</tr>
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<td>High school degree only</td>
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<td>31</td>
</tr>
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<td>Some college/college graduate</td>
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<td>23</td>
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<tr>
<td>Current</td>
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<td><strong>Hard drug use (any crack, cocaine, or heroin)</strong></td>
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<td></td>
</tr>
<tr>
<td>Never</td>
<td>50</td>
<td>13</td>
</tr>
<tr>
<td>Former</td>
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<td>47</td>
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<tr>
<td>Current</td>
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<td>41</td>
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<tr>
<td><strong>Lifetime sexual behavior</strong></td>
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<tr>
<td>Ever had receptive anal sex among women</td>
<td>61</td>
<td>40</td>
</tr>
<tr>
<td>No. of vaginal partners among women, median (IQR)</td>
<td>8 (3–20)</td>
<td></td>
</tr>
<tr>
<td>No. of vaginal partners among heterosexual men, median (IQR)</td>
<td>20 (5–38)</td>
<td></td>
</tr>
<tr>
<td>No. of anal sex partners among MSM, median (IQR)</td>
<td>13 (3–38)</td>
<td></td>
</tr>
<tr>
<td>No. of oral sex partners performed on, median (IQR)</td>
<td>4 (1–9)</td>
<td></td>
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<tr>
<td><strong>Ever engaged in rimming (oral-anal)</strong></td>
<td>95</td>
<td>26</td>
</tr>
<tr>
<td><strong>Current (past 6 months) sexual behavior</strong></td>
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<td></td>
</tr>
<tr>
<td>Recent receptive anal sex among women</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>Recently had vaginal sex among women</td>
<td>78</td>
<td>51</td>
</tr>
<tr>
<td>Recently had vaginal sex among heterosexual men</td>
<td>89</td>
<td>54</td>
</tr>
<tr>
<td><strong>HIV-related biological measures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nadir CD4 cell count, median (IQR)</td>
<td>169 (62–286)</td>
<td></td>
</tr>
<tr>
<td>&gt;250 cells/mL</td>
<td>120</td>
<td>32</td>
</tr>
<tr>
<td>100–250 cells/mL</td>
<td>133</td>
<td>35</td>
</tr>
<tr>
<td>&lt;100 cells/mL</td>
<td>128</td>
<td>34</td>
</tr>
<tr>
<td>Current CD4 T-cell count, median (IQR)</td>
<td>304 (183–502)</td>
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</tr>
<tr>
<td>≥500 cells/mL</td>
<td>97</td>
<td>25</td>
</tr>
<tr>
<td>200–499 cells/mL</td>
<td>173</td>
<td>45</td>
</tr>
<tr>
<td>&lt;200 cells/mL</td>
<td>115</td>
<td>30</td>
</tr>
<tr>
<td>HIV RNA load, median (IQR)</td>
<td>5583 (400–41 635)</td>
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</tr>
<tr>
<td>&lt;400 copies/µL</td>
<td>129</td>
<td>34</td>
</tr>
<tr>
<td>401–20 000 copies/µL</td>
<td>108</td>
<td>29</td>
</tr>
<tr>
<td>≥20 000 copies/µL</td>
<td>141</td>
<td>37</td>
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<table>
<thead>
<tr>
<th>Characteristic</th>
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<tr>
<td>Recent receptive anal sex among MSM</td>
<td>29</td>
<td>42</td>
</tr>
<tr>
<td>Recently performed oral sex (1 or more partners)</td>
<td>137</td>
<td>35</td>
</tr>
<tr>
<td>Always used condoms for vaginal and anal sex</td>
<td>143</td>
<td>40</td>
</tr>
</tbody>
</table>

Table 1 continued.

Abbreviations: HIV, human immunodeficiency virus; HPV, human papillomavirus; IQR, interquartile range; MSM, men who have sex with men.

* Includes heterosexual and homosexual females.

b Comparing anal vs oral, \( P < .001 \).

median follow-up of 24.0 months (IQR = 18.6–24.5). In this analysis, 38% of all anal and oral infections were persistent (positive for all the visits following the initial positive visit), 26% were intermittent (varied between positive and negative throughout the visits), and 37% were cleared (negative for at least 2 consecutive visits and not positive for any subsequent visits; Figure 1).

Given these patterns of infection, we considered both a single negative and 2 consecutive negative definitions for
<table>
<thead>
<tr>
<th>Baseline Characteristics of HOPE Participants</th>
<th>Prevalent Infection at Baseline</th>
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<th>Incident Infection</th>
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<tr>
<td></td>
<td>Adjusted PR (95% CI)(^{a})</td>
<td>Adjusted HR (95% CI)(^{a})</td>
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</tr>
<tr>
<td></td>
<td>Anal HPV</td>
<td>Oral HPV</td>
<td>Anal HPV</td>
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<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20.7–42.1 (quartile 1)</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
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<tr>
<td>42.2–46.4 (quartile 2)</td>
<td>0.84 (.67–1.1)</td>
<td>0.85 (.47–1.5)</td>
<td>1.2 (.84–1.7)</td>
</tr>
<tr>
<td>46.5–51.3 (quartile 3)</td>
<td>0.96 (.78–1.2)</td>
<td>0.92 (.48–1.8)</td>
<td><strong>0.56 (.38–.84)</strong></td>
</tr>
<tr>
<td>51.4–60.2 (quartile 4)</td>
<td><strong>0.67 (.52–.86)</strong></td>
<td>0.83 (.44–1.6)</td>
<td><strong>0.58 (.37–.90)</strong></td>
</tr>
<tr>
<td></td>
<td>(P) trend = .004</td>
<td>(P) trend = .38</td>
<td>(P &lt; .001) (^{b})</td>
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<tr>
<td>Sexual orientation</td>
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<tr>
<td>Female</td>
<td>REF</td>
<td>REF</td>
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</tr>
<tr>
<td>MSM</td>
<td>0.84 (.64–1.1)</td>
<td>1.1 (.57–2.0)</td>
<td>0.89 (.58–1.4)</td>
</tr>
<tr>
<td>Heterosexual men</td>
<td><strong>0.47 (.37–.59)</strong></td>
<td>1.3 (.74–2.2) (^{c})</td>
<td><strong>0.64 (.46–.88)</strong> (^{d})</td>
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<td>Current tobacco smoker</td>
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<td>REF</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td>Yes</td>
<td>1.2 (1.0–1.4)</td>
<td>1.2 (.73–2.0)</td>
<td>0.95 (.68–1.3)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0 (never)</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td>1–5</td>
<td>1.2 (1.0–1.5)</td>
<td>1.3 (.87–1.8)</td>
<td>1.0 (.69–1.5)</td>
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<tr>
<td>6 or more</td>
<td><strong>1.5 (1.1–2.1)</strong></td>
<td>1.4 (.78–2.4)</td>
<td>1.1 (.66–1.8)</td>
</tr>
<tr>
<td></td>
<td>(P) trend = .17</td>
<td>(P) trend = .27</td>
<td>(P) trend = .27</td>
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<tr>
<td>No. of lifetime oral sex partners</td>
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</tr>
<tr>
<td>0 (never)</td>
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<td>0.73 (.39–1.4)</td>
<td>0.83 (.38–1.8)</td>
<td>0.94 (.46–1.9)</td>
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<td>6 or more</td>
<td>0.94 (.38–1.4)</td>
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<td>(P) trend = .73</td>
<td>(P) trend = .73</td>
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<td>No</td>
<td>REF</td>
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<td>Yes</td>
<td>1.1 (.56–2.2)</td>
<td>1.1 (.56–2.2)</td>
<td><strong>0.41 (1.0–.89)</strong></td>
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<td></td>
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<td>(P) trend = .13</td>
<td>(P) trend = .13</td>
</tr>
<tr>
<td>No. of recent anal sex partners (receptive)</td>
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<td>0 (never)</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
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<tr>
<td>1</td>
<td>1.3 (1.0–1.7)</td>
<td>0.67 (.43–1.0)</td>
<td>1.5 (.70–3.2)</td>
</tr>
<tr>
<td>2+</td>
<td>1.2 (.84–1.6)</td>
<td>1.1 (.51–2.3)</td>
<td>2.1 (.87–5.2)</td>
</tr>
<tr>
<td></td>
<td>(P) trend = .33</td>
<td>(P) trend = .54</td>
<td>(P) trend = .54</td>
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<tr>
<td>No. of recent oral sex partners (performed)</td>
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<td></td>
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</tr>
<tr>
<td>0 (never)</td>
<td>REF</td>
<td>REF</td>
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<tr>
<td>1</td>
<td>1.6 (.86–2.9)</td>
<td>1.6 (.86–2.9)</td>
<td>1.5 (.70–3.2)</td>
</tr>
<tr>
<td>2+</td>
<td>1.6 (.83–3.1)</td>
<td>1.6 (.83–3.1)</td>
<td>2.1 (.87–5.2)</td>
</tr>
<tr>
<td></td>
<td>(P) trend = .59</td>
<td>(P) trend = .59</td>
<td>(P) trend = .59</td>
</tr>
<tr>
<td>Condom use for anal or vaginal sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Always</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td>Never/sometimes</td>
<td>1.1 (.88–1.3)</td>
<td>0.91 (.68–1.2)</td>
<td>0.91 (.68–1.2)</td>
</tr>
<tr>
<td>Nadir CD4 T-cell count</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;250 cells/mL</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td>100–250 cells/mL</td>
<td>0.89 (.72–1.1)</td>
<td>0.82 (.42–1.6)</td>
<td>1.4 (.94–2.1)</td>
</tr>
<tr>
<td>&lt;100 cells/mL</td>
<td>0.84 (.65–1.1)</td>
<td>1.4 (.71–2.6)</td>
<td>1.0 (.63–1.5)</td>
</tr>
<tr>
<td></td>
<td>(P) trend = .98</td>
<td>(P) trend = .23</td>
<td>(P) trend = .44</td>
</tr>
<tr>
<td>Current CD4 T-cell count</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥500 cells/mL</td>
<td>REF</td>
<td>REF</td>
<td>REF</td>
</tr>
<tr>
<td>200–499 cells/mL</td>
<td><strong>1.4 (1.1–1.7)</strong></td>
<td>1.8 (.88–3.5)</td>
<td><strong>1.5 (1.1–2.2)</strong></td>
</tr>
<tr>
<td>&lt;200 cells/mL</td>
<td><strong>1.6 (1.3–2.1)</strong></td>
<td>1.1 (.44–2.7)</td>
<td>1.1 (.71–1.8)</td>
</tr>
</tbody>
</table>
clearance. Regardless of the clearance definition, anal HPV infections were significantly more likely to persist than oral infections (Table 4, Figure 2). After 6 months, 63% of prevalent anal infections were significantly more likely to persist than oral infections (PR = 1.4 [95% CI, 1.1–1.7]; Table 4). Over the course of the entire 2 and a half year study, prevalent anal HPV infections were approximately twice as likely to persist as prevalent oral HPV infections when clearance was defined by a single negative test (HR = 1.9 [95% CI, 1.6–2.3], P < .001; Figure 2A) or 2 consecutive negative tests (HR = 2.0 [95% CI, 1.5–2.6], P < .001; Figure 2C). Incident anal infections had a nonsignificantly higher persistence rate compared to incident oral infections using the single negative test definition (HR = 1.3 [95% CI, .99–2.3], P = .06; Figure 2B), and a modestly higher persistence rate using the 2 consecutive negative definition of clearance (HR = 1.6 [95% CI, 1.0–2.4], P = .03; Figure 2D). Results were similar when excluding those individuals with missing intermittent infections.

### Factors Related to Anal and Oral HPV Persistence

Adjusted WLW models were used to evaluate factors independently associated with anal and oral HPV infection persistence (Table 5). Heterosexual males were less likely than MSM and women to have persistent anal HPV (aHR = 0.73 [95% CI, 0.57–0.92]) but not oral HPV (aHR = 1.4 [95% CI, 0.91–2.0], test for interaction P = .02). Age, current tobacco use, and current and nadir CD4 T-cell count at baseline were not associated with anal or oral HPV persistence (Table 5). When anal and oral infections were included in the same model, anal infections were significantly more likely to persist than oral infections (aHR = 1.5 [95% CI, 1.2–1.9]), as were prevalent compared to incident HPV infections (aHR = 4.0 [95% CI, 3.5–4.8]). Risk factors for persistence were similar among the 207 individuals with at least 2 follow-up visits following their first detection of HPV and between oncogenic and nononcogenic HPV types (Supplementary Table 1). In addition, associations between risk factors and patterns of persistent HPV infection (calculated using multinomial logistic regression with GEE) were similar to the WLW analysis except that the anal HPV persistence pattern was even stronger than the pattern of oral HPV persistence (adjusted odds ratio = 2.0 95% CI, [1.1–3.7]; Supplementary Table 2).

### Table 3. Incidence Rates of Oral and Anal Human Papillomavirus (HPV) Infection per 1000 Person-months and Adjusted Hazard Ratios for Anal Compared to Oral HPV Incidence

<table>
<thead>
<tr>
<th>HPV Type</th>
<th>Incidence Rate (per 1000 Person-months)</th>
<th>Adjusted HRb (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anal HPV</td>
<td>Oral HPV</td>
</tr>
<tr>
<td>Overall HPV</td>
<td>145</td>
<td>31</td>
</tr>
<tr>
<td>Women (n = 153)</td>
<td>184</td>
<td>22</td>
</tr>
<tr>
<td>Men who have sex with men (n = 69)</td>
<td>165</td>
<td>31</td>
</tr>
<tr>
<td>Heterosexual men (n = 168)</td>
<td>96</td>
<td>38</td>
</tr>
<tr>
<td>Oncogenic HPV</td>
<td>60</td>
<td>9.6</td>
</tr>
<tr>
<td>Nononcogenic HPV</td>
<td>85</td>
<td>22</td>
</tr>
<tr>
<td>HPV vaccine types (6, 11, 16, 18)</td>
<td>17</td>
<td>4.3</td>
</tr>
<tr>
<td>HPV16</td>
<td>6.9</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HPV, human papillomavirus; HR, hazard ratio.

* a Hazard ratios calculated using the Wei-Lin-Weissfeld method (Cox proportional hazard with generalized estimating equation) adjusting for age, gender/sexual preference, tobacco, number of recent sexual partners (anal/vaginal), number of lifetime sexual partners, and nadir and current CD4 T-cell counts.

* b Test for interaction comparing heterosexual men to MSM and women, P < .001.

* c Test for interaction comparing oncogenic and nononcogenic types, P = .01.
DISCUSSION

To our knowledge, this is one of the first prospective studies of the natural history of anal and oral HPV infection in HIV-infected individuals. The higher prevalence, incidence, and persistence of anal vs oral HPV infections we observed likely contribute to the higher risk of anal as compared to oral HPV-associated cancers in this population [4, 5].

The higher prevalence of anal vs oral HPV infections observed in this study is consistent with prior reports [10, 12, 22]. Our data indicate that the higher prevalence is due to a combination of a considerably higher incidence rate and a modestly higher persistence rate of anal as compared to oral HPV infections.

These data support a hypothesis of an influence of anatomic site of infection on the natural history of HPV. Possible factors contributing to the observed differences in incidence include variation in the frequency of sexual behaviors related to transmission, local mucosal immunity differences such as the continuous flow of saliva and associated immunoglobulins in the oral region, sample collection differences, and a higher propensity for epithelial microtrauma in the anal region [23]. The different methods for oral (rinse) as compared to anal (swab) sampling might affect detection of persistent infection; however, research has shown similar rates of HPV type-specific agreement for oral (rinse), anal (swab), and cervical (brush) infections with repeat sampling [14, 16, 24].

With regard to sexual behavior, the observed incidence of anal HPV infection was high among MSM, but also among women and heterosexual men. A high anal HPV prevalence among men and women in the absence of receptive anal sex is consistent with other recent studies involving HIV-infected [11] and HIV-uninfected individuals [25, 26]. It has been suggested that nonpenetrative sexual behaviors and auto-inoculation through HPV shedding from vaginal discharge could lead to anal HPV infection [11, 26–28]. Indeed, HPV type-specific concordance of anal and genital infections has been observed among heterosexual men and women reporting never having anal sex [11, 26–28]. Similar to another recent study [29], we found that anal HPV detected among heterosexual men was less common and less likely to persist than in MSM and women. Notably, the incidence of oral HPV infections was higher among heterosexual men than MSM and women. This is consistent with the higher prevalence of oral HPV infection among men [30] as well as higher rates of HPV-associated oropharyngeal cancer among men in the United States [31].

We observed a large proportion of type-specific infections to have an intermittent pattern of detection at both anal and oral sites in this HIV-infected population. Similar patterns have been previously reported for cervical HPV in both HIV-infected [6] and uninfected [32–34] women. The intermittent pattern of detection of persistent infection may reflect the episodic nature of shedding and transmission, as well as the continuous mucosal immune response to HPV, which could induce clearance of infection once it is detected [35–37].
and HIV-uninfected [32, 33] individuals. It is unclear as to whether intermittent detection is representative of newly acquired infection, reactivation of latent infection, or rather limitations in sampling or fluctuation of HPV loads around the lower limits of assay detection. We acknowledge that some of the newly detected infections classified as incident likely represent true prevalent infections with intermittent detection. In support of this, incident anal and oral HPV infections were observed among individuals who reported no recent anal or oral sex. In the cervical literature, it remains unclear as to whether consistent HPV detection vs intermittent HPV detection carries different risks with regard to disease progression. However, HIV-infected women with transient cervical HPV infections have a 5-fold increased risk of precancer compared to women without cervical HPV infection [34].

Similar to previous studies, baseline oral and anal HPV prevalence was associated with reduced CD4 T-cell count [11, 12]. Yet, unlike other anogenital HPV studies [7, 29, 35, 36], persistence of oral and anal HPV was not associated with severity of immunosuppression. This difference may be explained by our limited sample size or by the fact that the risk factor information such as tobacco use and sexual behavior were only collected at baseline. The lack of time-updated measures limits the interferences between HPV persistence and the risk factors of interest as they are prone to unmeasured confounding or time dependent bias [37, 38].

There were several limitations to this study. This population of urban HIV-infected MSM, women, and heterosexual men posed several challenges to retention including relocation, incarceration, and death that led to nonoptimal loss to follow-up and missing intermittent visits. However, those lost to follow-up were similar in baseline characteristics (CD4, drug use) to those who continued to participate throughout the study, and results were similar in the multinomial pattern analysis (restricted to those with 4+ visits) compared to the WLW analysis (included all participants). In addition, risk factors were only available at study baseline, and we have likely underestimated the true prevalence of oral HPV infection in the study.

Figure 2. Kaplan–Meier survival curves comparing the time to clearance of anal vs oral human papillomavirus (HPV) infections, using a single negative (A and B) and 2 consecutive negative (C and D) definitions of clearance. Anal (black) and oral (gray) HPV infections are shown. P values and hazard ratios are from unadjusted Wei-Lin-Weissfeld model.
population by restricting our analysis to the 37 HPV types represented on the line blot [39, 40]. Participants were recruited through a convenience sample and may not reflect all HIV-infected individuals in this clinic setting, or the larger HIV-infected community. Given the unique aspects of the cohort, including HIV-related immunosuppression and heavy drug use, these results should not be generalized to healthier populations.

The study also had notable strengths. The cohort used well-validated statistical and laboratory methods [7, 14, 16] to explore, for one of the first times, the type-specific oral HPV natural history and to compare this to anal HPV infection in the same individuals. The study population included individuals with a wide range of CD4, including severely immunosuppressed individuals, and included MSM, heterosexual men, and women.

HIV-infected individuals appear able to clear many anal and oral HPV infections, but persistent and intermittent infections remain common. Higher anal than oropharyngeal cancer rates in HIV-infected individuals may be explained both by higher incidence of infection and higher persistence of anal compared to oral HPV infection. Further research is needed to better understand the natural history of anal and oral HPV infection, including the potential impact of screening and the prophylactic HPV vaccines, particularly among these groups at greater risk for HPV-associated cancer.

### Supplementary Data

Supplementary materials are available at The Journal of Infectious Diseases online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyrighted. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

### Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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