A Comparison of the Natural History of HPV Infection and Cervical Abnormalities among HIV-Positive and HIV-Negative Women in Senegal, Africa

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Abstract

Background: There is evidence of an interaction between HIV and human papillomavirus (HPV) resulting in increased HPV-associated morbidity and cancer mortality among HIV-positive women. This study aims to determine how the natural history of cervical HPV infection differs by HIV status.

Methods: A total of 1,320 women (47% were positive for HIV-1 and/or HIV-2) were followed for an average of two years in Senegal, West Africa between 1994 and 2010. Cytology (with a sub-sample of histology) and HPV DNA testing were performed at approximately 4-month intervals yielding data from over 7,900 clinic visits. Competing risk modeling was used to estimate rates for transitioning between three clinically relevant natural history stages: Normal, HPV, and HSIL (high-grade squamous intraepithelial lesions). Among HIV-positive women, exploratory univariate analyses were conducted examining the impact of HPV type, infection with multiple HPV types, HIV type, CD4+ count, and age.

Results: HIV-positive women had higher rates of progression and lower rates of regression compared with HIV-negative women (i.e., adverse transitions). HIV-positive women had a 2.55 [95% confidence interval (CI), 1.69–3.86; P < 0.0001] times higher rate of progression from HPV to HSIL than HIV-negative women (with 24-month absolute risks of 0.18 and 0.07, respectively). Among HIV-positive women, HPV-16/18 infection and CD4+ count <200/mm³ were associated with adverse transitions.

Conclusions: Adverse HIV effects persist throughout HPV natural history stages.

Impact: In the limited-resource setting of sub-Saharan Africa where cervical cancer screening is not widely available, the high-risk population of HIV-positive women may be ideal for targeted screening.

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Introduction

Human papillomavirus (HPV) is the necessary cause of squamous cervical cancer (1), is highly transmissible, and generally acquired closely after sexual debut (2, 3). Persistent infection can lead to the development of precancerous lesions which, in the absence of treatment or an effective immune response, can progress to cancer. Approximately 40 genotypes infect the genital tract and are classified on the basis of oncogenic potential with high-risk types 16 and 18 accounting for roughly 70% of cervical cancer (4). There is evidence of an interaction between human immunodeficiency virus (HIV) and HPV, with HIV-positive women at an increased risk for HPV detection, precancerous lesions, and cervical cancer compared with HIV-negative women (5–13). Studies have shown that HIV-positive women are 1.5 to 8 times more likely to have cervical cancer than HIV-negative women (9, 11, 14–17).

Despite numerous studies describing the increased burden of HPV and cervical disease among HIV-positive women, few have longitudinally examined the natural history within a single study population and provided direct comparisons to HIV-negative women. Thus, estimates for the probability of transitioning between each natural history stage (i.e., progression and regression) are limited, as well as our understanding of the point at which the natural history of HPV diverges for HPV-positive and HIV-negative women. We estimate and compare the probability of transitioning between three clinically relevant natural history stages [Normal, HPV, and high-grade precancerous lesions (HSIL)] for HIV-positive and HIV-negative women using data from multiple cohort studies conducted in Senegal, West Africa.

Materials and Methods

Sample

Data from six studies conducted from 1994 to 2010 in Senegal were used for the present analysis (Table 1). Protocols have been...
described elsewhere (9, 10, 18–25). Women age ≥15 at outpatient clinics were screened for participation in longitudinal research with HIV testing at baseline, as well as cervical cytology and HPV DNA sampling roughly every four months for at least two years. Recruitment occurred at two infectious disease, two family planning, and two sexually transmitted disease clinics in or around Dakar. Studies were approved by the University of Washington and Senegalese Human Subjects Review Boards with informed consent obtained from each subject. Data were deidentified and shared variables across the studies were pooled for analysis.

HIV serology and lymphocyte testing
Blood samples were tested for HIV-1 and HIV-2 antibodies using an enzyme-linked immunosorbent assay (ELISA; Genetic Systems), a microwell plate enzyme immunoassay (HIV 1/2 EIA; Sano Diagnostics Pasteur), or by rapid HIV testing (Determine Alere, Inc.). HIV-1 and HIV-2 infections were distinguished by a peptide-based assay, although the assay varied by study (Genie II, Alere, Inc.). HIV-1 and HIV-2 infections were distinguished by a microwell plate enzyme immunoassay (HIV 1/2 EIA; Sano Diagnostics Pasteur; or Immunocomb II, bispot, Orgenics). For HIV-positive women, peripheral blood was analyzed with a FACSCount analyzer (Becton Dickinson Biosciences) to determine number of CD4+ cells per microliter.

Cytologic and histologic testing
Conventional Pap smears were used and evaluated in Dakar until 1998; thereafter, the Thin Prep monolayer cell preparation system (Cytyc Corp.) was used and evaluated by a cytopathologist at a cytology center in Seattle, WA. Results were classified according to the Bethesda system (atypical squamous cells of undetermined significance, ASCUS; low-grade squamous intraepithelial lesion, LSIL; high-grade squamous intraepithelial lesions, HSIL; ref. 26). All slides obtained before 1998, those classified as LSIL or worse, and a random subset of negative slides, were re-read in Seattle, WA. Protocols for all six parent studies called for colposcopically directed biopsies and treatment for women with evidence of HSIL or invasive cervical cancer (ICC). Biopsy/treatment participation was low in earlier studies, in part, due to delays resulting from samples being sent to and re-read in Seattle. Representative hematoxylin and eosin–stained slides were prepared from paraffin-embedded biopsy specimens and reviewed by a blinded cytopathologist. World Health Organization (WHO) pathology criteria were used to classify specimens (19).

HPV DNA detection and typing
PCRs assays for detection of HPV DNA were performed. Laboratory methods evolved over time with expansion of type-specific probes (Table 1). Testing was initially performed by use of HPV L1 consensus primers, HPV type-specific oligonucleotide probes, and a generic probe (27). This method yielded type-specific identification of HPV 6/11, 16, 18, 31/33/35/39, 45/56, and 51/52. With new probes available, in 1998 HPV detection and typing analyses were performed via a PCR-based reverse-line strip test method (Roche Molecular Systems) with probes for types 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 57, 58, 59, 66, 68, 73, 82, 83, and 84 (28). In 2000, a Luminex-based testing approach was adopted with additional probes for 61, 62, 64, 67, 69, 70, 71, 72, 81, IS39, and CP6108 (29).

Natural history stage classification
In combination with HPV DNA results, cervical histology was used when available, with cytology in all other cases, to classify women at each visit as: Normal (HPV-negative), HPV (HPV-positive with one or more type in the absence of HSIL), or HSIL (HPV-positive with one or more type in the presence of HSIL). HSIL was defined on the basis of the presence of HSIL, CIN2, or CIN3. Because of a demonstrated lack of reproducibility for cytologic and histologic interpretations of low-grade lesions (i.e., ASCUS, LSIL, and CIN1), these results were not used to inform stage classifications (30). Transitions to ICC were not examined due to small numbers and possible HSIL treatment effects.

Statistical analyses
Competing risk modeling was used to estimate cumulative incidence functions and the probability of a specific transition over time (31). Follow-up time was set as the midpoint between visits (32). At each visit, natural history stage was classified as either incident (i.e., the stage differed from the preceding visit) or prevalent (i.e., the baseline visit or the stage was the same as the preceding visit). As HPV can be transient, restricting analyses to women with incident classification to eliminate left-censoring may

Table 1. Overview of included studies

<table>
<thead>
<tr>
<th>No.</th>
<th>Study title</th>
<th>Study duration</th>
<th>Inclusion criteria</th>
<th>Study sample*</th>
<th>Type-specific HPV DNA detection</th>
<th>Relevant references</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Natural history of cervical neoplasia in HIV-1 and HIV-2</td>
<td>1994-1999</td>
<td>Age ≥ 15</td>
<td>755 (291 HIV–)</td>
<td>12 types up to 1998</td>
<td>(9, 10, 18)</td>
</tr>
<tr>
<td>2</td>
<td>Control of HIV-1 by HIV-2 associated immune responses</td>
<td>2000-2006</td>
<td>Age ≥ 15</td>
<td>121 (119 HIV+)</td>
<td>38 types</td>
<td>(22)</td>
</tr>
<tr>
<td>3</td>
<td>Epidemiology of HIV-1/HIV-2 dual infection</td>
<td>2001-2005</td>
<td>ART naive</td>
<td>7 (7 HIV+)</td>
<td>38 types</td>
<td>(23)</td>
</tr>
<tr>
<td>4</td>
<td>Developing new approaches for cervical cancer control</td>
<td>2002-2007</td>
<td>Age ≥ 15</td>
<td>3 (3 HIV+)</td>
<td>38 types</td>
<td>(19)</td>
</tr>
<tr>
<td>5</td>
<td>Antiretroviral therapy for HIV-2 infection in Senegal</td>
<td>2005 - ongoing</td>
<td>Age ≥ 16</td>
<td>48 (48 HIV+)</td>
<td>38 types</td>
<td>(20, 25)</td>
</tr>
<tr>
<td>6</td>
<td>HIV-associated DNA hyper-methylation in cervical cancer</td>
<td>2005-2010</td>
<td>Age ≥ 18</td>
<td>386 (150 HIV+)</td>
<td>38 types</td>
<td>(21, 24)</td>
</tr>
</tbody>
</table>

*aSample size for the present study differs from the total samples reported in prior publications due to missing HIV status and/or the lack of longitudinal cytology/histology and HPV DNA data.
produce bias. For example, eliminating women who are classified as Normal throughout follow-up (prevalent classification), leads to overestimation of the probability of transitioning from Normal to HPV as only women with prior HPV detection who become HPV-negative during follow-up contribute to incident Normal. Thus, to bound results, analyses were calculated separately for prevalent and incident natural history stages.

The following exploratory analyses were conducted on covariates of interest: age (≤25 vs. >25), CD4+ count (<200/mm^3 vs. ≥200/mm^3), HPV type (16/18 vs. all others), HIV type (1 vs. 2), and concurrent infection with multiple HPV types (>1 vs. 1 type). These analyses were restricted to transitions from Normal and HPV due to limited numbers for HSIL. For HPV-16/18 typespecific analyses, women were classified on the basis of the presence of either one of both of these types (33). Women dually infected with HIV-1 and HIV-2 were removed from HPV type-specific analyses due to small numbers (n = 52).

The Gray’s method was used to test for statistical differences in cumulative incidence functions (34). Robust variances were used when multiple observations from the same woman were included when estimating a transition. Schoenfeld residuals were examined to assess the proportional hazards assumption. Analyses were conducted using SAS 9.4 software (SAS Institute).

Results

Demographics

Of 1,320 women, the majority were in their thirties, Muslim, with no more than a primary school education (Table 2). Forty-percent of married women were in a polygamous relationship. Forty-seven percent of women were HIV-positive, of which roughly two thirds were infected with HIV-1. Antiretroviral therapy (ART) was reported by 31% of HIV-positive women. Twenty-two percent were infected with HIV-1. ART use (%, ever) was 45.5% (95% CI, 31.4–39.0) and concurrent infection with multiple HPV types (>1 vs. 1 type).

Most women were followed for over two years (median, 796 days; IQR, 377–1,224 days) with clinic visits approximately every 4 months. 24-month predicted probability of progression, 39.4% were incident. HIV-positive women were more likely to be commercial sex workers (CSW). 24-month predicted probability of regression to Normal, 36.1% were incident. HIV-positive women had a lower level of education, and were less likely to be currently married or report using contraception than HIV-negative women.

Progression and regression

Of 1,079 cases classified as Normal, 56.3% were incident. HIV-positive Normal women had a 1.58 times higher rate of HPV detection than HIV-negative women [95% confidence interval (CI), 1.32–1.89] (Table 3). The 24-month predicted probability of HPV detection for HIV-positive women was 0.66 (95% CI, 0.60–0.73) and 0.82 (95% CI, 0.78–0.87) for prevalent and incident classification of Normal, respectively, compared with 0.50 (95% CI, 0.44–0.56) and 0.66 (95% CI, 0.60–0.73) for HIV-negative women (Fig. 1A). Women identified as incident Normal had a 1.58 times higher rate of HPV detection than prevalent cases (95% CI, 1.33–1.88). HPV-positive Normal women also had a 1.53 times higher rate of progression to HSIL than HIV-negative women, although this association was not significant (95% CI, 0.73–3.21). The 24-month predicted probability of HSIL for HIV-positive women was 0.04 (95% CI, 0.02–0.08) and 0.07 (95% CI, 0.04–0.12) for prevalent and incident classification of Normal, respectively, compared with 0.03 (95% CI, 0.01–0.06) and 0.04 (95% CI, 0.02–0.08) for HIV-negative women (Fig. 1B). Women identified as incident Normal had an increased rate of progression to HSIL than prevalent cases, although this was not significant (Table 3).

Of 1,265 cases of HPV detection, 39.4% were incident. HIV-positive women had a 0.46 times lower rate of regression from HPV to Normal than HIV-negative women (95% CI, 0.39–0.54). The 24-month predicted probability of regression to Normal for HIV-positive women was 0.56 (95% CI, 0.50–0.62) and 0.78 (95% CI, 0.74–0.83) for prevalent and incident HPV detection.
respectively, compared with 0.83 (95% CI, 0.80–0.87) and 0.96 (95% CI, 0.94–0.99) for HIV-negative women (Fig. 1C). Women with incident HPV detection had a 1.87 times higher rate of regression to Normal than women with prevalent detection (95% CI, 1.60–2.18). HIV-positive women with HPV had a 2.55 times higher rate of progression to HSIL than HIV-negative
Table 3. Hazard ratios for HIV-positive and HIV-negative Senegalese women

<table>
<thead>
<tr>
<th>Initial health stage</th>
<th>Total</th>
<th>n</th>
<th>HR (95% CI)</th>
<th>p</th>
<th>Transition health stage</th>
<th>n</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>HPV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1079</td>
<td>512</td>
<td></td>
<td></td>
<td></td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV</td>
<td>509</td>
<td>298</td>
<td>1.58 (1.32–1.89)</td>
<td>&lt;0.0001</td>
<td>17</td>
<td>1.53 (0.73–3.21)</td>
<td>0.26</td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>570</td>
<td>214</td>
<td>ref.</td>
<td></td>
<td></td>
<td>11</td>
<td>ref.</td>
<td></td>
</tr>
<tr>
<td>Incident classification</td>
<td>607</td>
<td>298</td>
<td>1.58 (1.35–1.88)</td>
<td>&lt;0.0001</td>
<td>18</td>
<td>1.69 (0.79–3.61)</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>Prevalent classification</td>
<td>472</td>
<td>214</td>
<td>ref.</td>
<td></td>
<td></td>
<td>10</td>
<td>ref.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HSIL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV</td>
<td>1265</td>
<td>764</td>
<td></td>
<td></td>
<td></td>
<td>126</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>634</td>
<td>308</td>
<td>0.46 (0.39–0.54)</td>
<td>&lt;0.0001</td>
<td>87</td>
<td>2.55 (1.69–3.86)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>631</td>
<td>456</td>
<td>ref.</td>
<td></td>
<td></td>
<td>39</td>
<td>ref.</td>
<td></td>
</tr>
<tr>
<td>Incident classification</td>
<td>499</td>
<td>327</td>
<td>1.87 (1.60–2.18)</td>
<td>&lt;0.0001</td>
<td>51</td>
<td>0.87 (0.60–1.25)</td>
<td>0.44</td>
<td></td>
</tr>
<tr>
<td>Prevalent classification</td>
<td>766</td>
<td>437</td>
<td>ref.</td>
<td></td>
<td></td>
<td>75</td>
<td>ref.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HSIL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV</td>
<td>179</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
<td>118</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>117</td>
<td>14</td>
<td>0.57 (0.26–1.29)</td>
<td>0.18</td>
<td>81</td>
<td>1.06 (0.71–1.59)</td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>62</td>
<td>11</td>
<td>ref.</td>
<td></td>
<td></td>
<td>37</td>
<td>ref.</td>
<td></td>
</tr>
<tr>
<td>Incident classification</td>
<td>109</td>
<td>17</td>
<td>1.57 (0.70–3.49)</td>
<td>0.27</td>
<td>71</td>
<td>1.02 (0.71–1.48)</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>Prevalent classification</td>
<td>70</td>
<td>8</td>
<td>ref.</td>
<td></td>
<td></td>
<td>47</td>
<td>ref.</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Normal, HPV-negative; HPV, HPV-positive; HSIL, higher-grade squamous intraepithelial lesion; CI, confidence interval. *Transition numbers (by row) do not sum to the total provided as women remained in the same state for the duration of follow-up or transitioned to cervical cancer. Transitions to cancer were not examined due to extremely limited sample sizes.

women (95% CI, 1.69–3.86). The 24-month predicted probability of progression to HSIL for HIV-positive women was 0.18 (95% CI, 0.13–0.23) and 0.20 (95% CI, 0.16–0.25) for incident and prevalent HPV detection, respectively, compared with 0.07 (95% CI, 0.05–0.11) and 0.08 (95% CI, 0.06–0.12) for HIV-negative women (Fig. 1D). Those with prevalent HPV detection had a slightly increased rate of progression to HSIL than incident cases, although this was not significant.

Of 179 cases of HSIL, 60.9% were incident. HIV-positive women had a 0.57 times lower rate of regression from HSIL to Normal than HIV-negative women (95% CI, 0.26–1.29). The 12-month predicted probability of regression to Normal for HIV-positive women was 0.09 (95% CI, 0.04–0.19) and 0.14 (95% CI, 0.08–0.24) for prevalent and incident HSIL, respectively, compared with 0.16 (95% CI, 0.07–0.34) and 0.23 (95% CI, 0.14–0.39) for HIV-negative women (Fig. 1E). Women with incident HSIL had a 1.57 times higher rate of regression to Normal than women with prevalent classification, although this association was not significant. HIV-positive and HIV-negative women with HSIL had a similar rate of regression to HPV (relative rate, 1.06; 95% CI, 0.71–1.59). For HIV-positive women the 12-month predicted probability of regression to HPV ranged from 0.70 (95% CI, 0.60–0.79) to 0.68 (95% CI, 0.56–0.84) for incident and prevalent HSIL, respectively, compared with 0.67 (95% CI, 0.52–0.86) and 0.67 (95% CI, 0.54–0.81) for HIV-negative women (Fig. 1G). The rate of regression to HPV was similar for both prevalent and incident cases of HSIL.

Potential effect modifiers among HIV-positive women

HIV-positive women with CD4+ counts <200 had a 2.86 times higher rate of transitioning from Normal to HSIL than women with higher CD4+ counts (95% CI, 0.95–8.58; Table 4). Low CD4+ count was also associated with a higher rate of progression from HPV to Normal (1.83; 95% CI, 1.07–3.14), and a lower rate of regression from HPV to Normal (0.57; 95% CI, 0.39–0.83).

HIV-positive Normal women with HPV-16/18 had a 4.62 times higher rate of progression to HSIL than those infected with other HPV types (95% CI, 1.10–19.42). Similarly, those with HPV-16/18 infection had a higher rate of progressing from HPV to HSIL (2.20; 95% CI, 1.34–3.62) and a lower rate of progression to Normal (0.35; 95% CI, 0.23–0.54) compared with those infected with other HPV types. Rates for acquisition of HPV (Normal to HPV) were similar across HPV type sub-groupings.

HIV-positive women with multiple HPV types had a higher rate of progression to HSIL (2.33; 95% CI, 1.40–3.88) than those with a single HPV type. HIV-positive women with multiple HPV types also had a 0.34 times lower rate of progression from HPV to Normal than women with a single HPV type (95% CI, 0.25–0.47). In contrast, progression rates from Normal to HPV and Normal to HSIL were similar for those who acquired multiple HPV types and those who acquired a single type.

Among Normal HIV-positive women, those age ≤25 years had a 1.56 times higher rate of incident HPV detection than those >25 (95% CI, 1.14–2.14). Age associations for the other transitions examined were nonsignificant.

Among Normal HIV-positive women, those with HIV-1 had a 1.85 times higher rate of incident HPV detection than those with HIV-2 (95% CI, 1.38–2.49). Similarly, women with HIV-1 had a 1.69 times higher rate of progression from HPV to HSIL compared with women with HIV-2 (95% CI, 0.94–3.03). Women with HIV-1 also had a lower rate of progression from HPV to Normal than those with HIV-2 (0.83; 95% CI, 0.64–1.08), although this association was not statistically significant. In contrast, those with HIV-1 had a lower rate of progression from Normal to HSIL (0.48; 95% CI, 0.19–1.21). Mutual adjustment for baseline age and CD4+ count (as surrogate measures of duration and severity of HIV infection), did not affect these findings.

Discussion

As HIV-positive women are at an increased risk of cervical cancer, understanding the distinct natural history within this population is essential for informing targeted prevention efforts. We found that HIV-positive women had higher rates of incident...
HPV detection and progression to HSIL, as well as lower rates of regression from HSIL and HPV infection when compared with HIV-negative women. The most notable difference between HIV-positive and HIV-negative women was the more than doubled rate of progression from HPV to HSIL (although absolute risk remained low). True transition probabilities likely lie between the incident and prevalent curves as a function of age and sexual activity.

Although analyses of potential effect modifiers should be interpreted with caution due to limited sample sizes, overall results suggest that HIV-positive women with baseline CD4⁺ counts <200 (cells/µL) or infection with HPV-16/18 had higher rates of progression and lower rates of regression. Consistent with other research (35, 36), this study found increased infection detection of multiple HPV types in HIV-positive women compared with HIV-negative women, but also demonstrated that infection with multiple types increased progression and decreased regression rates from HPV. This is particularly relevant as >1 type was present in 57% of visits in which HIV-positive women had HPV detection, in comparison with 28% among HIV-negative women.

Evidence regarding the role of HIV type on the natural history of HPV is conflicting (9, 10, 24, 37–41), with some research indicating that HIV-2 is more strongly associated with HPV-related disease than HIV-1. In contrast, the present analysis found HIV-1 to be more strongly associated with adverse transitions than HIV-2 (with the notable exception of a lower probability of transitioning from Normal to HSIL). HIV-1 has a shorter incubation period, higher transmissibility, and more rapid development of immunosuppression compared with HIV-2 (22, 42). Thus, it is biologically plausible that women with HIV-1 are at greater risk due to more severe immunosuppression. However, longer survival among women with HIV-2 (43) may result in higher lifetime risk due to extended time to develop cervical cancer.

This study has limitations. The present analysis focused on three stages of natural history: Normal (HPV-negative), HPV (HPV-positive with one or more type and the absence of HSIL), or HSIL (HPV-positive with one or more type and the presence of HSIL). Incident, stage differed from the preceding visit; Prevalent, baseline visit or stage was the same as the preceding visit.

### Table 4. Univariate analyses of potential effect modifiers, HIV-positive women

<table>
<thead>
<tr>
<th>Initial health stage</th>
<th>Transition health stage</th>
<th>Total n</th>
<th>HR (95% CI)</th>
<th>P</th>
<th>Total n</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CD4⁺ count &lt; 200</strong></td>
<td><strong>HPV</strong></td>
<td>57</td>
<td>29</td>
<td>1.09 (0.72–1.67)</td>
<td>0.68</td>
<td>4</td>
<td>2.86 (0.95–8.58)</td>
</tr>
<tr>
<td><strong>CD4⁺ count ≥ 200</strong></td>
<td><strong>HPV</strong></td>
<td>423</td>
<td>260</td>
<td>ref.</td>
<td>—</td>
<td>13</td>
<td>ref.</td>
</tr>
<tr>
<td><strong>HPV - 16/18</strong></td>
<td><strong>HPV</strong></td>
<td>27</td>
<td>24</td>
<td>0.97 (0.64–1.49)</td>
<td>0.90</td>
<td>3</td>
<td>4.62 (1.30–19.42)</td>
</tr>
<tr>
<td><strong>HPV - Other</strong></td>
<td><strong>HPV</strong></td>
<td>206</td>
<td>189</td>
<td>ref.</td>
<td>—</td>
<td>5</td>
<td>ref.</td>
</tr>
<tr>
<td><strong>HPV - Multiple Types</strong></td>
<td><strong>HPV</strong></td>
<td>71</td>
<td>64</td>
<td>1.07 (0.79–1.43)</td>
<td>0.67</td>
<td>3</td>
<td>1.37 (0.35–5.69)</td>
</tr>
<tr>
<td><strong>HPV - Single Type</strong></td>
<td><strong>HPV</strong></td>
<td>162</td>
<td>149</td>
<td>ref.</td>
<td>—</td>
<td>5</td>
<td>ref.</td>
</tr>
<tr>
<td><strong>Age ≤ 25</strong></td>
<td><strong>HPV</strong></td>
<td>69</td>
<td>47</td>
<td>1.56 (1.14–2.14)</td>
<td>0.0060</td>
<td>1</td>
<td>0.41 (0.05–3.10)</td>
</tr>
<tr>
<td><strong>Age &gt; 25</strong></td>
<td><strong>HPV</strong></td>
<td>436</td>
<td>249</td>
<td>ref.</td>
<td>—</td>
<td>16</td>
<td>ref.</td>
</tr>
<tr>
<td><strong>HIV-1</strong></td>
<td><strong>HPV</strong></td>
<td>316</td>
<td>205</td>
<td>1.85 (1.38–2.49)</td>
<td>&lt;0.0001</td>
<td>8</td>
<td>0.48 (0.19–1.21)</td>
</tr>
<tr>
<td><strong>HIV-2</strong></td>
<td><strong>HPV</strong></td>
<td>155</td>
<td>74</td>
<td>ref.</td>
<td>—</td>
<td>9</td>
<td>ref.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Initial health stage</th>
<th>Transition health stage</th>
<th>Total n</th>
<th>HR (95% CI)</th>
<th>P</th>
<th>Total n</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Normal</strong></td>
<td><strong>HSIL</strong></td>
<td>116</td>
<td>38</td>
<td>0.57 (0.39–0.83)</td>
<td>0.003</td>
<td>23</td>
<td>1.83 (1.07–3.14)</td>
</tr>
<tr>
<td><strong>CD4⁺ count &lt; 200</strong></td>
<td><strong>HSIL</strong></td>
<td>477</td>
<td>261</td>
<td>ref.</td>
<td>—</td>
<td>58</td>
<td>ref.</td>
</tr>
<tr>
<td><strong>CD4⁺ count ≥ 200</strong></td>
<td><strong>HSIL</strong></td>
<td>176</td>
<td>29</td>
<td>0.35 (0.23–0.54)</td>
<td>&lt;0.0001</td>
<td>32</td>
<td>2.20 (1.34–3.62)</td>
</tr>
<tr>
<td><strong>HPV - 16/18</strong></td>
<td><strong>HSIL</strong></td>
<td>473</td>
<td>186</td>
<td>ref.</td>
<td>—</td>
<td>42</td>
<td>ref.</td>
</tr>
<tr>
<td><strong>HPV - Other</strong></td>
<td><strong>HSIL</strong></td>
<td>527</td>
<td>66</td>
<td>0.34 (0.25–0.47)</td>
<td>&lt;0.0001</td>
<td>51</td>
<td>2.53 (1.40–4.38)</td>
</tr>
<tr>
<td><strong>HPV - Multiple Types</strong></td>
<td><strong>HSIL</strong></td>
<td>322</td>
<td>149</td>
<td>ref.</td>
<td>—</td>
<td>23</td>
<td>ref.</td>
</tr>
<tr>
<td><strong>HPV - Single Type</strong></td>
<td><strong>HSIL</strong></td>
<td>87</td>
<td>46</td>
<td>1.29 (0.89–1.87)</td>
<td>0.17</td>
<td>13</td>
<td>1.14 (0.57–2.27)</td>
</tr>
<tr>
<td><strong>Age ≤ 25</strong></td>
<td><strong>HSIL</strong></td>
<td>545</td>
<td>261</td>
<td>ref.</td>
<td>—</td>
<td>70</td>
<td>ref.</td>
</tr>
<tr>
<td><strong>Age &gt; 25</strong></td>
<td><strong>HSIL</strong></td>
<td>425</td>
<td>192</td>
<td>0.83 (0.64–1.08)</td>
<td>0.17</td>
<td>63</td>
<td>1.69 (0.94–3.03)</td>
</tr>
<tr>
<td><strong>HIV-1</strong></td>
<td><strong>HSIL</strong></td>
<td>163</td>
<td>94</td>
<td>ref.</td>
<td>—</td>
<td>16</td>
<td>ref.</td>
</tr>
<tr>
<td><strong>HIV-2</strong></td>
<td><strong>HSIL</strong></td>
<td>95</td>
<td>38</td>
<td>ref.</td>
<td>—</td>
<td>10</td>
<td>ref.</td>
</tr>
</tbody>
</table>

Abbreviations: Normal, HPV-negative; HPV, HPV-positive with one or more type in the absence of HSIL; HSIL, HPV-positive with one or more type with the presence of HSIL; Incident, stage differed from the preceding visit; Prevalent, baseline visit or stage was the same as the preceding visit.

*Note that transition numbers (by row) do not sum to total as some women remained in the same state for the duration of follow-up. HPV-type specific analyses for transitions from Normal (the initial state) were conducted based on the type acquired, whereas analyses of transitions from HPV (the initial state) were conducted on the basis of what type women had while HPV-positive.
Africa. HPV-16 and HPV-18 were tested for in each study included in the analysis; therefore, we were able to examine the roles of these highly oncogenic types separate from other types. Further, this sample includes registered CSWs. As CSWs are estimated to represent roughly 25% of new HIV cases in Africa, this population is particularly relevant for coinfection research (44). Finally, factors known to impact HPV natural history were minimal in this sample (e.g., oral contraception use, smoking, prior cervical cancer screening/treatment, and HPV vaccination).

Our findings suggest that targeted screening programs for the high-risk population of HIV-positive women are needed, in addition to HPV vaccination of youth before HIV infection. However, optimal screening modality, frequency, triage, and treatment threshold remain unknown, requiring both expert clinical review and cost-effectiveness examination.

Several studies and pilot projects have demonstrated the feasibility of implementing cervical cancer screening and treatment in low-resource settings (45), although significant economic and infrastructural challenges remain (46). Although screening with cytology has been widely adopted in high-resource settings resulting in major declines in cervical cancer incidence over the past 60 years, significant laboratory, equipment, and clinical expertise requirements have limited the capacity to establish cytology in low-resource settings (46, 47). Furthermore, cytology has low reproducibility and sensitivity in comparison with other strategies, necessitating frequent screening to achieve high effectiveness (30, 47). As such, a substantial effort has been made to identify and evaluate screening strategies that are both contextually relevant for the high-risk setting of sub-Saharan Africa. Hybrid Capture 2 (HC2) HPV testing is highly sensitive and reproducible with the potential for self-collection of samples (48), yet requires significant investment in laboratory equipment and technician expertise (46). Both cytology and HPV testing involve laboratory processing time leading to delays in obtaining results and an additional clinic visit if treatment is needed. Visual inspection with acetic acid (VIA) may be most suitable to low-resource settings as it involves naked eye inspection of the cervix (yielding immediate results), and requires little clinical expertise and no laboratory equipment for processing samples. However, inter-observer differences in subjectively determining positivity, concerns regarding over-treatment, and the potential for false negatives to remain undetected may reduce the effectiveness of VIA (46). The more recently developed careHPV test offers the benefits of standard HPV testing, yields rapid results (roughly 2 hours of processing time), uses mobile battery operated processing equipment, and requires minimal technical training (46, 49). Both VIA and rapid HPV testing can be implemented as part of a same day 'screen and treat' approach, minimizing losses to follow-up and delayed treatment. Immediate treatment with cryotherapy has minimal infrastructure requirements and can be provided by nurses and midwives (46). In contrast, surgical treatment with conization or loop electrosurgical excision procedure (LEEP) require significant infrastructure and technical training, and are further limited by the lack of pathology services in sub-Saharan settings (50). These various factors for testing and treatment must be considered to provide contextually relevant screening recommendations.

Importantly, both test and treatment effectiveness is reduced when applied to HIV-positive women adding uncertainty regarding optimal cervical cancer prevention strategies for this high-risk population (51–56). For instance, given the high prevalence of HPV among HIV-positive women, HPV testing as a stand-alone strategy may be inefficient for identifying women for targeted follow-up (due to a low positive predictive value such that a positive HPV test is not in itself actionable and other intermediate steps may be required). Furthermore, although HIV-positive women have significantly higher rates of adverse transitions than HIV-negative women, absolute risk remains low that could indicate that testing frequencies currently used among the general population may be extended to HIV-positive women. However, increased false negatives among the HIV-positive population may indicate the need for more frequent testing, and potential poor retention in care for certain settings (i.e., rural with limited access to follow-up care) may necessitate aggressive treatment of pre-cancer lesions.

In summary, there is a pressing need for targeted screening in the high-risk population of HIV-positive women. These efforts can subsequently be used to inform the eventual implementation of comprehensive population-based screening paradigms that are not yet widely available in the limited resource setting of sub-Saharan Africa (57). Given the distinct natural history of HPV among HIV-positive women (as demonstrated in our analyses), as well as varying test and treatment attributes, it is important to quantitatively compare the potential impact of screening strategies to understand how these factors collectively impact HPV-associated morbidity and mortality. In the absence of comprehensive cost-effectiveness analyses specific to low-resource settings of sub-Saharan Africa, frequent screening with VIA beginning at the time of HIV diagnosis with conservative triage of positive cases may be worth examining. Identifying optimal targeted prevention strategies is essential given modeling evidence, suggesting that cervical cancer among HIV-positive women may increase in the future due to extended life expectancy resulting from ART (58, 59).

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): H.K. Whitham, H. Chu, J.M. Oakes, A.R. Lifson, N.B. Kiviat, S. Ba, S.L. Kulasingam
Writing, review, and/or revision of the manuscript: H.K. Whitham, S.E. Hawes, H. Chu, A.R. Lifson, N.B. Kiviat, G.S. Gottlieb, S. Ba, M.P. Sy, S.L. Kulasingam
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): H.K. Whitham, S.E. Hawes, N.B. Kiviat, P.S. Sow, G.S. Gottlieb, S. Ba
Study supervision: J.M. Oakes, N.B. Kiviat, S. Ba, S.L. Kulasingam
Other (study nurse and follow patients on the daily basis, send data to investigators, and share thoughts and suggestions regarding patients health and concerns): M.P. Sy

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References

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