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# 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 human immunodeficiency virus (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 to HIV-negative women (i.e. adverse transitions). HIV-positive women had a 2.55 (95% CI: 1.69–3.86; P < 0.0001) times higher rate of progression from HPV to HSIL than HIV-negative

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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/mm$^3$ 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.

### Keywords

Human papillomavirus; human immunodeficiency virus; cervical cancer natural history; transition probabilities; competing risk

## 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 pre-cancerous 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 based on 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, pre-cancerous lesions, and cervical cancer compared to 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 HIV-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 pre-cancerous lesions (HSIL)) for HIV-positive and HIV-negative women using data from multiple cohort studies conducted in Senegal, West Africa.

## Materials & 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 de-identified 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, Seattle, WA, USA), a microwell plate enzyme immunoassay (HIV 1/2 EIA; Sanofi Diagnostics Pasteur, Paris, France), or by rapid HIV testing (Determine Alere, Inc, Jena, Germany). HIV-1 and HIV-2 infections were distinguished by a peptide-based assay, although the assay varied by study (Genie II, Genetic Systems; Multispot, Sanofi Diagnostics Pasteur; or Immunocomb II, bispot, Orgenics, Yavne, Israel). For HIV-positive women, peripheral blood was analyzed with a FACSCount analyzer (Becton Dickinson Biosciences, San Jose, CA, USA) 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., Boxborough, MA) was used and evaluated by a cytopathologist in Seattle, USA. 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) (26). All slides obtained prior to 1998, those classified as LSIL or worse, and a random subset of negative slides, were re-read in Seattle.

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 hemotoxylin-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

Polymerase chain reactions (PCRs) assays for detection of HPV DNA were performed. Lab 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, Alameda, CA) 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 based on the presence of HSIL, CIN2, CIN3, or CIS. Due to 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 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 type specific analyses, women were classified based on the presence of either one of both of these types (33). Women dually infected with HIV-1 and HIV-2 were removed from HIV type specific analyses due to small numbers (n=52).

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, Cary, NC).

## Results

### Demographics (Table 2)

Of 1,320 women, the majority were in their thirties, Muslim, with no more than a primary school education. Forty-percent of married women were in a polygynous 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-five percent were classified as having AIDS. Median CD4+ count at baseline was 406 cells/

μL. 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. HIV-positive women were more likely to be commercial sex workers (CSWs). Most women were followed for over two years (median = 796 days, IQR: 377–1,224 days) with clinic visits approximately every four months. At baseline, roughly 36%, 59%, and 5% of women were classified as *Normal*, *HPV*, and *HSIL*, respectively.

## Progression and Regression (Table 3)

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% CI: 1.32–1.89). 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 to 0.50 (95% CI: 0.44–0.56) and 0.66 (95% CI: 0.60–0.73) for HIV-negative women (Figure 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). HIV-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 to 0.03 (95% CI: 0.01–0.06) and 0.04 (95% CI: 0.02–0.08) for HIV-negative women (Figure 1B). Women identified as incident *Normal* had an increased rate of progression to *HSIL* than prevalent cases, although this was not significant.

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 to 0.83 (95% CI: 0.80–0.87) and 0.96 (95% CI: 0.94–0.99) for HIV-negative women (Figure 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 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 to 0.07 (95% CI: 0.05–0.11) and 0.08 (95% CI: 0.06–0.12) for HIV-negative women (Figure 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 to 0.16 (95% CI: 0.07–0.34) and 0.23 (95% CI: 0.14–0.39) for HIV-negative women (Figure 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) and 0.68 (95% CI: 0.56–0.84) for incident and prevalent *HSIL*, respectively, compared to 0.67 (95% CI: 0.52–0.86) and 0.67 (95% CI: 0.54–0.81) for HIV-negative women (Figure 1F). The rate of regression to *HPV* was similar for both prevalent and incident cases of *HSIL*.

### Potential Effect Modifiers among HIV-positive Women (Table 4)

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). Low CD4+ count was also associated with a higher rate of progression from *HPV* to *HSIL* (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 regression to *Normal* (0.35, 95% CI: 0.23–0.54) compared to 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 regression 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 non-significant.

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 to women with HIV-2 (95% CI: 0.94–3.03). Women with HIV-1 also had a lower rate of regression 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 to 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.

While 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 incident detection of multiple HPV types in HIV-positive women compared to 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 to 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 to 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). If a woman went from HPV-positive with type 16 to HPV-positive with type 18 in consecutive visits this was classified as a continuation of the *HPV* stage. This situation was unusual as many women had multiple HPV types such that one type was persistent during consecutive *HPV* visits. Histology was available for 10% of all clinic visits. Misclassification resulting from cytology likely leads to undetected cervical abnormalities (e.g. false negatives), such that some women are classified as *HPV* when in fact they are *HSIL*. Thus, detection of *HSIL* may be underestimated. However, it is important to note that histology is an imperfect gold standard with demonstrated low reproducibility (30). Data on ART were limited for several studies included in the analysis; therefore, the impact of CD4+ count was examined to indirectly capture some of these treatment effects. Further, this sample is largely comprised of women in their thirties who may have been previously infected with HPV, such that a

positive HPV test represents incident DNA detection rather than incident infection (i.e. potential reactivation effects).

This study has a number of strengths, most notably a large longitudinal sample to directly compare HIV-positive and HIV-negative women. These data allowed for the examination of the impact of HIV type, as both HIV-1 and HIV-2 are endemic to West 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 CSW are estimated to represent roughly 25% of new HIV cases in Africa, this population is particularly relevant for co-infection 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 prior to 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). While 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). Further, cytology has low reproducibility and sensitivity in comparison to 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 more 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 small lesions 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 two 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 in order 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, while HIV-positive women have significantly higher rates of adverse transitions than HIV-negative women, absolute risk remains low which 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 which 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).

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## Abbreviations

| | |
|---|---|
| **HIV** | human immunodeficiency virus |
| **AIDS** | autoimmune deficiency syndrome |

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|---|---|
| **HPV** | human papillomavirus |
| **ART** | antiretroviral therapy |
| **CSW** | commercial sex worker |
| **ASCUS** | atypical squamous cells of undetermined significance |
| **LSIL** | low-grade squamous intraepithelial lesion |
| **HSIL** | high-grade squamous intraepithelial lesion |
| **ICC** | invasive cervical cancer |
| **PCR** | polymerase chain reaction |
| **WHO** | World Health Organization |

## References


1. Munoz N, Castellsague X, de Gonzalez AB, Gissmann L. Chapter 1: HPV in the etiology of human cancer. Vaccine. 2006; 24(Suppl 3):S3/1–10.
2. Winer RL, Feng Q, Hughes JP, O'Reilly S, Kiviat NB, Koutsky LA. Risk of female human papillomavirus acquisition associated with first male sex partner. J Infect Dis. 2008; 197:279–82. [PubMed: 18179386]
3. Smith JS, Gilbert PA, Melendy A, Rana RK, Pimenta JM. Age-specific prevalence of human papillomavirus infection in males: a global review. J Adolesc Health. 2011; 48:540–52. [PubMed: 21575812]
4. Munoz N, Bosch FX, Castellsague X, Diaz M, de Sanjose S, Hammouda D, et al. Against which human papillomavirus types shall we vaccinate and screen? The international perspective. Int J Cancer. 2004; 111:278–85. [PubMed: 15197783]
5. Ahdieh L, Klein RS, Burk R, Cu-Uvin S, Schuman P, Duerr A, et al. Prevalence, incidence, and type-specific persistence of human papillomavirus in human immunodeficiency virus (HIV)-positive and HIV-negative women. J Infect Dis. 2001; 184:682–90. [PubMed: 11517428]
6. Cameron JE, Hagensee ME. Human papillomavirus infection and disease in the HIV+ individual. Cancer Treat Res. 2007; 133:185–213. [PubMed: 17672042]
7. Clifford GM, Goncalves MA, Franceschi S. Hpv, Group HIVS. Human papillomavirus types among women infected with HIV: a meta-analysis. AIDS. 2006; 20:2337–44. [PubMed: 17117020]
8. De Vuyst H, Lillo F, Broutet N, Smith JS. HIV, human papillomavirus, and cervical neoplasia and cancer in the era of highly active antiretroviral therapy. Eur J Cancer Prev. 2008; 17:545–54. [PubMed: 18941376]
9. Hawes SE, Critchlow CW, Faye Niang MA, Diouf MB, Diop A, Toure P, et al. Increased risk of high-grade cervical squamous intraepithelial lesions and invasive cervical cancer among African women with human immunodeficiency virus type 1 and 2 infections. J Infect Dis. 2003; 188:555–63. [PubMed: 12898443]
10. Hawes SE, Critchlow CW, Sow PS, Toure P, N'Doye I, Diop A, et al. Incident high-grade squamous intraepithelial lesions in Senegalese women with and without human immunodeficiency virus type 1 (HIV-1) and HIV-2. J Natl Cancer Inst. 2006; 98:100–9. [PubMed: 16418512]
11. Holmes RS, Hawes SE, Toure P, Dem A, Feng Q, Weiss NS, et al. HIV infection as a risk factor for cervical cancer and cervical intraepithelial neoplasia in Senegal. Cancer Epidemiol Biomarkers. 2009; 18:2442–6.
12. Kuhn L, Wang C, Tsai WY, Wright TC, Denny L. Efficacy of human papillomavirus-based screen-and-treat for cervical cancer prevention among HIV-infected women. AIDS. 2010; 24:2553–61. [PubMed: 20706107]

13. Minkoff H, Feldman J, DeHovitz J, Landesman S, Burk R. A longitudinal study of human papillomavirus carriage in human immunodeficiency virus-infected and human immunodeficiency virus-uninfected women. Am J Obstet Gynecol. 1998; 178:982–6. [PubMed: 9609571]
14. Mbulaiteye SM, Katabira ET, Wabinga H, Parkin DM, Virgo P, Ochai R, et al. Spectrum of cancers among HIV-infected persons in Africa: the Uganda AIDS-Cancer Registry Match Study. Int J Cancer. 2006; 118:985–90. [PubMed: 16106415]
15. Sitas F, Pacella-Norman R, Carrara H, Patel M, Ruff P, Sur R, et al. The spectrum of HIV-1 related cancers in South Africa. Int J Cancer. 2000; 88:489–92. [PubMed: 11054682]
16. Chaturvedi AK, Madeleine MM, Biggar RJ, Engels EA. Risk of human papillomavirus-associated cancers among persons with AIDS. J Natl Cancer Inst. 2009; 101:1120–30. [PubMed: 19648510]
17. Clifford GM, Polesel J, Rickenbach M, Dal Maso L, Keiser O, Kofler A, et al. Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. J Natl Cancer Inst. 2005; 97:425–32. [PubMed: 15770006]
18. Ali S, Niang MA, N'Doye I, Critchlow CW, Hawes SE, Hill AV, et al. Secretor polymorphism and human immunodeficiency virus infection in Senegalese women. J Infect Dis. 2000; 181:737–9. [PubMed: 10669366]
19. Feng Q, Balasubramanian A, Hawes SE, Toure P, Sow PS, Dem A, et al. Detection of hypermethylated genes in women with and without cervical neoplasia. J Natl Cancer Inst. 2005; 97:273–82. [PubMed: 15713962]
20. Gottlieb GS, Hawes SE, Wong KG, Raugi DN, Agne HD, Critchlow CW, et al. HIV type 2 protease, reverse transcriptase, and envelope viral variation in the PBMC and genital tract of ARV-naive women in Senegal. AIDS Res Hum Retroviruses. 2008; 24:857–64. [PubMed: 18544024]
21. Heitzinger K, Sow PS, Dia Badiane NM, Gottlieb GS, N'Doye I, Toure M, et al. Trends of HIV-1, HIV-2 and dual infection in women attending outpatient clinics in Senegal, 1990–2009. Int J STD AIDS. 2012; 23:710–6. [PubMed: 23104745]
22. Zheng NN, Kiviat NB, Sow PS, Hawes SE, Wilson A, Diallo-Agne H, et al. Comparison of human immunodeficiency virus (HIV)-specific T-cell responses in HIV-1- and HIV-2-infected individuals in Senegal. J Virol. 2004; 78:13934–42. [PubMed: 15564501]
23. Gottlieb GS, Sow PS, Hawes SE, Ndoye I, Coll-Seck AM, Curlin ME, et al. Molecular epidemiology of dual HIV-1/HIV-2 seropositive adults from Senegal, West Africa. AIDS Res Hum Retroviruses. 2003; 19:575–84. [PubMed: 12908935]
24. Hanisch RA, Sow PS, Toure M, Dem A, Dembele B, Toure P, et al. Influence of HIV-1 and/or HIV-2 infection and CD4 count on cervical HPV DNA detection in women from Senegal, West Africa. J Clin Virol. 2013; 58:696–702. [PubMed: 24210330]
25. Gottlieb GS, Badiane NM, Hawes SE, Fortes L, Toure M, Ndour CT, et al. Emergence of multiclass drug-resistance in HIV-2 in antiretroviral-treated individuals in Senegal: implications for HIV-2 treatment in resouce-limited West Africa. Clin Infect Dis. 2009; 48:476–83. [PubMed: 19143530]
26. National Cancer Institute Workshop. The 1988 Bethesda System for reporting cervical/vaginal cytological diagnoses. JAMA. 1989; 262:931–4. [PubMed: 2754794]
27. Kuypers JM, Critchlow CW, Gravitt PE, Vernon DA, Sayer JB, Manos MM, et al. Comparison of dot filter hybridization, Southern transfer hybridization, and polymerase chain reaction amplification for diagnosis of anal human papillomavirus infection. J Clin Microbiol. 1993; 31:1003–6. [PubMed: 8385147]
28. Gravitt PE, Peyton CL, Apple RJ, Wheeler CM. Genotyping of 27 human papillomavirus types by using L1 consensus PCR products by a single-hybridization, reverse line blot detection method. J Clin Microbiol. 1998; 36:3020–7. [PubMed: 9738060]
29. Feng Q, Cherne S, Winer RL, Balasubramanian A, Lee SK, Hawes SE, et al. Development and evaluation of a liquid bead microarray assay for genotyping genital human papillomaviruses. J Clin Microbiol. 2009; 47:547–53. [PubMed: 19144800]
30. Stoler MH, Schiffman M. Interobserver reproducibility of cervical cytologic and histologic interpretations: realistic estimates from the ASCUS-LSIL Triage Study. JAMA. 2001; 285:1500–5. [PubMed: 11255427]

31. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. Journal of the American Statistical Association. 1999; 94:496–509.
32. Law CG, Brookmeyer R. Effects of mid-point imputation on the analysis of doubly censored data. Stat Med. 1992; 11:1569–78. [PubMed: 1439361]
33. Bouvard V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, et al. A review of human carcinogens--Part B: biological agents. Lancet Oncol. 2009; 10:321–2. [PubMed: 19350698]
34. Gray RJ. A Class of K-Sample Tests for Comparing the Cumulative Incidence of a Competing Risk. Ann Stat. 1988; 16:1141–54.
35. De Vuyst H, Ndirangu G, Moodley M, Tenet V, Estambale B, Meijer CJ, et al. Prevalence of human papillomavirus in women with invasive cervical carcinoma by HIV status in Kenya and South Africa. Int J Cancer. 2012; 131:949–55. [PubMed: 21960453]
36. Firnhaber C, Zungu K, Levin S, Michelow P, Montaner LJ, McPhail P, et al. Diverse and high prevalence of human papillomavirus associated with a significant high rate of cervical dysplasia in human immunodeficiency virus-infected women in Johannesburg, South Africa. Acta Cytol. 2009; 53:10–7. [PubMed: 19248549]
37. Langley CL, Benga-De E, Critchlow CW, Ndoye I, Mbengue-Ly MD, Kuypers J, et al. HIV-1, HIV-2, human papillomavirus infection and cervical neoplasia in high-risk African women. AIDS. 1996; 10:413–7. [PubMed: 8728046]
38. Seck AC, Faye MA, Critchlow CW, Mbaye AD, Kuypers J, Woto-Gaye G, et al. Cervical intraepithelial neoplasia and human papillomavirus infection among Senegalese women seropositive for HIV-1 or HIV-2 or seronegative for HIV. Int J STD AIDS. 1994; 5:189–93. [PubMed: 8061090]
39. Vernon SD, Unger ER, Piper MA, Severin ST, Wiktor SZ, Ghys PD, et al. HIV and human papillomavirus as independent risk factors for cervical neoplasia in women with high or low numbers of sex partners. Sex Transm Infect. 1999; 75:258–60. [PubMed: 10615313]
40. La Ruche G, Ramon R, Mensah-Ado I, Bergeron C, Diomande M, Sylla-Koko F, et al. Squamous intraepithelial lesions of the cervix, invasive cervical carcinoma, and immunosuppression induced by human immunodeficiency virus in Africa. Dyscer-CI Group. Cancer. 1998; 82:2401–8. [PubMed: 9635533]
41. Rowhani-Rahbar A, Hawes SE, Sow PS, Toure P, Feng Q, Dem A, et al. The impact of HIV status and type on the clearance of human papillomavirus infection among Senegalese women. J Infect Dis. 2007; 196:887–94. [PubMed: 17703420]
42. Marlink, RGTS., editor. From the Ground Up: Building Comprehensive HIV/AIDS Care Programs in Resource-Limited Settings. Elizabeth Glaser Pediatric AIDS Foundation; 2009. Available from: http://ftguonline.org
43. Schim van der Loeff MF, Jaffar S, Aveika AA, Sabally S, Corrah T, Harding E, et al. Mortality of HIV-1, HIV-2 and HIV-1/HIV-2 dually infected patients in a clinic-based cohort in The Gambia. AIDS. 2002; 16:1775–83. [PubMed: 12218389]
44. Gouws E, Cuchi P. Focusing the HIV response through estimating the major modes of HIV transmission: a multi-country analysis. Sex Transm Infect. 2012; 88(Suppl 2):i76–85. [PubMed: 23172348]
45. Adefuye PO, Broutet NJ, de Sanjose S, Denny LA. Trials and projects on cervical cancer and human papillomavirus prevention in sub-Saharan Africa. Vaccine. 2013; 31(Suppl 5):F53–9. [PubMed: 24331748]
46. Sankaranarayanan R, Anorlu R, Sangwa-Lugoma G, Denny LA. Infrastructure requirements for human papillomavirus vaccination and cervical cancer screening in sub-Saharan Africa. Vaccine. 2013; 31(Suppl 5):F47–52. [PubMed: 24331747]
47. Denny L, Quinn M, Sankaranarayanan R. Chapter 8: Screening for cervical cancer in developing countries. Vaccine. 2006; 24(Suppl 3):S3/71–7.
48. Mitchell S, Ogilvie G, Steinberg M, Sekikubo M, Biryabarema C, Money D. Assessing women's willingness to collect their own cervical samples for HPV testing as part of the ASPIRE cervical cancer screening project in Uganda. Int J Gynaecol Obstet. 2011; 114:111–5. [PubMed: 21669428]

49. Levin CE, Sellors J, Shi JF, Ma L, Qiao YL, Ortendahl J, et al. Cost-effectiveness analysis of cervical cancer prevention based on a rapid human papillomavirus screening test in a high-risk region of China. Int J Cancer. 2010; 127:1404–11. [PubMed: 20049838]
50. Adesina A, Chumba D, Nelson AM, Orem J, Roberts DJ, Wabinga H, et al. Improvement of pathology in sub-Saharan Africa. Lancet Oncol. 2013; 14:e152–7. [PubMed: 23561746]
51. Anderson JR, Paramsothy P, Heilig C, Jamieson DJ, Shah K, Duerr A, et al. Accuracy of Papanicolaou test among HIV-infected women. Clin Infect Dis. 2006; 42:562–8. [PubMed: 16421802]
52. Heard I, Potard V, Foulot H, Chapron C, Costagliola D, Kazatchkine MD. High rate of recurrence of cervical intraepithelial neoplasia after surgery in HIV-positive women. J Acquir Immune Defic Syndr. 2005; 39:412–8. [PubMed: 16010162]
53. Reimers LL, Sotardi S, Daniel D, Chiu LG, Van Arsdale A, Wieland DL, et al. Outcomes after an excisional procedure for cervical intraepithelial neoplasia in HIV-infected women. Gynecol Oncol. 2010; 119:92–7. [PubMed: 20605046]
54. Chirenje ZM, Rusakaniko S, Akino V, Munjoma M, Mlingo M. Effect of HIV Disease in Treatment Outcome of Cervical Squamous Intraepithelial Lesions Among Zimbabwean Women. J Low Genit Tract Dis. 2003; 7:16–21. [PubMed: 17051039]
55. Gilles C, Manigart Y, Konopnicki D, Barlow P, Rozenberg S. Management and outcome of cervical intraepithelial neoplasia lesions: a study of matched cases according to HIV status. Gynecol Oncol. 2005; 96:112–8. [PubMed: 15589589]
56. Massad LS, Fazzari MJ, Anastos K, Klein RS, Minkoff H, Jamieson DJ, et al. Outcomes after treatment of cervical intraepithelial neoplasia among women with HIV. J Low Genit Tract Dis. 2007; 11:90–7. [PubMed: 17415113]
57. Sankaranarayanan R, Budukh AM, Rajkumar R. Effective screening programmes for cervical cancer in low- and middle-income developing countries. Bulletin of the World Health Organization. 2001; 79:954–62. [PubMed: 11693978]
58. Cobucci RN, Lima PH, de Souza PC, Costa VV, Cornetta MD, Fernandes JV, et al. Assessing the impact of HAART on the incidence of defining and non-defining AIDS cancers among patients with HIV/AIDS: A systematic review. J Infect Public Health. 2014
59. Atashili J, Smith JS, Adimora AA, Eron J, Miller WC, Myers E. Potential impact of antiretroviral therapy and screening on cervical cancer mortality in HIV-positive women in sub-Saharan Africa: a simulation. PloS One. 2011; 6:e18527. [PubMed: 21483701]

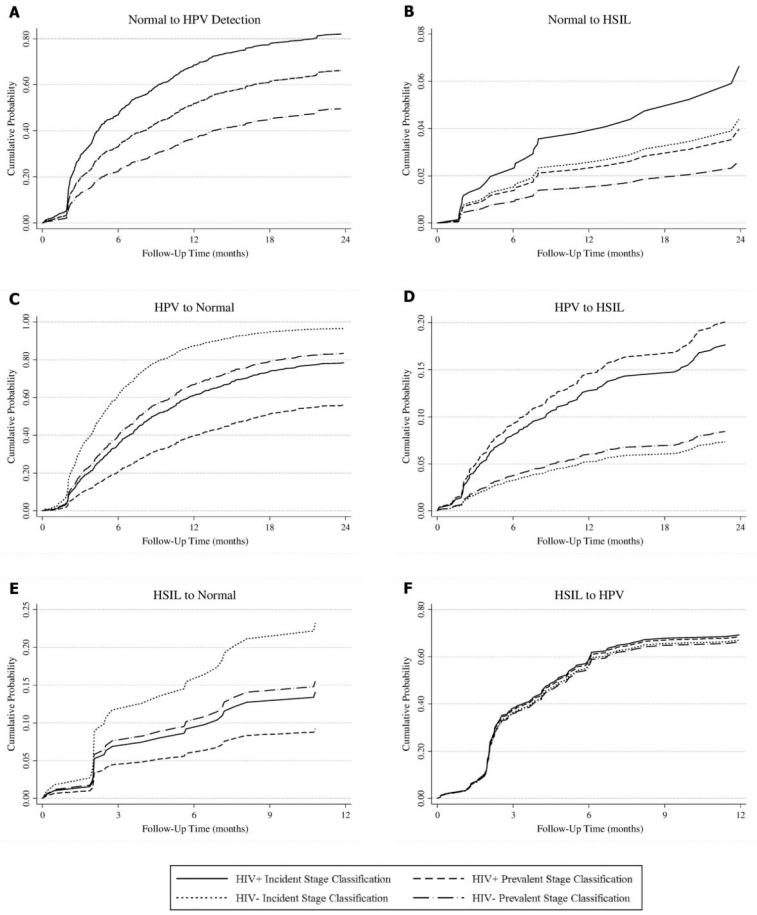


**Figure 1.**

Predicted cumulative probabilities for HIV-positive and HIV-negative Senegalese women [a]

a: Note different x- and y- axis scaling between figures

**Table 1**

Overview of included studies

| No. | Study Title | Study duration | Inclusion criteria | Study sample[a] | Type-specific HPV DNA detection | Relevant references |
|---|---|---|---|---|---|---|
| 1 | Natural history of cervical neoplasia in HIV-1 and HIV-2 | 1994 – 1999 | Age ≥15 | 755 (291 HIV+) | 12 types up to 1998<br>27 types thereafter | (9, 10, 18) |
| 2 | Control of HIV-1 by HIV-2 associated immune responses | 2000 – 2006 | Age ≥15<br>ART naïve | 121 (119 HIV+) | 38 types | (22) |
| 3 | Epidemiology of HIV-1/HIV-2 dual infection | 2001 – 2005 | Age ≥15<br>HIV-1/2+<br>On ART | 7 (7 HIV+) | 38 types | (23) |
| 4 | Developing new approaches for cervical cancer control | 2002 – 2007 | Age ≥15 | 3 (3 HIV+) | 38 types | (19) |
| 5 | Antiretroviral therapy for HIV-2 infection in Senegal | 2005 – ongoing | Age ≥16<br>HIV-2+<br>On ART | 48 (48 HIV+) | 38 types | (20, 25) |
| 6 | HIV-associated DNA hyper-methylation in cervical cancer | 2005 – 2010 | Age ≥18 | 386 (150 HIV+) | 38 types | (21, 24) |

[a]Sample 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.

## Table 2

Baseline characteristics of pooled study sample

| Characteristic | HIV− (n = 702) | HIV+ (n = 618) | Total N = 1,320 |
|---|---|---|---|
| Age (years) | | | |
| Median | 34 | 35 | 35 |
| Interquartile range | 27–44 | 29–42 | 28–43 |
| Age at Sexual Debut (years) | | | |
| Median | 17 | 17 | 17 |
| Interquartile range | 15–19 | 15–19 | 15–19 |
| Lifetime sex partners (%) | | | |
| None | 0.6 | 0.2 | 0.4 |
| One | 45.5 | 31.4 | 39.0 |
| 2–5 | 25.1 | 34.9 | 28.6 |
| 6–10 | 1.7 | 1.8 | 1.8 |
| >10 | 27.1 | 31.7 | 30.2 |
| Religion (%) | | | |
| Muslim | 85.5 | 89.9 | 87.8 |
| Christian | 14.1 | 9.7 | 11.8 |
| Other/None | 0.4 | 0.4 | 0.4 |
| Marital status (%) | | | |
| Married (monogamy) | 34.4 | 26.7 | 30.9 |
| Married (polygamy) | 25.5 | 14.7 | 20.5 |
| Never married | 15.4 | 8.9 | 12.4 |
| Separated/divorced | 20.4 | 30.7 | 25.1 |
| Widowed | 4.3 | 19.0 | 11.1 |
| Education (%) | | | |
| None | 42.6 | 50.5 | 46.3 |
| Primary School | 30.1 | 33.3 | 31.6 |
| Secondary School | 24.3 | 15.2 | 20.0 |
| University | 3.0 | 1.0 | 2.1 |
| Follow-up duration (days) | | | |
| Median | 780 | 812 | 796 |
| Interquartile range | 368–1,155 | 384–1,344 | 377–1,224 |
| Interval between clinic visits (days) | | | |
| Median | 139 | 134 | 136 |
| Interquartile range | 122–232 | 119–238 | 121–235 |
| Baseline cervical natural history stage (%) | | | |
| Normal | 31.8 | 41.0 | 36.1 |
| HPV | 64.1 | 52.3 | 58.5 |
| HSIL | 4.1 | 6.7 | 5.4 |
| Commercial sex worker (%) | 24.8 | 30.4 | 27.4 |
| Cigarette Use (%, ever) | 15.4 | 18.9 | 17.0 |

| Characteristic | HIV− (n = 702) | HIV+ (n = 618) | Total N = 1,320 |
|---|---|---|---|
| Contraception Use (%, ever) | 46.9 | 36.6 | 42.2 |
| Alcohol Consumption (%, ever) | 9.0 | 13.9 | 11.2 |
| *HIV-positive subsample* | | | |
| HIV-type (%) | | | |
| HIV-1 | - | 63.3 | - |
| HIV-2 | - | 28.3 | - |
| Dual HIV-1/2 infection | - | 8.4 | - |
| CD4+ count (cells/μL) | | | |
| Median | - | 406 | - |
| Interquartile range | - | 241–620 | - |
| ART use (%, ever) | - | 30.8 | - |
| AIDS [a] (%) | - | 25.1 | - |

[a]Classified as either having CD4+ count <200 recorded at any point during follow-up or a WHO Stage 4 AIDS defining event.

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**Table 3**

Hazard ratios for HIV-positive and HIV-negative Senegalese women [a]

| | | Transition Health Stage | | | | | |
|---|---|---|---|---|---|---|---|
| **Initial Health Stage** | **Total** | **N** | **Hazard ratio** | ***P*-value** | **n** | **Hazard ratio** | ***P*-value** |
| | | *HPV* | | | *HSIL* | | |
| *Normal* | 1079 | 512 | | | 28 | | |
| HIV+ | 509 | 298 | 1.58 (1.32–1.89) | <0.0001 | 17 | 1.53 (0.73–3.21) | 0.26 |
| HIV− | 570 | 214 | ref. | - | 11 | ref. | - |
| Incident classification | 607 | 298 | 1.58 (1.33–1.88) | <0.0001 | 18 | 1.69 (0.79–3.61) | 0.17 |
| Prevalent classification | 472 | 214 | ref. | - | 10 | ref. | - |
| | | *Normal* | | | *HSIL* | | |
| | Total | N | Hazard ratio | *P*-value | n | Hazard ratio | *P*-value |
| *HPV* | 1265 | 764 | | | 126 | | |
| HIV+ | 634 | 308 | 0.46 (0.39–0.54) | <0.0001 | 87 | 2.55 (1.69–3.86) | <0.0001 |
| HIV− | 631 | 456 | ref. | - | 39 | ref. | - |
| Incident classification | 499 | 327 | 1.87 (1.60–2.18) | <0.0001 | 51 | 0.87 (0.60–1.25) | 0.44 |
| Prevalent classification | 766 | 437 | ref. | - | 75 | ref. | - |
| | | *Normal* | | | *HPV* | | |
| | Total | N | Hazard ratio | *P*-value | n | Hazard ratio | *P*-value |
| *HSIL* | 179 | 25 | | | 118 | | |
| HIV+ | 117 | 14 | 0.57 (0.26–1.29) | 0.18 | 81 | 1.06 (0.71–1.59) | 0.77 |
| HIV− | 62 | 11 | ref. | - | 37 | ref. | - |
| Incident classification | 109 | 17 | 1.57 (0.70–3.49) | 0.27 | 71 | 1.02 (0.71–1.48) | 0.91 |
| Prevalent classification | 70 | 8 | ref. | - | 47 | ref. | - |

[a]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.

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.

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**Table 4**

Univariate analyses of potential effect modifiers, HIV-positive women [a]

| | | Transition Health Stage | | | | | |
|---|---|---|---|---|---|---|---|
| **Initial Health Stage** | **Total** | **n** | **Hazard ratio** | ***P*-value** | **N** | **Hazard ratio** | ***P*-value** |
| | | *HPV* | | | *HSIL* | | |
| *Normal* | | | | | | | |
| CD4+ count < 200 | 57 | 29 | 1.09 (0.72–1.67) | 0.68 | 4 | 2.86 (0.95–8.58) | 0.06 |
| CD4+ count ≥ 200 | 423 | 260 | ref. | - | 13 | ref. | - |
| HPV - 16/18 | 27 | 24 | 0.97 (0.64–1.49) | 0.90 | 3 | 4.62 (1.10–19.42) | 0.04 |
| HPV - Other | 206 | 189 | ref. | - | 5 | ref. | - |
| HPV - Multiple Types | 71 | 64 | 1.07 (0.79–1.43) | 0.67 | 3 | 1.37 (0.33–5.69) | 0.66 |
| HPV - Single Type | 162 | 149 | ref. | - | 5 | ref. | - |
| Age ≤ 25 | 69 | 47 | 1.56 (1.14–2.14) | 0.0060 | 1 | 0.41 (0.05–3.10) | 0.39 |
| Age > 25 | 436 | 249 | ref. | - | 16 | ref. | - |
| HIV-1 | 316 | 205 | 1.85 (1.38–2.49) | <0.0001 | 8 | 0.48 (0.19–1.21) | 0.12 |
| HIV-2 | 155 | 74 | ref. | - | 9 | ref. | - |
| | | *Normal* | | | *HSIL* | | |
| | Total | n | Hazard ratio | *P*-value | n | Hazard ratio | *P*-value |
| *HPV* | | | | | | | |
| CD4+ count < 200 | 116 | 38 | 0.57 (0.39–0.83) | 0.003 | 23 | 1.83 (1.07–3.14) | 0.0282 |
| CD4+ count ≥ 200 | 477 | 261 | ref. | - | 58 | ref. | - |
| HPV - 16/18 | 176 | 29 | 0.35 (0.23–0.54) | <0.0001 | 32 | 2.20 (1.34–3.62) | 0.0018 |
| HPV - Other | 473 | 186 | ref. | - | 42 | ref. | - |
| HPV - Multiple Types | 327 | 66 | 0.34 (0.25–0.47) | <0.0001 | 51 | 2.33 (1.40–3.88) | 0.0011 |
| HPV - Single Type | 322 | 149 | ref. | - | 23 | ref. | - |
| Age ≤ 25 | 87 | 46 | 1.29 (0.89–1.87) | 0.17 | 13 | 1.14 (0.57–2.27) | 0.72 |
| Age > 25 | 545 | 261 | ref. | - | 70 | ref. | - |
| HIV-1 | 425 | 192 | 0.83 (0.64–1.08) | 0.17 | 63 | 1.69 (0.94–3.03) | 0.08 |
| HIV-2 | 163 | 94 | ref. | - | 16 | ref. | - |

[a] 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, while analyses of transitions from *HPV* (the initial state) were conducted based on what type women had while HPV-positive.

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.