Effect of Human Immunodeficiency Virus Infection on Human Papillomavirus Clearance among Women in Senegal, West Africa

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Abstract

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Background. Persistent infection with human papillomavirus (HPV) is associated with development of cervical-related disease.

Methods. A total of 174 Senegalese women completed health questionnaires and were tested for Human Immunodeficiency Virus (HIV) upon enrollment, as well as were tested HPV at baseline and during follow up. The 2-year cumulative incidence of

clearance of type-specific HPV infection was estimated by Kaplan-Meier methods. Marginal Cox proportional hazards models stratified by incident/prevalent HPV infection were used to evaluate the effect of HIV status and type on HPV clearance.

Results. Incident HPV infections in HIV-positive women were 34% less likely to be cleared than those in HIV-negative women (adjusted HR=0.66, 95% CI: 0.44-0.99), but the association was not significant for prevalent HPV infections (adjusted HR=1.16, 95% CI: 0.81-1.67). For HIV-positive women, we observed no significant association between HIV type and clearance of HPV infection among incident HPV infections (HIV-2 vs HIV-1: adjusted HR=1.61, 95% CI: 0.93-2.80; Dually infected vs HIV-1: HR=1.50, 95% CI: 0.87-2.57) and among prevalent HPV infections (HIV-2 vs HIV-1: adjusted HR=0.77, 95% CI: 0.23-2.66; Dually infected vs HIV-1: HR=0.71, 95% CI: 0.36-1.38). Incident HPV infections in women with CD4 cell counts ≤500 were 37% less likely to be cleared than those in women with CD4 cell counts >500 (adjusted HR=0.63, 95% CI: 0.41-0.97), but the association was not significant for prevalent HPV infections (adjusted HR=0.87, 95% CI: 0.46-1.63).

Conclusions. HIV infection reduces the likelihood of clearance of incident HPV infection. CD4 cell count is considered as a more effective predictor of HPV clearance than HIV type.

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Chapter 1. INTRODUCTION

Infection with high-risk human papillomavirus (HPV) is a universally recognized causative agent of invasive cervical cancer (ICC) and its precursor lesions, cervical intraepithelial neoplasia (CIN) [1,2]. At least 40 genotypes of HPV can infect the genital area [3] and are classified on the basis of oncogenic potential with high-risk types 16 and 18 accounting for over 70% of cervical cancers [4]. Most HPV infections are self-limited and asymptomatic [3], but persistent detection of HPV is associated with an increased risk of CIN and ICC [5,6]. There is evidence that infection with human immunodeficiency virus (HIV) is associated with persistence of HPV infection [6-8]. HIV-induced immunosuppression can limit ability of the immune system to effectively control HPV infection, leading to an individual at greater risk of persistent infection [9]. Despite numerous studies describing the increased risk of HPV detection and cervical-related disease in HIV-positive women [10,11], few have examined the natural history of HPV infection longitudinally and provided a direct comparison to HIV-negative women.

HIV-1 is the most common type of HIV and extends worldwide. Distinct from HIV-1, HIV-2 is endemic in West Africa and often neglected in the global campaign to end the AIDS epidemic [12]. Despite many similarities, there are important differences between HIV-1 and HIV-2, including lower transmissibility, limited immune system attack and reduced likelihood of progression to AIDS of HIV-2 infection compared to HIV-1 infection [13]. There is a lack of

information on the influence of HIV type on HPV infection. HIV-2 probably have less of an effect on clearance of HPV infection due to less severe immunosuppression.

In spite of advances in cervical cancer screening and HPV vaccine development, implementing screening and vaccination programs in Sub-Saharan Africa has proven to be challenging due to financial, logistical and sociocultural factors [14]. Therefore, many important questions remain regarding the impact of HIV infection on HPV infection and subsequent development of cervical cancer. The situation has become more complicated in the era of highly active antiretroviral therapy (ART) [15], because the effect of ART on HPV infection and cervical lesions is still debatable [16]. A previous study assessed the relationship between HIV infection and HPV clearance from cohorts in the 1990s, but the study was conducted during the pre-ART era, with less specific and inconsistent HPV detection methods, and the analyses only evaluated prevalent HPV infections instead of incident infections [8]. In the present longitudinal analyses, we assessed the effect of HIV status and HIV type on the clearance of type-specific HPV infection among women in Senegal, West Africa. Furthermore, we examined the role played by CD4 cell count in clearing HPV infection among HIV-infected women.

Chapter 2. METHODS

2.1 Data collection

Data for the present analysis were obtained from a cohort study conducted in Dakar, Senegal, West Africa between 2006 and 2010, which recruited women older than 15 years presenting to an outpatient primary care clinic (Pikine) with low HIV prevalence (<1%) and an outpatient

infectious disease clinic (Fann) with high HIV prevalence (>10%) [17]. Subjects were excluded from participation if they were pregnant or didn't have an intact cervix. All participants provided written informed consent upon enrollment. The protocol was approved by the Institutional Review Boards of both the University of Washington and the University of Dakar.

Upon enrollment, a physical examination and a structured interview soliciting demographic and health information, including reproductive and sexual history, were given. Blood samples were collected for HIV-1 and HIV-2 testing, and for lymphocyte subset analysis. At baseline and at each 4-month follow-up visit, cervical swab samples were collected for HPV detection and typing.

2.2 HIV serology and lymphocyte testing

Serologic assays for HIV-1 and HIV-2 were performed on all participants' blood samples collected at baseline using a two-test sequence, as described elsewhere [18,19]. Initial testing was performed for the presence of either HIV-1 or HIV-2 antibodies. Positive samples were confirmed with a peptide-based membrane immunoassay that distinguish HIV-1 and HIV-2 antibodies. Whole blood collected in EDTA tubes from HIV-infected women was analyzed using the fluorescence activated cell sorter (FACS) Count analyzer to determine the number of CD4+ cells per microliter of blood.

2.3 HPV DNA detection and typing

Cervical cellular samples were tested for HPV DNA with a polymerase chain reaction (PCR) assay using MY09 and MY11 L1 consensus primers, HPV type-specific oligonucleotide probes, and a generic probe, with amplification of the cellular β-globin gene as a control, as previously described [19-21]. The presence of any HPV DNA was determined by PCR amplification followed by dot blot hybridization using a generic probe. Positive samples were subsequently reamplified to assess presence of 38 HPV types (6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 57, 58, 59, 61, 62, 64, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82, 83 ,84, IS39 (a subtype of HPV-82) and CP6108) mainly using a liquid bead microarray assay [22,23].

2.4 Statistical analysis

Analyses were restricted to women infected by HPV at baseline or during follow-up and with at least two subsequent visits with HPV test results. Demographic and behavioral characteristics of subjects at enrollment were summarized with frequency distributions of categorical variables separately for HIV-negative and HIV-positive subjects.

Given that an individual can be infected by multiple HPV genotypes simultaneously or be infected with the same HPV genotype multiple times, type-specific HPV infection, rather than individual, was treated as the unit of analysis. Multiple infections were identified and analyzed separately by HPV genotype. Untyped infections were excluded in the analyses. Cumulative incidence of clearance of type-specific HPV infection by HIV status and HIV type was

estimated by Kaplan-Meier methods. To reduce the likelihood of misclassification induced by false-negative results, HPV clearance was defined as two consecutive HPV-negative test results after an HPV positive test. The time at risk was calculated from initial detection of HPV to non-detection of HPV at the second time or the last sample in the study.

Marginal Cox proportional hazards models were fitted to evaluate the effect of HIV status (HIV positive vs HIV negative) on clearance of HPV infection among all subjects and the effect of HIV type (HIV-1 vs HIV-2 vs dual HIV-1/HIV-2) on clearance of HPV infection among HIV-positive subjects. Analyses were stratified by HPV infection type (prevalent vs incident infection) by including the interaction term of exposure and HPV infection type in the models. Prevalent infection was defined as detection of HPV at baseline and incident infection was defined as initial detection of HPV during follow up. Results were reported as hazard ratios (HRs) for HPV clearance with their 95% confidence intervals. Robust variance estimates were used to account for within-subject correlations. Potential confounding factors were chosen *a priori*, including age at enrollment (<35, 35-49 and ≥50), lifetime number of sex partners at enrollment (1, 2 and ≥3) and concurrent infection with multiple (>1) HPV types at initial detection of type-specific HPV infection (yes/no).

Separate models were fitted to assess the effect of HIV status on clearance of high-risk HPV (HR-HPV) infection and clearance of low-risk HPV (LR-HPV) infection, with the following 18 types classified as HR-HPV types based on their oncogenic potential: 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82 and IS39 [24]. Furthermore, we evaluated the effect of CD4 cell counts on HPV clearance among HIV-positive subjects. *A priori*, HIV-positive

subjects were classified into 2 categories based on CD4 cell counts at enrollment: ≤500 and >500 cells/μL. Analyses were performed utilizing R version 4.0.2. All statistical tests were 2-tailed with significance level $\alpha=0.05$.

Chapter 3. RESULTS

3.1 Characteristics of participants and infections

Among 174 women we identified 684 HPV infections at baseline or during follow-up which met inclusion criteria of having at least two subsequent HPV negative results after initial detection. The median age of the 174 women was 42, ranging from 20 to 70. The majority of the participants didn't use contraceptives (86.2%) and didn't smoke (98.3%). Compared to HIV-negative women (n=75), women with HIV-1 and/or HIV-2 infection (n=99) were more likely to be recruited at the Fann clinic, be younger, be single, have fewer children, have a greater lifetime number of sex partners and were more likely to use condoms at baseline (Table 4.1). Among the 684 HPV infections, 188 (27.5%) were in HIV-negative women, 406 (59.4%) were in HIV-1 infected women, 54 (7.9%) were in HIV-2 infected women and 36 (5.3%) were in HIV-1/2 dually infected women. Of these HPV infections, 295 (43.1%) were incident infections and 389 (56.9%) were prevalent infections, 405 (59.2%) were HR-HPV genotypes and 279 (40.8%) were LR-HPV genotypes.

3.2 Association of HIV status and HPV clearance

Among incident HPV infections, the 2-year cumulative incidence of HPV clearance was 84.0% (95% CI: 72.3%-92.6%) in HIV-negative women and 75.8% (95% CI: 68.7%-82.3%) in HIV-positive women. Among prevalent HPV infections, the 2-year cumulative incidence of HPV clearance was 47.6% (95% CI: 38.3%-57.9%) in HIV-negative women and 51.2% (95% CI: 44.0%-58.8%) in HIV-positive women (**Error! Reference source not found.**). In univariate analyses (data not shown), prevalent HPV infections showed a significant reduction in likelihood of clearance than incident infections compared with incident HPV infections (HR=0.50, 95% CI: 0.38-0.67). In the multivariate model (Table 4.2), we observed the association between HIV status and clearance of HPV infection significantly differ between incident and prevalent HPV infections ($p = 0.02$). Among incident HPV infections, those in HIV infected women were less likely to be cleared than those in HIV uninfected women (adjusted HR=0.66, 95% CI: 0.44-0.99). Among prevalent HPV infections, no significant association between HIV status and HPV clearance was observed (adjusted HR=1.16, 95% CI: 0.81-1.67).

Similar patterns were observed when stratifying HPV infections by low or high risk. We found a significant reduction in the likelihood of HPV clearance comparing infections in HIV infected women to those in HIV uninfected women among incident LR-HPV infections (adjusted HR=0.55, 95% CI: 0.33-0.92), but an insignificant association among prevalent LR-HPV infections (adjusted HR=1.45, 95% CI: 0.82-2.59). For HR-HPV infections, the associations for incident versus prevalent infections showed a similar pattern but were attenuated and not

statistically significant (adjusted HR=0.75, 95% CI: 0.44-1.29, and adjusted HR=1.02, 95% CI: 0.67-1.53, respectively).

3.3 Association of HIV type, CD4 cell count and HPV clearance

Among incident HPV infections, the 2-year cumulative incidence of HPV clearance was 75.0% (95% CI: 67.2%-82.2%) for HIV-1 infected women, 80.9% (95% CI: 60.3%-94.9%) for HIV-2 infected women and 64.0% (95% CI: 36.6%-89.9%) for HIV-1/2 dually infected women. Among prevalent HPV infections, the 2-year cumulative incidence of HPV clearance was 54.0% (95% CI: 46.3%-62.1%) for HIV-1 infected women and 21.4% (95% CI: 7.0%-55.1%) for HIV-1/2 dually infected women (data for HIV-2 infected women with prevalent HPV infections were limited so unable to estimate 2-year cumulative incidence) (**Error! Reference source not found.**). For HIV-positive women (**Error! Reference source not found.**), no significant association between HIV type and clearance of HPV was observed among incident HPV infections (adjusted HR=1.61, 95% CI: 0.93-2.80 for comparison between those in HIV-2 and HIV-1 infected women; adjusted HR=1.50, 95% CI: 0.87-2.57 for comparison between those in HIV-1/2 dually infected and HIV-1 women) or among prevalent HPV infections (adjusted HR=0.77, 95% CI: 0.23-2.66 for comparison between those in HIV-2 and HIV-1 infected women; adjusted HR=0.71, 95% CI: 0.36-1.38 for comparison between those in HIV-1/2 dually infected and HIV-1 women).

Separately, incident HPV infections in women with CD4 cell counts ≤500 showed a significant reduction in likelihood of clearance compared with those in women with CD4 cell counts >500

(adjusted HR=0.63, 95% CI: 0.41-0.97). The association, however, was insignificant among prevalent HPV infections (adjusted HR=0.87, 95% CI: 0.46-1.63).

Chapter 4. DISCUSSION

4.1 Principal findings

The analyses demonstrated a difference between HPV incident and prevalent infections in the effect of HIV on clearance of type-specific HPV infection among women in Senegal, Africa. Among incident HPV infections, those in HIV-positive women were less likely to be cleared than those in HIV-negative women, and those in HIV infected women with CD4 cell counts ≤500 were less likely to be cleared than those in HIV infected women with CD4 cell counts >500. However, these associations were not observed among prevalent HPV infections. We found no evidence of association between HIV type and clearance of HPV infection among HIV infected women.

A number of cross-sectional studies of HPV infection among Sub-Saharan African women have been conducted, indicating HIV-positive women are more likely to harbor HPV than HIV-negative women [10, 21, 25]. More importantly, since persistent infection with HPV is a necessary cause of cervical cancer, research into HPV persistence and clearance can provide key strategies to determine the high-risk populations that need better monitoring [26], especially in Africa where resources for implementing screen and HPV vaccine programs are limited [14].

Although we did not observe any association between HIV status and clearance of prevalent HPV infection, HIV-positive women in our study had a significant reduction in the likelihood of clearance of incident HPV infection, compared with HIV-negative women. The finding for incident HPV infections is consistent with most other research [6-8]. For example, Whitham et al. [6] used data obtained from six studies in Senegal that included some of the same women assessed in our analysis. They observed that HIV-positive women had a 0.46 times (95% CI: 0.39-0.54) lower possibility of regression from HPV to normal than HIV-negative women. When analyzing prevalent cases of HPV infection, several studies [8, 27-29] indicated inconsistent conclusions. Although some studies [8,27] provided evidence of a reduction in the likelihood of HPV clearance among HIV-positive women, comparing with HIV-negative women, other studies [28,29] reported that HIV serostatus did not have an impact on clearance of any HPV, HR-HPV or LR-HPV. The duration of prevalent HPV infection is likely to be underestimated due to left censoring. Using prevalent HPV infections potentially attenuates the association between HIV infection and HPV clearance if the impact of HIV is noticeable at the beginning of an HPV infection, or if difference in duration is noticeable only after an extended period of infection (for example, after at least a year of HPV infection). Incident infection is probably more effective to assess the effect of HIV infection on clearance of HPV infection.

Few prior studies evaluated evidence regarding the impact of HIV type on HPV infection [6, 8, 21]. Some research [8,21] indicated that HIV-2 is associated with lower risk of HPV detection and persistent HPV infection comparing with HIV-1, but the associations were attenuated by adjustment for CD4 cell count. This suggests that HIV type affects HPV infection,

at least to some degree, through the mechanism of CD4 cell depletion. Compared with HIV-1, lower pathogenicity of HIV-2 may permit the host to mount more effective, sustained T-cell immunity to control HPV infection [30]. Interestingly, the present analysis found no association between HIV type and clearance of HPV infection among HIV infected women even without adjustment for CD4 cell counts. Meanwhile, we observed the association between lower CD4 cell count and lower likelihood of clearance of HPV infection among incident HPV infections, consistent with most other studies [6-8,21,29,31]. One possible explanation for these findings is that CD4 cell count may be on the causal pathway of the relationship between HIV type and HPV clearance, but in the era of highly active ART, early initiation of ART with high CD4 cell count in Africa attenuates the association between HIV type and CD4 cell count, which may subsequently weaken the relationship between HIV type and HPV clearance. A systematic review [32] also suggested that CD4 cell count may have a more instrumental role in HPV infection persistence and cervical oncogenesis than either HIV type or ART use.

4.2 Strengths and limitations

This study has a number of strengths, most notably a longitudinal sample to compare HPV clearance in HIV-positive and HIV-negative women. It allows us to better identify the sequence of HIV infections and HPV infections, understand their potential causal relationships and provide insight into progression of HPV infection over time. Furthermore, data collected from a unique sample allows us to assess the effect of HIV type, as both HIV-1 and HIV-2 are endemic to West Africa. Another strength is we evaluated the effect of HIV infection on natural history of HPV infection at the infection level, instead of at the individual level. It expands the

sample size and takes advantage of the richness of the data collection, which included detection of 38 HPV types assessed over numerous study visits. Finally, we examined the difference in effect of HIV infection between prevalent and incident HPV infections and reported the results separately for prevalent and incident HPV infections to reduce the bias caused by underestimated duration of prevalent infections.

Several limitations in our study should be noted. First, it is still possible that the estimated effects were confounded by unmeasured factors, though we took multiple potential confounders into account. For example, information on ART was unavailable in the study. As we mentioned above, ART may be an important factor confounding the relationship between HIV infection and HPV clearance. However, we examined the impact of CD4 cell count to capture some of the treatment effect indirectly. Additionally, several studies [16,32] suggested a limited effect of ART on HPV infection and cervical lesions. The second limitation is a modest number of women recruited, although each participant was sampled repeatedly. The small sample size may have limited our ability to detect statistical significance when stratifying analysis by prevalent/incident HPV infection. In particular, the infections were stratified into 4 cross-strata by HPV infection type and HPV DNA risk type to assess the relationship between HIV status and clearance of HR/LR-HPV infection separately. Infection-level analyses expanded the sample size and avoided the violation of positivity assumptions, but we were still unable to assess effect of HIV type on clearance of HR/LR-HPV infection among HIV infected women. Finally, some variables may be time-varying, but we did not consider the variability. For example, CD4 cell counts are not constant through the whole study and CD4 cell counts at

the most recent visit seems to play a more important role in HPV clearance than baseline CD4 cell counts. However, it may not be a main concern because the data showed CD4 cell counts over time were generally concentrated near the baseline value.

4.3 Conclusion

In summary, we found that HIV-positive women were less like to clear incident HPV infection in Senegal, West Africa. Among HIV-positive women, CD4 cell count is considered as a more effective predictor of HPV clearance than HIV type. In the limited resource setting of Sub-Saharan Africa, targeted cervical cancer screening programs for the high-risk population of HIV-positive women, especially populations with low CD4 cell count, are needed. In addition, HPV vaccination programs should be aimed at populations which are at high risk for HIV infection since HIV is associated with reduced ability to clear HPV infections. Further studies assessing the potential long-term impact of antiretroviral therapy on persistence of HPV infection at the population level and investigating its mechanisms at the individual level are needed.

Table 4.1. Baseline demographic, behavioral and health characteristics of 174 Senegalese women with HPV infection, in 2006-2010, by HIV status, n (%)

	HIV Negative (n=75)	HIV Positive (n=99)	Overall (N=174)
Clinic			
Fann	14 (18.7)	97 (98.0)	111 (63.8)
Pikine	61 (81.3)	2 (2.0)	63 (36.2)
Age			
<35	14 (18.7)	19 (19.2)	33 (19.0)
35-49	33 (44.0)	66 (66.7)	99 (56.9)
≥50	28 (37.3)	14 (14.1)	42 (24.1)
Marital status			
Not married currently	10 (13.5)	44 (45.4)	54 (31.6)
Mono married	20 (27.0)	30 (30.9)	50 (29.2)
Poly married	44 (59.5)	23 (23.7)	67 (39.2)
Missing	1 (1.3)	2 (2.0)	3 (1.7)
Parity			
0	7 (9.4)	12 (12.4)	19 (11.1)
1-4	17 (23.0)	61 (62.9)	78 (45.6)
≥5	50 (67.6)	24 (24.7)	74 (43.3)
Missing	1 (1.3)	2 (2.0)	3 (1.7)
Lifetime sex partners			
1	45 (60.0)	42 (43.8)	87 (50.9)
2	20 (26.7)	36 (37.5)	56 (32.7)
≥3	10 (13.3)	18 (18.7)	28 (16.4)
Missing	0 (0)	3 (3.0)	3 (1.7)
Birth control method			
Condom	1 (1.3)	8 (8.1)	9 (5.2)
Other	12 (16.0)	3 (3.0)	15 (8.6)
None	62 (82.7)	88 (88.9)	150 (86.2)
Current smoking			
Yes	1 (1.3)	2 (2.0)	3 (1.7)
No	74 (98.7)	96 (98.0)	170 (98.3)
Missing	0 (0)	1 (1.0)	1 (0.6)
HIV type			
HIV-1	-	79 (79.8)	-
HIV-2	-	15 (15.1)	-
HIV-1/2	-	5 (5.1)	-
CD4 cell count (cells/μL)			
≤200	-	21 (22.3)	-
201-500	-	42 (44.7)	-
>500	-	31 (33.0)	-
Missing	-	5 (5.1)	-

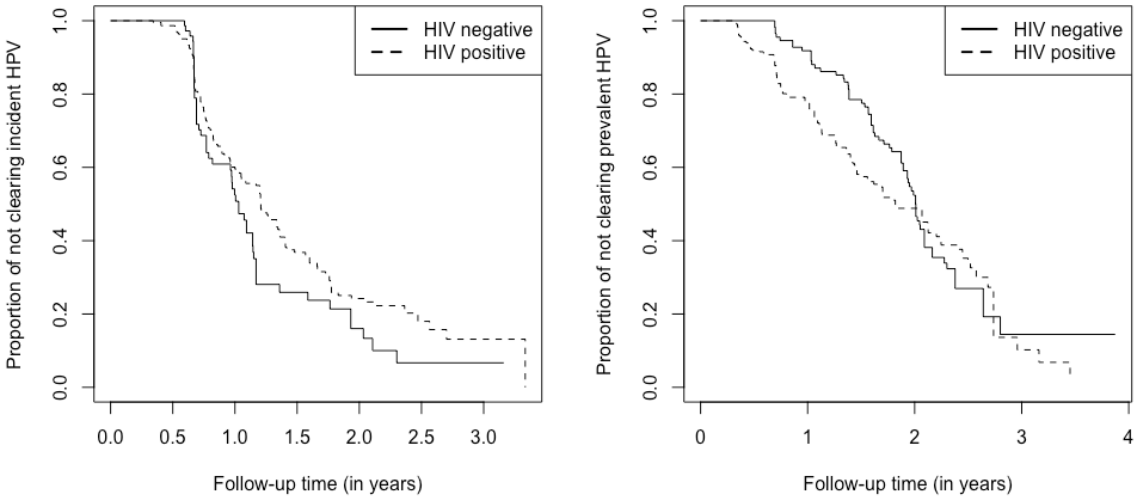

Figure 4.1. Cumulative incidence of clearing HPV infection for 174 Senegalese women with HPV infection, in 2006-2010, by HIV status. Left panel, among incident HPV infections, 340 person-years at risk. Right panel, among prevalent HPV infections, 546 person-years at risk.

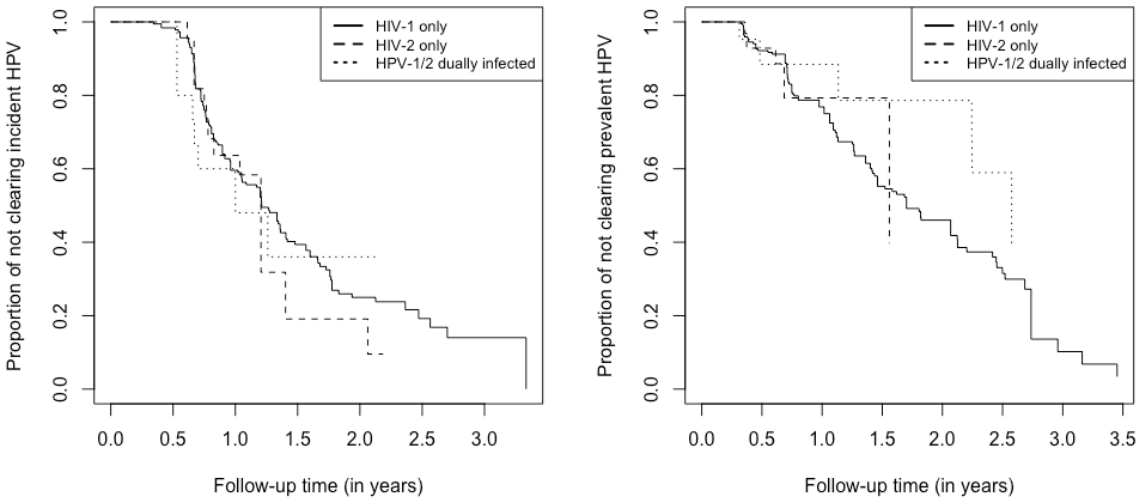

Figure 4.2. Cumulative incidence of clearing HPV infection for 99 HIV-positive Senegalese women with HPV infection, in 2006-2010, by HIV type. Left panel, among incident HPV infections, 263 person-years at risk. Right panel, among prevalent HPV infections, 344 person-years at risk.

Table 4.2. Hazard ratios for the association of HIV status and clearance of HPV infection among 174 Senegalese women with HPV infection, in 2006-2010

	Incident HPV Infections[a]			Prevalent HPV Infections[a]			p-value[d]
	Events[b]	Person-Years	HR (95% CI)[c]	Events	Person-Years	HR (95% CI)[c]	
Any HPV							
HIV-	54	77	ref.	70	203	ref.	-
HIV+	149	263	0.66 (0.44-0.99)	126	344	1.16 (0.81-1.67)	0.02
High-risk HPV[e]							
HIV-	27	38	ref.	50	138	ref.	-
HIV+	83	133	0.76 (0.44-1.29)	77	217	1.02 (0.67-1.53)	0.37
Low-risk HPV[f]							
HIV-	27	40	ref.	20	64	ref.	-
HIV+	66	130	0.55 (0.33-0.92)	49	127	1.45 (0.82-2.59)	0.02

Abbreviation: HR = hazard ratio; CI = confidence interval; ref. = reference category.

[a] Incident HPV infections = HPV infections initially detected during follow up; prevalent HPV infections = HPV infections present at baseline.

[b] Events = number of clearances of type-specific HPV infection.

[c] Adjusted for the following covariates: age at enrollment, lifetime number of sex partners at enrollment and concurrent infection with multiple (>1) HPV types at initial detection of type-specific HPV infection.

[d] p-value for difference in HRs between incident and prevalent HPV infection.

[e] High-risk HPV types include 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82 and IS39.

[f] Low-risk HPV types include 6, 11, 26, 40, 42, 54, 55, 57, 61, 62, 64, 67, 69, 70, 71, 72, 81, 83 ,84 and CP6108.

Table 4.3. Hazard ratios for the association of HIV type, CD4 cell count and clearance of HPV infection among 99 HIV-positive Senegalese women with HPV infection, in 2006-2010

	Incident HPV Infections[a]			Prevalent HPV Infections[a]			p-value[d]
	Events[b]	Person-Years	HR (95% CI)[c]	Events	Person-Years	HR (95% CI)[c]	
HIV type							
HIV-1	124	224	ref.	113	289	ref.	-
HIV-2	17	25	1.61 (0.93-2.80)	6	28	0.77 (0.23-2.66)	0.23
Dually infected	8	14	1.50 (0.87-2.57)	7	27	0.71 (0.36-1.38)	0.02
CD4 cell count							
> 500	55	75	ref.	19	55	ref.	-
≤ 500	88	169	0.63 (0.41-0.97)	104	279	0.87 (0.46-1.63)	0.39

Abbreviation: HR = hazard ratio; CI = confidence interval; ref. = reference category.

[a] Incident HPV infections = HPV infections initially detected during follow up; prevalent HPV infections = HPV infections present at baseline.

[b] Events = number of clearances of type-specific HPV infection.

[c] Adjusted for the following covariates: age at enrollment, lifetime number of sex partners at enrollment and concurrent infection with multiple (>1) HPV types at initial detection of type-specific HPV infection.

[d] p-value for difference in HRs between incident and prevalent HPV infection.

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