The effect of polygamy on loss of human papillomavirus detection in Senegalese women

Meixin Zhang

A thesis
submitted in partial fulfillment of the
requirements for the degree of

Master of Science

University of Washington

2021

Committee:

Stephen E. Hawes

Rachel L. Winer

Program Authorized to Offer Degree:
Epidemiology

University of Washington

Abstract

The effect of polygamy on loss of human papillomavirus detection in Senegalese women

Meixin Zhang

Chair of the Supervisory Committee:

Stephen E. Hawes

Department of Epidemiology

Objectives: Persistent infection with human papillomavirus (HPV) can result in premalignant cervical lesions. Women in polygamous marriage are more likely to be re-exposed to HPV. Repeated exposure to HPV antigen may lead to shorter duration of infections by boosting the immune response. This study assessed the impact of polygamy on the clearance of HPV infection and assessed whether this association varies by HIV status or coinfection with multiple HPV types.

Methods: We used secondary data collected in two prospective cohort studies (between 1994-1998 and 2005-2011) conducted in Senegal, western Africa. Subjects were females aged 15 years or older, were married, were not pregnant, had an intact cervix, were HPV- positive at baseline or during 4-6 month follow-up visits, and with at least 2 follow-up visits following initial detection of HPV (n=235). The unit of analysis was each infection (288 prevalent infections and 290 incident infections). We conducted marginal Cox proportional hazard regression models to investigate the impact of polygamous marriage versus monogamous marriage on the clearance of HPV infection, adjusting for age, parity, lifetime number of sex partners, infection status (prevalent or incident), HIV status (HIV positive with $\geq$ 350 cells/μL CD4 count; HIV positive with $<$ 350 cells/μL CD4 count; HIV negative) and coinfection with other HPV types. We further assessed the effect modification of HIV status and coinfection with multiple HPV types.

Results: We included 289 infections that occurred among polygamously married women, and 289 infections that occurred among monogamously married women. Polygamously married subjects tended to be older, were more often HIV negative, had more children, and had a higher lifetime number of sex partners. We did not identify an association between polygamous marriage and HPV clearance (HR:0.97, 95% CI: 0.70-1.34). HIV status didn't modify this association (p-value=0.28). We observed a non-statistically significant positive association between polygamous marriage and HPV clearance (HR: 1.47, 95% CI: 0.82-2.65) in HIV positive women with $\geq$ 350 cells/μL CD4 counts, but not in HIV negative women (HR: 0.84, 95% CI: 0.57-1.19) or HIV positive women with $<$ 350 cells/μL CD4 counts (HR: 0.88, 95% CI: 0.35-2.19). Coinfection with multiple HPV types was not an effect modifier (p-value=0.97).

Conclusion: We conclude that polygamous marriage wasn't associated with HPV clearance, but there was a non-significantly positive association between marital status and HPV clearance. The potential reason for this difference may be the different sexual behavior or varied immune function among women by HIV status. This finding provides potential evidence of the re-exposure-related immune responses to HPV clearance.

Keywords: Polygamous marriage; HPV clearance; re-exposure to HPV antigen; immune response; HIV status

Introduction

Worldwide, cervical cancer is the fourth most common malignancy in women and causes approximately 570,000 incident cases annually, with 311,000 deaths[1]. Cervical cancer is the leading cause of cancer-related death in women in Africa[1]. Central and South America, the Caribbean, Sub-Saharan Africa, and Southern Asia have the highest cervical cancer incidence rates[2]. Human papillomavirus (HPV) infection is the causal agent for cervical cancer, 70% of which are caused by HPV types 16 and 18[3]. The majority of HPV infections are transient and clear spontaneously. However, in some cases, the persistent infection will result in the premalignant lesions of cervical intraepithelial neoplasia or adenocarcinoma in situ[2,4], which if left undetected and untreated, can develop into cervical cancer. Therefore, one crucial step to prevent cervical cancer is to identify and understand mechanisms for HPV persistence.

It is known that polygamy, which is culturally acceptable in many countries, is related to the increased probability of cervical cancer[5,6]. A previous study demonstrated that polygamy increases the risk of cervical cancer by two times, although this association was not statistically significant[7]. Theoretically, women in polygamous marriage are more likely to be re-exposed to HPV since their husbands have sex with more than one wife and tend to be the source of sexually transmitted infection (STI) transmission and carry multiple types of HPV and/or one type of HPV for a longer time. This pattern could explain the positive association between polygamous marriage and cervical cancer. However, whether women in polygamous marriages have a higher or lower rate of HPV persistence/clearance due to re-exposure to HPV remains unknown. Previous researchers noted that marriage is protective against long-term HPV persistence[8,9,10]. The potential reason for this association is that the repeated exposure to HPV antigen could boost the immune response, prolong the duration of high antibody titer, and thus lead to shorter HPV persistence[11]. Based on this evidence that re-exposure to HPV antigen could shorten the duration of HPV infection and the possible relationship that women in polygamous marriages are more likely to be repeatedly exposed to HPV antigen, we hypothesize that women in polygamous marriages have a higher likelihood of HPV clearance than women in monogamous marriages. There is no evidence of the causal effect of polygamy on HPV persistence or HPV clearance.

There are several factors associated with HPV clearance. STIs create inflammation and decrease epithelial barriers, potentially exposing basal epithelial cells to infection with HPV. HIV infection has been shown to be associated with a higher likelihood of HPV detection and a higher proportion of high-risk types and multiple types of HPV[3]. HIV infection also reduces HPV clearance through both immunosuppression[12] and increased risk of HPV infection with multiple types. Therefore, HIV infection could counteract the boost of immune response from re-exposure to HPV antigen, which might occur through polygamous marriage.

Coinfection with multiple HPV types is also associated with increased infection duration[13]. Coinfection may indicate that women’s immune system doesn’t respond to HPV virus as robustly, thus allowing the virus load to be high enough that it could be detected, and resulting in the continuous detection of each infection for a longer period. Because the immune system has to respond to each infection simultaneously, coinfection may also boost the immune response from repeated exposure to the same HPV antigen. Therefore, coinfection with multiple HPV types could potentially modify the association between polygamy and HPV clearance.

As such, our retrospective cohort study builds on prior work and utilizes secondary data from two prospective studies implemented among Senegalese women to examine the impact of polygamy on the clearance of HPV infection and whether this association is modified by HIV status and coinfection with multiple HPV types. This study's results are expected to inform how immune responses related to re-exposure to HPV might relate to HPV clearance/persistence.

Methods

Study Design and Study Setting

This study is a retrospective cohort study using secondary data collected in two prospective cohort studies conducted in Senegal, western Africa. Study 1, which aimed to investigate the natural history of cervical neoplasia in HIV-1 and HIV-2, enrolled subjects from Fann University Hospital between October 1, 1994 and January 1, 1998[14]. Study 2, that investigated HIV-associated DNA hyper-methylation in cervical cancer, enrolled subjects from Fann University Hospital and the Pikine outpatient clinics from October 2005 to September 2011. Studies were approved by the University of Washington and Senegalese Human Subjects Review Boards with informed consent obtained from each subject.

Study Subjects and Data Collection

Women who were aged 15 years or older, were not pregnant, had an intact cervix, presenting to the University of Dakar infectious disease clinic (Study 1), or Fann University Hospital or Pikine outpatient clinic (Study 2) were screened for participation. At screening, eligible women were offered serologic testing for HIV-1 and HIV-2 and cervical swabs testing for HPV DNA detection, a short-standardized screening interview that included questions about medical and sexual history, and a general physical examination. Women found to be infected by high-risk HPV types in Study 1 and any type of HPV in Study 2 were invited four weeks later in the return visit to enroll into the longitudinal study with follow-up visits. At the enrollment visit and at each 4–6 months subsequent follow-up visit, more detailed questionnaires about sexual behavior (time since last sex) and medical history were completed to obtain information regarding marital history, contraception use, age at first intercourse, the lifetime number of sexual partners, previous hospitalizations and the use of medications. Blood was collected at each visit for HIV testing, CD4 cell count, and HIV viral load quantification. Cervical cellular samples were obtained on each visit and sent to University of Washington for assessment of cervical abnormalities and HPV typing. HPV was tested by polymerase chain reaction (PCR) in Study 1, initially with HPV L1 consensus primers, HPV type-specific oligonucleotide probes, and a generic probe, which could identify 12 HPV types, low-risk (6/11) and high-risk (16, 18, 31/33/35/39, 45/56, and

51/52).[14]. Beginning in 1998 when the new probes was available, HPV detection and typing were done via a PCR-based reverse-line strip test method (Roche Molecular Systems) for low-risk types (6, 11, 40, 42, 54, 55, 57, 83) and high-risk types (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82, and 84).[15]. Luminex-based testing and typing method was adopted in Study 2, which combines polymerase chain reaction amplification with hybridization to fluorescence-labeled polystyrene bead microarrays with additional probes for low-risk types（61, 62, 64, 67, 69, 70, 71, 72, 81, and CP6108 which is now HPV-79) and high-risk type IS39 which is now HPV-82[16].

Exposure

In this analysis, the primary exposure of interest was being in a polygamous, as opposed to monogamous marriage as reported at baseline (screening). At the enrollment visit, women additionally reported the number of cowives they had. Based upon these two factors, 15 women were potentially misclassified, reporting monogamous marriages at baseline but listing ≥ 1 cowives (n=6) or reporting being a part of a polygamous marriages at baseline but listing 0 cowives (n=9). In a sensitivity analysis, we assessed the impact of defining the polygamous/monogamous marriage based on the number of cowives that women reported at enrollment.

Outcome

For this analysis, we defined the outcome, clearance of HPV, as 2 consecutive HPV-negative detections for the same HPV type (type-specific HPV clearance).

Covariates

We incorporated several other women-level and infection-level potential confounding factors that could relate to polygamous marriage and affect HPV clearance, including age (17-30, 31-40, 41-50, 51-60, 61-70), parity (0, 1-3, 4 or more), lifetime number of sex partners (continuous variable), and HPV infection status (prevalent or incident), HIV infection status (HIV positive with ≥ 350 cells/μL CD4 count; HIV positive with < 350 cells/μL CD4 count; HIV negative), and coinfection with multiple HPV types (yes or no at time of initial detection). We further assessed the effect modification by HIV status or by coinfection with multiple HPV types.

The HPV testing method changed during the period of Study 1, which could result in the inconsistent sensitivity of the detection across the two study cohorts. The likely differential misclassification before and after the transition to the new HPV detection method could result in different baseline hazards. Therefore, we stratified on detection methods (PCR-based and Luminex). We also stratified on dichotomous HPV risk type (high-risk vs. low-risk) to allow different baseline hazards for HPV clearance.

Statistical Analysis

Only non-sex workers who were married at baseline, had baseline (prevalent) or incident HPV-16 and/or HPV-18 in Study 1, any type HPV in Study 2, with at least 2 follow-up visits following initial detection during study were included in the analysis.

We first conducted descriptive analyses to understand the prevalence of each demographic and laboratory characteristic among the entire study population, as well as among the monogamously and polygamously married sub-populations, respectively.

The unit of the following analyses was each infection, including prevalent and incident infection that happened among either monogamous married or polygamous married women. We estimated the hazard ratio for type-specific HPV clearance using marginal Cox proportional hazards regression model, in which we used generalized estimating equations (GEE) to account for within-person correlation among women with multiple HPV infections at baseline or during follow-up, after adjusting for all potential confounding factors, stratifying on the detection methods and the HPV risk type to allow for differential baseline hazard of clearance. The duration of infection was measured from the initial detection of HPV to the second consecutive non-detection. We then built the similar marginal Cox proportional hazards regression model, incorporating the interaction term of marital status with HIV status and with multiple HPV infection, respectively. We conducted a sensitivity analysis by defining monogamous/polygamous marriage based on the number of cowives (women reporting having 0 cowives were classified as in monogamous marriages; women reporting having ≥1 cowives were classified as in polygamous marriages). Analyses were performed using R (version 4.0.5). All statistical tests were 2-sided, and the significance level was set at alpha=0.05.

Results

At baseline and during follow-ups, 578 HPV infections with at least two follow-up visits were identified among 235 married women, including 289 HPV infections among 122 monogamously married women and 289 HPV infections among 113 polygamously married women (Table 1). Of the 235 study subjects, 73.6% were from Fann University Hospital and 26.4% were from Pikine outpatient clinics, 42.6% were from cohort 1, and 57.4% were from cohort 2. Polygamously married subjects tended to be older, were more often HIV negative, had more children, had a higher lifetime number of sex partners, and were less likely to use birth control.

In the univariate regression models (Table 2), polygamous marital status was not associated with HPV clearance (HR: 1.01, 95% CI: 0.74-1.39). This remained true after adjusting for all the potential confounding variables (HR:0.97, 95% CI: 0.70-1.34). In regression models investigating potential effect modification by HIV status and multiple HPV infections (Table 3), we observed that neither HIV status nor coinfection with multiple HPV types modified the association between marital status and HPV clearance (p-value=0.28 and p-value=0.97, respectively). In subjects who were HIV positive with CD4 counts ≥ 350 cells/μL, polygamous marriage was positively related to HPV clearance (HR: 1.47, 95% CI: 0.82-2.65), although this association did not reach statistical significance. However, in HIV negative subjects and HIV positive subjects with CD4 counts < 350 cells/μL, we observed a non-significant inverted relationship (HR=0.84 (95% CI: 0.58-1.21) and HR=0.88 (95% CI: 0.35-2.19), respectively).

In the sensitivity analysis defining monogamous/polygamous marriage by the number of cowives instead of marital status that the subjects reported, similar findings were observed.

A potential reason for the non-significantly different association by HIV status might be that the sexual behaviors are different by HIV status. Therefore, we implemented a post-hoc analysis to assess whether sexual behaviors could partially explain this different association by HIV status. We analyzed the distribution of time since last sexual activity, which was the only measurement of sexual behavior in this study, in polygamously married and monogamously married women, by HIV status (HIV negative; HIV positive with CD4 counts ≥ 350 cells/μL; HIV positive with CD4 counts < 350 cells/μL) (S Table 2). Among HIV negative women and HIV positive women with CD4 counts < 350 cells/μL, polygamous married women were less likely to engage in sexual activity within last 7 days, compared with monogamous married women (41.9% vs. 60.8% in HIV negative women; 21.7% vs. 63.3% in HIV positive women with CD4 counts < 350 cells/μL). In HIV positive women with CD4 counts ≥ 350 cells/μL, polygamous married women were more likely to report sexual activity within last 7 days, compared with monogamous married women (52.1% vs. 40.0%).

Discussion

In our study, we did not identify an association between polygamous marriage and HPV clearance in HIV negative women or in HIV positive women with low CD4 counts. However, in HIV positive women with high CD4 counts, we observed a non-significant association between HPV clearance and polygamous marriage. In several previous studies conducted in countries where polygamy is illegal[8,9] or in a country where polygamous marriage is common[10], marriage was found to be protective against HPV persistence. The research from Ho[11] and their team demonstrated that subsequent exposure to HPV after seroconversion was related to sustained IgG detection. Although the presence of HPV IgG could prevent the reinfection, re-exposure to HPV virus could boost the immune response to HPV antigen, and therefore could keep the high-level of HPV antibody for a longer time and shorten the period from the initial detection of HPV until clearance. The results from these studies may partially explain the immune response to HPV re-exposure and the positive relationship we found between polygamous marriage and HPV clearance. Several other articles, on the other hand, discuss the potential for condom use to promote clearance by reducing continued viral exposure. In a longitudinal study, more consistent condom use was associated with HPV clearance[17]. Another randomized clinical trial also demonstrated this relationship and found that the use of condoms was associated with the regression of cervical intraepithelial neoplasia (CIN)[18]. However, we didn't take account condom use in our model because the use of condoms was rare in the included subjects. In addition, there was no substantial difference in condom use between monogamously married women and polygamously married women. Therefore, condom use cannot explain the non-significantly positive association between polygamous marriage and HPV clearance among HIV positive women with high CD4 counts.

In the present study, the non-significant positive relationship we found in HIV positive women with CD4 counts ≥ 350 cells/μL was not observed in HIV negative subjects and HIV positive subjects with CD4 counts < 350 cells/μL. In the post-hoc analysis, we investigated whether the disparity of time since last sex, which is the only measurement of sexual behavior in this study, in women with different HIV status could explain the effect modification of HIV status. Among HIV positive people with high CD4 counts, polygamously married women tended to have more recent sexual activities than monogamously married women. This relationship was inverted in HIV negative women and HIV positive women with low CD4 counts. Among HIV negative women and HIV positive women with low CD4 counts, polygamously married women tended to have less recent sexual activities than monogamously married women. We hypothesized that re-exposure to HPV antigen through polygamous marriage could promote the clearance of HPV. However, too distant sexual activities in polygamous married women may counteract the benefit of HPV clearance from polygamous marriage. Therefore, the different comparison of time since last sex between polygamously married women and monogamously married women by HIV status might be one reason why we observed the different association between marital status and HPV clearance by HIV status, and could also provide some evidence of the boosted immune response to HPV infection through sex-related re-exposure to HPV antigens. Other unmeasured sexual behaviors, including frequency of sex and number of sex partners by the husband, are either potential confounders or potential mediators that may explain our observations.

Another potential explanation for our differential findings is the difference in the immune system among women with and without HIV infection. HIV negative women had a robust immune function, and HIV positive women with low CD4 counts had impaired immune function, no matter whether they were polygamously or monogamously married, but HIV positive women with high CD4 counts had partially impacted immune function. As a result, it may be that HIV negative women could respond to HPV antigen robustly without the boost of immune system through re-exposure to HPV antigen, and HIV positive women with low CD4 counts couldn't clear HPV effectively, even if they were re-exposed to HPV antigens. However, HIV positive women with high CD4 counts needed the stimulation of the immune response to effectively clear HPV. Therefore, the effect of polygamous marriage on HPV clearance was different by HIV status, and among HIV positive women with high CD4 counts, polygamous marriage was non-significantly associated with a higher possibility of HPV clearance.

This study has several strengths. First, we adjusted for covariates, including age, parity, lifetime number of sexual partners, incident versus prevalent infection status, HIV status and coinfection with multiple HPV types that could potentially confound the association between polygamous marriage and HPV clearance, and stratified on covariates including HPV risk type and HPV detection method that could affect the baseline likelihood of HPV clearance. Second, HPV clearance was defined as 2 consecutive HPV negative detections instead 1 negative detection to reduce potential misclassification due to false-negative detection. Furthermore, HPV clearance was type specific. To be specific, instead of defining HPV clearance as 2 consecutive negative detection of any HPV type, we defined HPV clearance as 2 consecutive negative detections of the same HPV type. Third, most studies have used prevalent infections, but we included both prevalent and incident cases, so that we could magnify the sample size and generalize our findings. We also had the ability to assess differential HPV clearance of incident infections versus prevalent infections.

A number of study limitations also exist. First, there may be unmeasured confounders due to lack of direct information regarding the husband's number of concurrent non-marital partners or lifetime number of sex partners, and whether the husband actually has sex with each wife. Second, misclassification of marital status might exist. For example, a number of monogamous married women reported that their husband had more than one wife, or polygamous married women reported that their husband only had one wife. However, when we defined marital status using the number of cowives in the sensitivity analysis, we obtained similar results. Furthermore, our study did not account for potential changes in marital status during follow-ups, as we only captured baseline marital status. Another source of limitation is the uncertainty about when actual clearance occurred because women visited every 4-6 months and clearance and reinfection might occur between two visits. Last, we want to know if polygamy is associated with development of cancer, but we only are assessing whether it is associated with HPV persistence, which is a surrogate for invasive cancer.

In conclusion, overall we found that polygamous marriage wasn't associated with HPV clearance. However, in HIV positive women with high CD4 counts, polygamous marriage was found to be related to higher likelihood of HPV clearance non-significantly, but we did not find this non-significant positive association in HIV negative women or HIV positive women with low CD4 counts. Different sexual behavior or varied immune function among women by HIV status may be the reason for this difference by HIV status. This study furthers our understanding of the association between polygamous marriage and HPV clearance and re-exposure-related immune response to HPV persistence/clearance.

Tables and Figures

Table 1. The characteristics of the 235 monogamously or polygamously married women with prevalent or incident HPV infection in Senegal at baseline.

	Monogamous Married Women (N=122)	**Polygamous Married Women (N=113)**	**Overall (N=235)**
Clinic			
Fann[1]	105 (86.1%)	68 (60.2%)	173 (73.6%)
Pikine[2]	17 (13.9%)	45 (39.8%)	62 (26.4%)
Cohort[3]			
1	67 (54.9%)	33 (29.2%)	100 (42.6%)
2	55 (45.1%)	80 (70.8%)	135 (57.4%)
Age at baseline			
Median (IQR)	33.0 (27.0-42.0)	42.0 (36.0-49.0)	37.5 (30.0-45.8)
Missing	1 (0.8%)	0 (0%)	1 (0.4%)
Parity			
0	16 (13.1%)	11 (9.7%)	27 (11.5%)
1-3	58 (47.5%)	26 (23.0%)	84 (35.7%)
≥4	47 (38.5%)	76 (67.3%)	123 (52.3%)
Missing	1 (0.8%)	0 (0%)	1 (0.4%)
Base HIV status			
Negative	61 (50.0%)	73 (64.6%)	134 (57.0%)
HIV-1	46 (37.7%)	32 (28.3%)	78 (33.2%)
HIV-2	10 (8.2%)	4 (3.5%)	14 (6.0%)
Dual HIV-1 and HIV-2	5 (4.1%)	4 (3.5%)	9 (3.8%)
HIV Status			
Negative	61 (50.0%)	73 (64.6%)	134 (57.0%)
Positive with CD4 count ≥ 350 cells/μL	32 (26.2%)	19 (16.8%)	51 (21.7%)
Positive with CD4 count ≥ 350 cells/μL	27 (22.1%)	20 (17.7%)	47 (20.0%)
Missing	2 (1.6%)	1 (0.9%)	3 (1.3%)
Lifetime number of sex partners			

	Monogamous Married Women (N=122)	Polygamous Married Women (N=113)	Overall (N=235)
The most recent sexual activity			
Within last 7 days	51.0 (53.1%)	35.0 (36.5%)	86.0 (44.8%)
8-30 days ago	17.0 (17.7%)	33.0 (34.4%)	50.0 (26.0%)
31-365 days ago	24.0 (25.0%)	20.0 (20.8%)	44.0 (22.9%)
over 1 year ago	4.00 (4.2%)	8.00 (8.3%)	12.0 (6.3%)
Missing	26.0 (21.3%)	17.0 (15.0%)	43.0 (18.3%)
1	76 (62.3%)	55 (48.7%)	131 (55.7%)
2	39 (32.0%)	52 (46.0%)	91 (38.7%)
≥3	5 (4.0%)	5 (4.4%)	10 (4.3%)
Missing	2 (1.6%)	1 (0.9%)	3 (1.3%)
Birth control method at baseline			
None	79 (70.5%)	73 (80.2%)	152 (74.9%)
Pill	6 (5.4%)	6 (6.6%)	12 (5.9%)
Inject	5 (4.5%)	1 (1.1%)	6 (3.0%)
Condoms	5 (4.5%)	6 (6.6%)	11 (5.4%)
Other	17 (15.2%)	5 (5.5%)	22 (10.8%)
Missing	10 (8.2%)	22 (19.5%)	32 (13.6%)
Number of other wives			
0	116 (95.1%)	9[4] (8.0%)	125 (53.2%)
≥1	6[5] (4.9%)	104 (92.0%)	110 (46.8%)

[1] Fann University Hospital
[2] Pikine outpatient clinics
[3] Cohort 1: enrolled subjects between October 1, 1994 and January 1, 1998 in Senegal; Cohort 2: enrolled subjects from October 2005 to September 2011 in Senegal.
[4] 9 reported 0 other wives and is inconsistent with polygamous marriage.
[5] 6 reported ≥1 other wives and is inconsistent with monogamous marriage.

Table 2. Unadjusted and adjusted hazard ratios (HRs) for HPV clearance comparing infections among polygamously married women with infections among monogamously married women.

	HR(95% CI)	
	Unadjusted[1]	Adjusted[2]
Monogamously married	1.00 (reference)	1.00 (reference)
Polygamously married	1.01 (0.74-1.39)	0.97 (0.70-1.34)

[1] Stratified on HPV detection method (PCR-based or Luminex) and high-risk HPV status (yes or no).
[2] Stratified on HPV detection method and high-risk HPV status, and adjusted for age, parity, lifetime number of sex partners, infection status (prevalent or incident), HIV status (negative, positive with CD4 count ≥ 350 cells/μL, positive with CD4 count < 350 cells/μL), and coinfection with other HPVs (yes or no).

Table 3. Hazard ratio (HR) for HPV clearance comparing infections happened among polygamous married women and infections happened among monogamous married women, by HIV status or HPV coinfection status.

	HR (95% CI)	p-value[1]
HIV status (Model 1[2])		0.28
Negative	0.84 (0.58-1.21)	
Positive with CD4 count ≥ 350	1.47 (0.82-2.65)	
Positive with CD4 count < 350	0.88 (0.35-2.19)	
Coinfection with other HPV(s) (Model 2[3]**)**		0.97
No	0.96 (0.58-1.59)	
Yes	0.97 (0.64-2.46)	

[1] p-values are for interaction term of marital status and HIV status/HPV coinfection status.
[2] Stratified on HPV detection method and high-risk HPV status, adjusted for all potential confounders, and incorporate interaction term of marital status and HIV status.
[3] Stratified on HPV detection method and high-risk HPV status, adjusted for all potential confounders, and incorporate interaction term of marital status and HPV coinfection status.

S Table 1. The distribution of HPV types by infection status[1].

	Prevalent Infection (N=288)	Incident Infection (N=290)	Overall (N=578)
High-risk HPV types (n=399)			
HPV-16	47 (23.2%)	31 (15.8%)	78 (19.5%)
HPV-18	28 (13.8%)	25 (12.8%)	53 (13.3%)
HPV-58	14 (6.9%)	22 (11.2%)	36 (9.0%)
HPV-52	17 (8.4%)	14 (7.1%)	31 (7.8%)
HPV-45	7 (3.4%)	23 (11.7%)	30 (7.5%)
HPV-53	19 (9.4%)	9 (4.6%)	28 (7.0%)
HPV-31	11 (5.4%)	11 (5.6%)	22 (5.5%)
HPV-51	9 (4.4%)	12 (6.1%)	21 (5.3%)
HPV-33	13 (6.4%)	4 (2.0%)	17 (4.3%)
HPV-73	9 (4.4%)	6 (3.1%)	15 (3.8%)
HPV-66	6 (3.0%)	7 (3.6%)	13 (3.3%)
HPV-59	5 (2.5%)	7 (3.6%)	12 (3.0%)
HPV-35	5 (2.5%)	4 (2.0%)	9 (2.3%)
HPV-39	4 (2.0%)	5 (2.6%)	9 (2.3%)
HPV-56	3 (1.5%)	6 (3.1%)	9 (2.3%)
HPV-82	4 (2.0%)	4 (2.0%)	8 (2.0%)
HPV-68	2 (1.0%)	6 (3.1%)	8 (2.0%)
Low-risk HPV types (n=179)			
HPV-54	13 (15.3%)	15 (16.0%)	28 (15.6%)
HPV-62	14 (16.5%)	10 (10.6%)	24 (13.4%)
HPV-61	11 (12.9%)	12 (12.8%)	23 (12.8%)
HPV-83	7 (8.2%)	11 (11.7%)	18 (10.1%)
HPV-81	10 (11.8%)	5 (5.3%)	15 (8.4%)
HPV-84	5 (5.9%)	9 (9.6%)	14 (7.8%)
HPV-6	5 (5.9%)	6 (6.4%)	11 (6.1%)
HPV-70	3 (3.5%)	6 (6.4%)	9 (5.0%)
HPV-55	2 (2.4%)	7 (7.4%)	9 (5.0%)
HPV-42	3 (3.5%)	2 (2.1%)	5 (2.8%)

	Prevalent Infection (N=288)	Incident Infection (N=290)	Overall (N=578)
HPV-79	3 (3.5%)	2 (2.1%)	5 (2.8%)
HPV-72	2 (2.4%)	2 (2.1%)	4 (2.2%)
HPV-40	3 (3.5%)	1 (1.1%)	4 (2.2%)
HPV-67	2 (2.4%)	2 (2.1%)	4 (2.2%)
HPV-11	2 (2.4%)	2 (2.1%)	4 (2.2%)
HPV-71	0 (0%)	2 (2.1%)	2 (2.1%)

[1] Prevalent infection: infection occurred at baseline; Incident infection: infection occurred during follow-ups.

S Table 2. The distribution`·n of time of the most recent sexual activity among monogamous married women and polygamous women within each HIV status stratum.

The most recent sexual activity	HIV-		HIV+ CD4 count >=350		HIV+ CD4 count < 350	
	Monogamous (N=98)	**Polygamous (N=139)**	**Monogamous (N=91)**	**Polygamous (N=57)**	**Monogamous (N=96)**	**Polygamous (N=91)**
Within last 7 days	45 (60.8%)	52 (41.9%)	32 (40.0%)	25 (52.1%)	49 (63.3%)	18 (21.7%)
8-30 days ago	13 (17.6%)	30 (24.2%)	13 (16.3%)	8 (16.7%)	1 (1.3%)	20 (24.1%)
31-365 days ago	16 (21.6%)	32 (25.8%)	14 (17.5%)	14 (29.2%)	26 (33.8%)	37 (44.6%)
over 1 year ago	0 (0%)	10 (8.1%)	21 (26.3%)	1 (2.1%)	1 (1.3%)	8 (9.6%)
Missing	24 (24.5%)	15 (10.8%)	11 (12.1%)	9 (15.8%)	19 (19.8%)	8 (8.8%)

Reference

1. Arbyn M, Weiderpass E, Bruni L, et al. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. *Lancet Glob Heal*. 2020;8(2):e191-e203. doi:10.1016/S2214-109X(19)30482-6
2. Small W, Bacon MA, Bajaj A, et al. Cervical cancer: A global health crisis. *Cancer*. 2017;123(13):2404-2412. doi:10.1002/cncr.30667
3. Hanisch RA, Sow PS, Toure M, 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(4):696-702. doi:10.1016/j.jcv.2013.10.012
4. Cohen PA, Jhingran A, Oaknin A, Denny L. Cervical cancer. *Lancet*. 2019;393(10167):169-182. doi:10.1016/S0140-6736(18)32470-X
5. Haque A, Kouriba B, Aïssatou N, Pant A. Eliminating cervical cancer in Mali and Senegal, two sub-Saharan countries: Insights and optimizing solutions. *Vaccines*. 2020;8(2):1-11. doi:10.3390/vaccines8020181
6. Shahramian I, Heidari Z, Mahmoudzadeh-Sagheb HR, Moradi A, Forghani F. Prevalence of HPV infection and high risk HPV genotypes (16, 18), amongmonogamous and polygamouswomen, in Zabol, Iran. *Iran J Public Health*. 2011;40(3):113-121.
7. El Khair MM, Mhand RA, El Mzibri M, Ennaji MM. Risk factors of invasive cervical cancer in Morocco. *Cell Mol Biol*. 2009;55(SUPP.1):1175-1185. doi:10.1170/134
8. Sycuro LK, Long FX, Hughes JP, et al. Persistence of genital human papillomavirus infection in a long-term follow-up study of female university students. *J Infect Dis*. 2008;198(7):971-978. doi:10.1086/591625
9. Kim JW, Song SH, Jin CH, Lee JK, Lee NW, Lee KW. Factors affecting the clearance of high-risk human papillomavirus infection and the progression of cervical intraepithelial neoplasia. *J Int Med Res*. 2012;40(2):486-496. doi:10.1177/147323001204000210
10. Famooto A, Dareng EO, Olawande O, et al. Clearance of type-specific, low-risk, and high-risk cervical human papillomavirus infections in HIV-negative and HIV-positive women. *J Glob Oncol*. 2018;2018(4). doi:10.1200/JGO.17.00129
11. Ho GYF, Studentsov YY, Bierman R, Burk RD. Natural History of Human Papillomavirus Type 16 Virus-Like Particle Antibodies in Young Women. *Cancer Epidemiol Biomarkers Prev*. 2004;13(1):110-116. doi:10.1158/1055-9965.EPI-03-0191
12. Rowhani-Rahbar A, Hawes SE, Sow PS, et al. The impact of HIV status and type on the clearance of human papillomavirus infection among Senegalese women. *J Infect Dis*. 2007;196(6):887-894. doi:10.1086/520883
13. Trottier H, Mahmud S, Prado JCM, et al. Type-specific duration of human papillomavirus infection: Implications for human papillomavirus screening and vaccination. *J Infect Dis*. 2008;197(10):1436-1447. doi:10.1086/587698
14. Kuypers JM, Critchlow CW, Gravitt PE, 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(4). doi:10.1128/jcm.31.4.1003-1006.1993
15. 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(10). doi:10.1128/jcm.36.10.3020-3027.1998
16. Feng Q, Cherne S, Winer RL, et al. Development and evaluation of a liquid bead microarray assay for genotyping genital human papillomaviruses. *J Clin Microbiol*. 2009;47(3).

doi:10.1128/JCM.01707-08

17. Shew ML, Fortenberry JD, Tu W, et al. Association of condom use, sexual behaviors, and sexually transmitted infections with the duration of genital human papillomavirus infection among adolescent women. *Arch Pediatr Adolesc Med*. 2006;160(2). doi:10.1001/archpedi.160.2.151
18. Hogewoning CJA, Bleeker MCG, Van Den Brule AJC, et al. Condom use promotes regression of cervical intraepithelial neoplasia and clearance of human papillomavirus: A randomized clinical trial. *Int J Cancer*. 2003;107(5). doi:10.1002/ijc.11474