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Int J STD AIDS. Author manuscript; available in PMC 2021 November 23.

Published in final edited form as:

Int J STD AIDS. 2021 November ; 32(13): 1212–1220. doi:10.1177/09564624211030766.

LONGER DURATION OF ANTIRETROVIRAL THERAPY IS ASSOCIATED WITH DECREASED RISK OF HUMAN PAPILLOMAVIRUSES DETECTION IN KENYAN WOMEN LIVING WITH HIV

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Abstract

Objective: A longitudinal study was conducted among women living with HIV in Kenya to determine if duration of anti-retroviral (ART) usage altered detection and persistence of oncogenic (high risk) human papillomaviruses (HR-HPV).

Methods: Women living with HIV without cervical dysplasia were enrolled at a cervical cancer screening clinic. Three cervical swabs, HIV viral loads, and CD4 cell counts were obtained at enrollment and at two annual visits. HPV genotyping was performed on swabs (Roche Linear Array). Linear regression models assessed effects of ART duration on HR-HPV detection and persistence.

Results: Seventy-seven women, median age 38 years, completed three study visits and were included in the analysis. The mean time from HIV diagnosis to enrollment was 9.6 years (SD 3.9 years). The mean ART duration was 6.2 years (SD 3.1 years). Most women had undetectable HIV viral loads and CD4 cell counts above 500 cells/L. Each additional year of ART use reduced the likelihood of detection of HR-HPV by 10-15% and persistent detection of A9 HR-HPV by 20%.

Conclusion: Among Kenyan women living with HIV, longer duration of ART use was associated with significantly reduced risk of all detection and persistent detection of HR-HPV.

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Keywords

Human papillomavirus; HIV; anti-retroviral therapy; Kenya; women

INTRODUCTION

Cervical cancer causes nearly 300,000 deaths annually worldwide, 90% of which occur among women living in low- and middle-income countries, including Kenya (1–7). Oncogenic types of human papillomaviruses (“high-risk”, or HR-HPV) are the causative agents of cervical cancer (8) and persistent detection of HR-HPV is associated with an increased risk of invasive disease (9–13). Women living with human immunodeficiency virus (HIV)-infection have a higher incidence of HR-HPV infection and cervical cancer compared to HIV-negative women (14–29). Although progress is being made, HIV prevalence in Kenya is still 6.9% among women aged 15 to 64 years (30).

Several studies indicate that anti-retroviral therapy (ART) reduces the risk of HR-HPV detection while other studies show limited or no benefit (25, 31–39). Recent meta-analyses concluded that ART usage is associated with decreased risk of overall HR-HPV detection among women living with HIV, but most studies were cross-sectional and few included sub-Saharan women (25, 40, 41). Therefore, an analysis was performed utilizing data from a cohort of women enrolled in a longitudinal study to determine the effects of ART duration with detection and persistence of HR-HPV.

METHODS

Ethical considerations

Study approval was granted from the Moi Teaching Referral Hospital (MTRH) and Moi University School of Medicine, Eldoret, Kenya, the Kenya Medical Research Institute’s Scientific and Ethics Review Unit (KEMRI-SERU) and the Institutional Review Board of Indiana University School of Medicine (Protocol Number: IUCRO-0492). All study participants received a written copy of the consent (English or Swahili).

Nature of study and study participants

The overall longitudinal observational cohort study, conducted in Eldoret, Kenya was designed to identify factors associated with HPV detection and persistence (26, 42). Women ages 18 to 45 years were screened for cervical cancer at the Academic Model Providing Access to Healthcare (AMPATH) Cervical Cancer Screening Program in Eldoret, Kenya, beginning in October of 2015, using visual inspection with acetic acid (VIA), the standard screening method for cervical cancer in Kenya, and those who screened negative were offered enrollment. The overall study enrolled 116 Women living with HIV; 77 of these women who attended all three clinic visits were included in this analysis.

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Demographic and behavioral factors

Demographic and behavioral factors including age, marital status, educational level, home ownership, walking distance to health care, number of lifetime sex partners, and age of first sex age were assessed at enrollment.

Sample collection and HPV typing/analysis

A cervical swab was collected, followed by VIA at the enrollment visit and the Years 1 and 2 follow-up visits. Cervical swabs were stored in 1 mL PBS and frozen at −80° C until HPV testing was performed using the Roche Linear Array HPV Genotyping Tests (LA-HPV) as previously described (26). Only samples with amplification of the human β-globin control gene were included in this analysis. HPV types detected in the LA-HPV were grouped into the following categories as indicated in Tables 3, 4, and 5.

HIV-related data collection

Data collected from the AMPATH Electronic Medical Record System (AMRS) included HIV viral load (copies/mL) and CD4 cell count at diagnosis (cells/μL), date of HIV diagnosis, date of initial ART prescription, and specific ART regimens prescribed. The duration of ART usage was determined by adding the years receiving ART prior to enrollment plus the time receiving ART during the two-year study. HIV viral load and CD4 cell counts were measured at all study visits.

Antiretroviral therapy categorization

ART medications utilized in Kenya during the study period were the nucleoside reverse transcriptase inhibitors, or NRTIs (tenofovir, zidovudine, stavudine, lamivudine and emtricitabine), the non-nucleoside reverse transcriptase inhibitors, or NNRTIs (efavirenz and nivirapine), and other agents such the protease inhibitors, or PIs (lopinovir, atazanovir, and ritonavir), and integrase strand transferase inhibitors, or INSTIs (dolutegravir). The PIs and INSTIs were grouped together as an “Other” category due to their infrequent use.

Definitions of non-persistent detection and persistent HPV detection

For each woman, four possible “detection patterns” were defined for each of 37 HPV types:

Pattern 1: No detection: No HPV detected in swabs at any visit.

Pattern 2: Non-persistent detection: HPV detected in only one swab sample.

Pattern 3: 1-year persistent detection: HPV detected in two consecutive annual swabs.

Pattern 4: 2-year persistent detection: HPV detected in swabs obtained two years apart.

Therefore, there were 37 type-specific HPV detection records from each participant and a total of 2,849 (77 women × 37 HPV types) type-specific HPV detection records from the 77 study participants. As an example, a participant may have had HPV types 18 and 33 detected at enrollment, and HPV 33 detected at Year 1 but not Year 2. This participant thus had one “non-persistent detection” record for HPV 18, and a “1-year persistent detection” record for HPV 33, and “no detection” records for the other HPV types. She would therefore contribute

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one “non-persistent detection” record and one “1-year persistent detection” for any HPV type, for all HR-HPV types, for those HR-HPV types designated by the International Agency for Research on Cancer (IARC) (43), for A9 types, for non-16 A9 types, and for vaccine HR-HPV types.

Statistical analysis

For HPV, patterns of “1-year persistent detection” and “2-year persistent detection” were combined as “persistent detection” for subsequent analysis. Generalized estimating equation (GEE) logistic regression models were fit to examine associations between overall HPV detection (“non-persistent detection” and/or “1-year persistent detection” and/or “2-year persistent detection” vs. “no detection”) and duration of ART use. Furthermore, GEE logistic regression models were fit to examine associations between persistent HPV detection (“1-year persistent detection” and/or “2-year persistent detection” vs. “no detection” and/or “non-persistent detection”) and duration of ART use. Demographic and behavioral characteristics were included in models as potential confounders.

For each HPV detection outcome, two steps of model fitting were conducted. First, univariate GEE logistic regression models were fit for an HPV detection outcome with ART duration, CD4 cell counts and demographic and behavioral characteristics variables. Second, multivariable GEE logistic regression models were fit for HPV detection outcomes with ART duration, CD4 cell counts and demographic and behavioral characteristic variables with a p-value <0.20 from univariate models to fit a parsimonious multivariable models of HPV detection outcomes by including limited number of covariates that demonstrated potential associations with the outcome. The p<.2 rule was an arbitrary criterion for selecting variables from univariate models (44). ART duration and CD4 cell counts were included in multivariable models regardless of their p-values in univariate models. Analyses were performed using SAS Version 9.4 (SAS Inc., Cary, NC, 2016).

RESULTS

Participant Characteristics

In the main study, 116 women living with HIV were enrolled; 92 attended the Year 1 visit and 88 attended the Year 2 visit. The 77 women who completed three clinic visits were included in this analysis (Table 1).

HIV diagnosis, CD4 cell counts and HIV viral load

The mean time from HIV diagnosis to enrollment was 9.6 years (SD 3.9 years). CD4 cell counts and HIV viral load measurements are shown in Table 2. CD4 cell counts rose during the study; most women had undetectable HIV viral load measurements.

ART usage

At enrollment, 76 of the 77 (98.7%) participants had been prescribed ART. All 77 women had been prescribed ART at the Year 1 and Year 2 visits. The mean duration of ART at the Year 2 visit was 6.2 years (SD 3.9 years). The number and percentage of women prescribed a regimen consisting of NRTIs + NNRTI (two NNRTI regimens combined) was 70 (91%)

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at enrollment, 66 (85.8%) at year 1, and 54 (70.2%) at year 2. The number and percentage of women in the NRTIs + "other" category increased throughout the study: 6 (7.8%) at enrollment, 11 (14.3%) at Year 1 and 23 (29.9%) at the Year 2 visit.

A statistical analysis was performed to determine if there were specific combinations of ART medications associated with a reduction in HR-HPV detection or persistence. No association of any specific ART regimen with reduced HR-HPV detection were found, but the number of women receiving several ART combinations was small.

HPV detection

All 77 women had adequate cervical swab samples for analysis. At enrollment, any type of HPV was detected in 41 of 77 women (53.2%); a HR-HPV type was detected in 32 (41.6%); a LR-HPV was detected in 27.3%. The most frequently detected HR-HPV types during the study were HPV 58 (12 total detections, 8 non-persistent and 3 persistent), HPV 16 (10 total detections, 7 non-persistent and 3 persistent), and HPV 59 (10 total detections, 9 non-persistent and 1 persistent). The most frequently detected "low-risk" (LR)-HPV types detected were HPV 83 (13 total detections, 7 non-persistent and 6 persistent), HPV 84 (13 total detections, 9 non-persistent and 4 persistent), and HPV 62 (13 total detections, 9 non-persistent and 4 persistent).

Association of ART duration and HPV detection

The median years of ART and HPV detection patterns are shown in Table 3. Logistic regression analyses were conducted to assess associations of ART duration with 1) overall HPV detection and 2) HPV persistence. Individual HPV types were not included in analyses because of the modest numbers for any given type. For overall HPV detection (i.e., non-persistent detection/1-year persistent detection/2-year persistent detection), longer duration ART use was associated with lower risk of detection of any HPV (OR 0.90, 95%CI=0.83-0.97), HR-HPV (OR 0.87, 95%CI=0.80-0.96), IARC HR-HPV (OR 0.90, 95%CI=0.81-0.99), A9 HPV (OR 0.85, 95%CI=0.75-0.96), A7 HPV (OR 0.87, 95%CI=0.76-1.00), vaccine-protected HR-HPV (OR 0.86, 95%CI=0.76-0.98) and vaccine-unprotected HR-HPV (OR 0.86, 95%CI=0.77-0.97) (Table 4). This indicates that for each additional year of ART use, the likelihood of detection of the above HPV group was reduced by 10-15%. A greater number of lifetime sex partners was associated with a higher likelihood of detection of any HPV, HR-HPV, IARC HR-HPV, vaccine-unprotected HR-HPV, and LR-HPV, and walking distance to health care ≥ 60 mins was associated with a higher likelihood of detection of LR-HPV (Table 4).

Logistic regression analysis was also performed to assess associations of ART duration with persistent HPV detection (Table 5). A longer duration of ART use was associated with reduced risk of A9 HPV persistence (OR 0.80, 95%CI=0.65-0.97), indicating that for each additional year of ART use, the risk of persistent detection of an A9 HPV type was reduced by 20% (Table 5). Older age was associated with a lower chance of persistent A9 HPV detection, more than secondary school education was associated with a lower risk of persistent detection of any HPV, and a greater number of life time sex partner and younger age of sex debut were associated with higher risk of persistent detection of LR-HPV types.

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DISCUSSION

The effects of ART on HR-HPV detection and persistence in women living with HIV are not fully understood. In this longitudinal study, we found that the duration of ART use was associated with significantly reduced risk of detections of any HPV, HR-HPV, IARC HR-HPV, A9 HPV, A7 HPV, vaccine-protected HR-HPV and vaccine-unprotected HR-HPV. This effect of ART use was independent of CD4 cell counts.

Several previous cross-sectional analyses have been conducted among in women living in sub-Saharan Africa. De Vuyst et al., analyzed data from 498 Kenyan women living with HIV, comparing HR-HPV detection in those receiving ART for two years or longer to those not receiving ART (45). Women receiving ART, especially those with CD4 counts greater than 500 cells per uL, had less detection of HR-HPV compared to women not receiving ART. Ezechi et al., analyzed cervical samples from 220 Nigerian women living with HIV for HR-HPV (46). Women receiving ART had a lower risk of HR-HPV detection compared to those not receiving ART. In contrast, an evaluation of Ugandan women living with HIV, most of whom had HR-HPV detected prior to ART initiation, there was no reduction of HPV detection during a follow-up period of six months (47).

Longitudinal studies of the effects of ART, such as the current study, are important because persistent HR-HPV detection is a critical risk factor for development of cervical cancer. Kelly et al., described the effects of ART on HR-HPV detection in a prospective study of women living in either Burkina Faso (N=615) or South Africa (N=623) (48). HPV analysis of cervical samples was performed at enrollment and at the end of the 16-month study. Logistic regression was used to estimate associations of ART and HIV-related factors with HR-HPV, and results were adjusted for baseline CD4 cell count. Among the women in Burkina Faso, long-duration ART users (>2 years) had a lower risk of HR-HPV prevalence compared to short-duration ART users (<2 years). In another prospective study, Zeier et al., analyzed the effect of ART on HPV detection in cervical samples from South African women living with HIV (49). Women who initiated ART had a significantly reduced the risk HPV detection; every month of ART use reduced detection risk of any HPV type by 9%.

Our study differs from these prior longitudinal studies in the following ways. First, nearly all women in our study were receiving ART at enrollment, and the precise date of ART initiation was available through AMPATH medical records providing an ability to conduct a rigorous statistical evaluation of ART duration and HR-HPV detection. Second, the Roche Linear Array assay was conducted on all cervical samples at three time-points, increasing the power to detect and provide type-specific HPV data. This also allowed us to characterize detections as non-persistent or persistent, an important biological distinction. Third, we were able to utilize demographic and behavioral data collected for the study to construct linear regression models. Behavioral, socio-economic and environmental factors for women living in sub-Saharan Africa are likely to influence HPV infection rates and development of HPV-associated malignancies. As expected, a higher number of lifetime sexual partners was associated with an increased risk of HR-HPV detection of several groups of HR-HPV types and persistent detection of LR-HPV types. Fourth, for most women, CD4 cell counts were available and were also incorporated into linear regression models. Lastly, most women had

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documented suppression of HIV replication. This feature allowed us to ask if the benefit of longer use of ART occurred in women in spite of excellent HIV suppression.

Although our study is limited by the modest number of women enrolled, this was partially overcome by repeated sampling, providing more statistical power. In addition, while women received ART medications at clinic visits, we cannot be sure that compliance was 100%, although most women achieved HIV suppression and had excellent CD4 cell counts, especially at the Year 1 and Year 2 visits. Another limitation is that we did not have the power to detect an effect on HPV detection or persistence associated with specific ART regimens, due to limited heterogeneity in the ART regimens used in this cohort. It has been hypothesized that certain antiretroviral agents may have an effect on HR-HPV infection (50). Some protease inhibitors may alter antigen processing by dendritic cells (51). However, the effect of specific ART regimens on persistent HR-HPV detection and development of cancer is not known.

In conclusion, we found that ART duration was associated with reducing the risk of detection and persistence of A9 HR-HPV types in a cohort of Kenyan women living with HIV who had good control of HIV. Future studies are needed to determine if specific ART regimens are more effective than others in reducing HR-HPV detection and persistence, and to determine the specific immunological defects that remain in women living with HIV treated with effective ART, because such women remain at risk for cervical cancer in spite of ART use.

Acknowledgement:

Supported by National Cancer Institute (U.S.A.) Grant U54 CA18015109 (P.J.L., D.R.B., O.O., co-Principal Investigators).

Conflict of interest statement:

Dr. Brown’s laboratory receives funding from several sources, including Merck and Co., Inc.

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Table 1.

Demographic and behavioral characteristics of 77 women at enrollment

Characteristics	Statistics
Median age in years (IQR)	38.0 (34.0, 41.0)
Married n (%)	25 (32.5)
More than secondary school education n (%)	5 (6.5)
Home ownership n (%)	14 (18.2)
Walking distance to health care >=60 mins n (%)	9 (11.7)
Median number of lifetime sex partners (IQR)	3 (3, 5)
Median age of first sex in years (IQR)	17 (15, 19)

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Table 2.

CD4 counts and HIV viral load data for three study visits among 77 women

CD4 (cells/μL)	n of women with available CD4 counts, Median (IQR) for women with available CD4 counts		
	Enrollment	Year 1	Year 2
	75, 537 (391, 775)	76, 612 (482, 724)	73, 616 (486, 810)
Viral Load (copies/mL)	n of women with available viral load, n of women with detectable viral load, Median (IQR) for women with detectable viral load		
	Enrollment	Year 1	Year 2
	77, 16, 1373 (133, 9747)	77, 5, 398 (218, 7081)	77, 4, 90 (48, 5697)

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Table 3.

HPV detection patterns and years of ART use among type-specific HPV detection records

HPV detection records	Detection pattern	n (%)	Median years of ART use (IQR)
Any HPV[1] n=2849 (77 women × 37 types)	No Detection	2644 (92.8)	6.2 (3.5-8.9)
	Incident Detection	137 (4.8)	4.1 (2.7-7.0)
	1-yr Persistent Detection	45 (1.6)	5.8 (2.8-8.1)
	2-yr Persistent Detection	23 (0.8)	5.7 (2.8-7.8)
HR-HPV[2] n=1694 (77 women × 22 types)	No Detection	1584 (93.5)	6.2 (3.5-8.9)
	Incident Detection	77 (4.5)	4.6 (2.6-7.1)
	1-yr Persistent Detection	22 (1.3)	4.8 (2.8-8.9)
	2-yr Persistent Detection	11 (0.6)	4.1 (2.6-7.8)
IARC HR-HPV[3] n=1001 (77 women × 13 types)	No Detection	922 (92.1)	6.2 (3.5-8.9)
	Incident Detection	53 (5.3)	6.0 (2.7-7.1)
	1-yr Persistent Detection	17 (1.7)	4.6 (3.0-9.2)
	2-yr Persistent Detection	9 (0.9)	4.1 (2.6-7.8)
A9 HPV[4] n=462 (77 women × 6 types)	No Detection	426 (92.2)	6.2 (3.5-8.9)
	Incident Detection	25 (5.4)	6.0 (2.8-6.8)
	1-yr Persistent Detection	5 (1.1)	3.0 (2.1-4.6)
	2-yr Persistent Detection	6 (1.3)	4.0 (2.6-6.6)
A7 HPV[5] n=385 (77 women × 5 types)	No Detection	353 (91.7)	6.2 (3.5-8.9)
	Incident Detection	25 (6.5)	4.6 (2.6-7.1)
	1-yr Persistent Detection	4 (1.0)	6.8 (4.4-8.1)
	2-yr Persistent Detection	3 (0.8)	2.8 (2.3-7.8)
Vaccine Protected HR-HPV[6] n=539 (77 women × 7 types)	No Detection	501 (92.9)	6.2 (3.5-8.9)
	Incident Detection	26 (4.8)	6.0 (2.6-6.8)
	1-yr Persistent Detection	6 (1.1)	3.8 (2.1-6.0)
	2-yr Persistent Detection	6 (1.1)	5.3 (3.8-7.8)
Vaccine Unprotected HR-HPV[7] n=1155 (77 women × 15 types)	No Detection	1083 (93.8)	6.2 (3.5-8.9)
	Incident Detection	51 (4.4)	4.1 (2.6-7.3)
	1-yr Persistent Detection	16 (1.4)	5.6 (3.2-9.3)
	2-yr Persistent Detection	5 (0.4)	2.8 (2.5-7.8)
LR-HPV[8] n=1155 (77 women × 15 types)	No Detection	1060 (91.8)	6.2 (3.5-8.9)
	Incident Detection	60 (5.2)	4.1 (3.2-6.9)
	1-yr Persistent Detection	23 (2.0)	6.2 (2.8-8.1)
	2-yr Persistent Detection	12 (1.0)	5.9 (3.8-8.6)

[1] Any HPV 6, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 45, 51, 52, 53, 54, 55, 56, 58, 59, 61, 62, 66, 67, 68, 69, 70, 71, 72, 73, 81, 82, 83, 84, CP6108, IS39

[2] HR-HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73, 82, IS39

[3] IARC HR-HPV 16, 18, 31, 33, 35, 39, 45, 51 52, 56, 58, 59, 66

[4] A9 HPV 16, 31, 33, 35, 52, 58

[5] A7 HPV 18, 39, 45, 59, 68

[6] Vaccine protected HR-HPV 16, 18, 31, 33, 45, 52, 58

[7] Vaccine unprotected HR-HPV 26, 35, 39, 51, 53, 56, 59, 66, 67, 68, 69, 70, 73, 82, IS39

[8] LR-HPV 6, 11, 40, 42, 54, 55, 61, 62, 64, 71, 72, 81, 83, 84, CP6108

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Table 4.

Logistic regression analysis of associations of overall HPV detection[1] with years of ART use, CD4 count and characteristics of women[2]

Variables	Any HPV[3]		HR HPV[4]		IARC HR-HPV[5]		A9 HPV[6]	
	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value
Years of ART use	0.90 (0.83-0.97)	0.005	0.87 (0.80-0.96)	0.004	0.90 (0.81-0.99)	0.024	0.85 (0.75-0.96)	0.010
CD4 (cells/μL)	1.00 (0.99-1.00)	0.306	1.00 (0.99-1.00)	0.994	1.00 (0.99-1.00)	0.915	1.00 (0.99-1.00)	0.542
Age in years	1.01 (0.97-1.05)	0.642	0.99 (0.95-1.04)	0.780	1.00 (0.96-1.04)	0.982	--	--
Married	--	--	--	--	--	--	--	--
More than secondary school education	--	--	--	--	--	--	--	--
Home ownership	0.56 (0.24-1.29)	0.172	--	--	--	--	--	--
Walking distance to health care ≥60 mins	1.41 (0.91-2.19)	0.122	--	--	--	--	--	--
Number of lifetime sex partners	1.01 (1.00-1.01)	<.001	1.01 (1.00-1.01)	<.001	1.01 (1.00-1.01)	<.001	--	--
Age of first sex in years	--	--	--	--	--	--	--	--
Variables	**A7 HPV[7]**		**Vaccine Protected HR-HPV[8]**		**Vaccine Unprotected HR-HPV[9]**		**LR-HPV[10]**	
	OR (95%CI)	**P-value**	**OR (95%CI)**	**P-value**	**OR (95%CI)**	**P-value**	**OR (95%CI)**	**P-value**
Years of ART use	0.87 (0.76-1.00)	0.046	0.86 (0.76-0.98)	0.024	0.86 (0.77-0.97)	0.015	0.91 (0.83-1.01)	0.066
CD4 (cells/μL)	1.00 (0.99-1.00)	0.370	1.00 (0.99-1.00)	0.280	1.00 (0.99-1.00)	0.702	1.00 (0.99-1.00)	0.073
Age in years	--	--	--	--	1.00 (0.94-1.05)	0.885	--	--
Married	--	--	--	--	--	--	--	--
More than secondary school education	2.10 (0.90-4.88)	0.085	0.98 (0.23-4.20)	0.983	--	--	--	--
Home ownership	0.44 (0.11-1.80)	0.252	--	--	--	--	0.43 (0.14-1.30)	0.134
Walking distance to health care ≥60 mins	--	--	--	--	--	--	1.77 (1.03-3.02)	0.038
Number of lifetime sex partners	--	--	--	--	1.01 (1.00-1.01)	<.001	1.01 (1.00-1.01)	<.001
Age of first sex in years	1.15 (0.97-1.36)	0.109	1.12 (1.00-1.25)	0.060	--	--	1.07 (0.99-1.16)	0.094

[1] Overall HPV detection was defined as patterns of “non-persistent detection”, “1-year persistent detection” and/or “2-year persistent detection”

[2] Characteristics of age, marital status, education, home ownership, walking distance to health care, number of lifetime sex partners and age of first sex with a P-value <0.20 from univariate analyses were selected to include in the model

[3] Any HPV: HPV 16,18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73, 82, IS39

[4] HR-HPV (High-Risk HPV): HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73, 82, IS39

[5] IARC HR-HPV: HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66

[6] A9 HPV: HPV 16, 31, 33, 35, 52, 58

[7] A7 HPV: HPV 18, 39, 45, 59, 68

[8] Vaccine protected HR-HPV: HPV 16, 18, 31, 33, 45, 52, 58

[9] Vaccine unprotected HR-HPV: HPV 26, 35, 39, 51, 53, 56, 59, 66, 67, 68, 69, 70, 73, 82, IS39

[10] LR-HPV (Low-Risk HPV): HPV 6, 11, 40, 42, 54, 55, 61, 62, 64, 71, 72, 81, 83, 84, CP6108

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Table 5.

Logistic regression analysis of associations of *persistent* HPV detection[1] with years of ART use, CD4 count and characteristics of women[2]

Variables	Any HPV[3]		HR HPV[4]		IARC HR-HPV[5]		A9 HPV[6]	
	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value
Years of ART use	0.91 (0.82-1.01)	0.067	0.92 (0.80-1.05)	0.227	0.90 (0.77-1.07)	0.232	0.80 (0.65-0.97)	0.024
CD4 (cells/μL)	1.00 (0.99-1.00)	0.788	1.00 (0.99-1.00)	0.870	1.00 (0.99-1.00)	0.825	1.00 (0.99-1.00)	0.717
Age in years	--	--	0.96 (0.90-1.02)	0.193	0.98 (0.91-1.05)	0.542	0.92 (0.84-1.00)	0.046
Married	--	--	--	--	0.53 (0.17-1.72)	0.293	--	--
More than secondary school education	0.24 (0.07-0.87)	0.030	--	--	--	--	--	--
Home ownership	0.62 (0.24-1.60)	0.326	--	--	--	--	--	--
Walking distance to health care ≥60 mins	--	--	--	--	--	--	2.21 (0.77-6.38)	0.143
Number of lifetime sex partners	--	--	--	--	--	--	--	--
Age of first sex in years	1.09 (0.99-1.21)	0.092	--	--	--	--	--	--
Variables	**A7 HPV[7]**		**Vaccine Protected HR-HPV[8]**		**Vaccine Unprotected HR-HPV[9]**		**LR-HPV[10]**	
	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value
Years of ART use	0.90 (0.73-1.13)	0.368	0.85 (0.70-1.03)	0.095	0.95 (0.80-1.12)	0.524	0.93 (0.81-1.06)	0.277
CD4 (cells/μL)	1.00 (0.99-1.00)	0.573	1.00 (0.99-1.00)	0.562	1.00 (0.99-1.00)	0.501	1.00 (0.99-1.00)	0.721
Age in years	--	--	--	--	0.96 (0.88-1.05)	0.359	1.01 (0.94-1.07)	0.874
Married	--	--	--	--	--	--	--	--
More than secondary school education	--	--	--	--	--	--	--	--
Home ownership	--	--	--	--	--	--	0.55 (0.18-1.66)	0.289
Walking distance to health care ≥60 mins	--	--	--	--	--	--	--	--
Number of lifetime sex partners	--	--	--	--	--	--	1.01 (1.00-1.01)	<.001
Age of first sex in years	--	--	--	--	--	--	1.16 (1.01-1.33)	0.037

[1]Persistent HPV detection was defined as patterns of “1-year persistent detection” and/or “2-year persistent detection”

[2]Characteristics of age, marital status, education, home ownership, walking distance to health care, number of lifetime sex partners and age of first sex with a P-value <0.20 from univariate analyses were selected to include in the model

[3]Any HPV: HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73, 82, IS39

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[4] HR-HPV (High-Risk HPV): HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73, 82, IS39

[5] IARC HR-HPV: HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66

[6] A9 HPV: HPV 16, 31, 33, 35, 52, 58

[7] A7 HPV: HPV 18, 39, 45, 59, 68

[8] Vaccine protected HR-HPV: HPV 16, 18, 31, 33, 45, 52, 58

[9] Vaccine unprotected HR-HPV: HPV 26, 35, 39, 51, 53, 56, 59, 66, 67, 68, 69, 70, 73, 82, IS39

[10] LR-HPV (Low-Risk HPV): HPV 6, 11, 40, 42, 54, 55, 61, 62, 64, 71, 72, 81, 83, 84, CP6

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Table 6.

Logistic regression analysis of associations of *persistent* HPV detection[1] with years of ART use, CD4 count and characteristics of women[2]

Variables	Any HPV[3]		HR HPV[4]		IARC HR-HPV[5]		A9 HPV[6]	
	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value
Years of ART use	0.91 (0.82-1.01)	0.067	0.92 (0.80-1.05)	0.227	0.90 (0.77-1.07)	0.232	0.80 (0.65-0.97)	0.024
CD4 (cells/μL)	1.00 (0.99-1.00)	0.788	1.00 (0.99-1.00)	0.870	1.00 (0.99-1.00)	0.825	1.00 (0.99-1.00)	0.717
Age in years	--	--	0.96 (0.90-1.02)	0.193	0.98 (0.91-1.05)	0.542	0.92 (0.84-1.00)	0.046
Married	--	--	--	--	0.53 (0.17-1.72)	0.293	--	--
More than secondary school education	0.24 (0.07-0.87)	0.030	--	--	--	--	--	--
Home ownership	0.62 (0.24-1.60)	0.326	--	--	--	--	--	--
Walking distance to health care ≥60 mins	--	--	--	--	--	--	2.21 (0.77-6.38)	0.143
Number of lifetime sex partners	--	--	--	--	--	--	--	--
Age of first sex in years	1.09 (0.99-1.21)	0.092	--	--	--	--	--	--
Variables	**A7 HPV[7]**		**Vaccine Protected HR-HPV[8]**		**Vaccine Unprotected HR-HPV[9]**		**LR-HPV[10]**	
	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value
Years of ART use	0.90 (0.73-1.13)	0.368	0.85 (0.70-1.03)	0.095	0.95 (0.80-1.12)	0.524	0.93 (0.81-1.06)	0.277
CD4 (cells/μL)	1.00 (0.99-1.00)	0.573	1.00 (0.99-1.00)	0.562	1.00 (0.99-1.00)	0.501	1.00 (0.99-1.00)	0.721
Age in years	--	--	--	--	0.96 (0.88-1.05)	0.359	1.01 (0.94-1.07)	0.874
Married	--	--	--	--	--	--	--	--
More than secondary school education	--	--	--	--	--	--	--	--
Home ownership	--	--	--	--	--	--	0.55 (0.18-1.66)	0.289
Walking distance to health care ≥60 mins	--	--	--	--	--	--	--	--
Number of lifetime sex partners	--	--	--	--	--	--	1.01 (1.00-1.01)	<.001
Age of first sex in years	--	--	--	--	--	--	1.16 (1.01-1.33)	0.037

[1]Persistent HPV detection was defined as patterns of “1-year persistent detection” and/or “2-year persistent detection”

[2]Characteristics of age, marital status, education, home ownership, walking distance to health care, number of lifetime sex partners and age of first sex with a P-value <0.20 from univariate analyses were selected to include in the model

[3]Any HPV: HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73, 82, IS39

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[4] HR-HPV (High-Risk HPV): HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73, 82, IS39

[5] IARC HR-HPV: HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66

[6] A9 HPV: HPV 16, 31, 33, 35, 52, 58

[7] A7 HPV: HPV 18, 39, 45, 59, 68

[8] Vaccine protected HR-HPV: HPV 16, 18, 31, 33, 45,52, 58

[9] Vaccine unprotected HR-HPV: HPV 26, 35, 39, 51, 53, 56, 59, 66, 67, 68, 69, 70, 73, 82, IS39

[10] L9-HPV (Low-Risk HPV): HPV 6, 11, 40, 42, 54, 55, 61, 62, 64, 71, 72, 81, 83, 84, CP6