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Detection of types of HPV among HIV-infected and HIV-uninfected Kenyan women undergoing cryotherapy or loop electrosurgical excision procedure

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Abstract

Objective: To assess the baseline types of HPV infection among HIV-positive and HIV-negative women in western Kenya undergoing cryotherapy or loop electrosurgical excision procedure (LEEP) for cervical intraepithelial neoplasia.

Methods: A prospective observational study was conducted of baseline HPV characteristics of women undergoing visual inspection with acetic acid (VIA) and cryotherapy or LEEP. After a positive VIA in HIV-positive and HIV-negative women, data on demographics, CD4 count, and use of antiretroviral therapy and a cervical swab were collected. HPV typing was performed using the Roche Linear Array.

Results: Of 175 participants, 86 (49.1%) were HIV-positive and had a higher prevalence of low-risk HPV types (odds ratio [OR] 5.28, *P*=0.005) compared with HIV-negative women. The most common high-risk (HR)-HPV types in HIV-positive women were HPV 16 (13.9%) and HPV 18 (11.1%). HIV-positive women requiring LEEP were more likely to have HR-HPV types (OR 6.67, *P*=0.012) and to be infected with multiple HR-HPV types (OR 7.79, *P*=0.024) compared to those undergoing cryotherapy.

Conclusion: HIV-positive women requiring LEEP versus cryotherapy had a higher prevalence of any HR-HPV type and multiple HR-HPV types. There were no such differences in HPV types identified among HIV-negative women.

KEYWORDS

Cryotherapy; Electrosurgery; HIV infections; Kenya; Papillomavirus infections; Uterine cervical dysplasia

1 | INTRODUCTION

Invasive cervical cancer (ICC) is among the most common malignancies in women in Kenya and throughout sub-Saharan Africa.[1] The incidence of ICC in Kenyan women is nearly four times the incidence among women in the United States.[2] Cervical cancer is caused by high-risk oncogenic (HR) types of HPV.[3–5] The HR-HPV types most commonly associated with ICC in western Kenya are HPV 16 and HPV 18.[6,7] It has been reported that HIV infection is associated with increased risk of HPV infection, high-grade cervical intraepithelial neoplasia (CIN), progression of CIN, and ICC.[6,8,9] Concurrent HIV infection has also been demonstrated to change the distribution of types of HPV prevalent in CIN.[10] Among HIV-infected women in Kenya, infection with HPV 53 and HPV 31 were found to be predictors of CIN-3 and CIN-2+ lesions,

respectively.[11] Kenya has a high prevalence of HIV infection; approximately 6.9% of Kenyan women have HIV.[12] To prevent ICC, WHO recommends screening for cervical neoplasia with visual inspection with acetic acid (VIA) followed by treatment with either loop electrosurgical excision procedure (LEEP) or cryotherapy.[13]

Given the high burden of cervical cancer and HIV infection in sub-Saharan Africa, there is a need to better characterize the prevalent types of HPV among women infected and uninfected with HIV in order to identify optimal prevention and treatment strategies. While studies have analyzed the prevalent types of HPV among HIV-infected women in sub-Saharan Africa, there is a paucity of studies comparing the types of HPV among HIV-infected and HIV-uninfected women needing treatment with LEEP or cryotherapy.[7,14] Starting in January 2016, the aim of the prospective cohort study was to follow women with cervical lesions in western Kenya over 36 months, in order to compare outcomes among HIV-infected and HIV-uninfected women treated with LEEP or cryotherapy. Presented here are the baseline prevalence of HPV infection, types of HPV identified, and demographic characteristics of the study population.

2 | MATERIALS AND METHODS

2.1 | Enrollment of participants

Study approval was granted by the local review board at Moi Teaching Referral Hospital (MTRH) and Moi University, Eldoret, Kenya, the Kenya Medical Research Institute's Scientific and Ethics Review Unit (KEMRI-SERU), the Institutional Review Boards of the Miriam Hospital, Brown University, and Indiana University School of Medicine. Women were enrolled at the Academic Model Providing Access to Healthcare (AMPATH) Cervical Cancer Screening Program (CCSP) at MTRH in Eldoret, Webuye County Hospital, and Chulaimbo County Hospital. The standard of care for cervical cancer screening is VIA performed by trained nursing staff. The nursing staff are re-evaluated and trained every 6 months to assure competency in performing VIA. ICC in women aged under 30 years has been diagnosed at these clinics so screening is started at the age of 18 years. All women aged 18–45 years living within 30 km of Eldoret, Webuye, or Chulaimbo who presented for screening at the CCSP were approached by a nurse if the women were VIA-positive to evaluate them for eligibility in a private room. Consent was discussed in English or Swahili, and the women signed and were then enrolled. Inclusion criteria included a positive VIA examination that same day and willingness to return semi-annually for 36 months. Eligibility for cryotherapy included only lesions that did not extend into the endocervical canal, were seen in their entirety at the transformation zone (TZ), had defined margins, and covered less than 75% of the TZ. The current standard of care for the CCSP is to proceed to cryotherapy with a double-freeze technique without biopsy for such lesions. Women who did not qualify for cryotherapy were seen the same day by a gynecologist who performed a colposcopy/biopsy. Women were referred for LEEP if the biopsy showed CIN 2/3. Women with ICC were referred for staging and treatment.

Information regarding the study and consent were reviewed and participants received a written copy of the consent (in English or Swahili). Exclusion criteria included the following: prior history of a positive VIA, abnormal cervical smear, or diagnosis of CIN or cervical cancer; signs or symptoms of a sexually transmitted infection; currently pregnant; inability to consent due to mental or physical disability; or an intervening medical illness that had rendered the patient unable to understand consent or to attend follow-up visits.

2.2 | Baseline interview and questionnaire

Structured in-person interviews of participants by trained research staff were conducted at enrollment to capture demographic, social, behavioral, and biological information, including age, marital status, education, home ownership, distance to the closest clinic, past medical history, number of lifetime sexual partners, age of sexual debut, percentage of condom-protected coital events, number of years of cumulative usage of contraception, number of pregnancies, history of screening for cervical cancer, history of tobacco use, and history of gonorrhea or chlamydia infections. For HIV-infected women, variables were collected from the AMPATH Medical Record System (AMRS) at enrollment including date of diagnosis of HIV, use of antiretroviral therapy (ART), HIV viral load, and CD4 count. This questionnaire was the same used in Ermel et al.[15] in 2019 in a different cohort of women.

2.3 | Sample collection

At enrollment, every participant underwent VIA carried out by a nurse or physician. A cervical swab was collected as part of the pelvic examination for HPV testing. Swabs were placed in standard transport media then frozen at −80°C.

2.4 | Enrollment goal of HIV-infected and HIV-uninfected women undergoing LEEP or cryotherapy

The aim was to enroll 90 HIV-infected and 90 HIV-uninfected women, divided among participants who underwent LEEP (45 HIV-infected and 45 HIV-uninfected) and who underwent cryotherapy (45 HIV-infected and 45 HIV-uninfected). Cohort selection was via convenient quota sampling. Enrollment of participants to study groups was conducted until a group had reached the enrollment quota of 45, after which no further participants were enrolled for that group. However, two HIV-uninfected women in the LEEP group were later found to be HIV-infected increasing the number of HIV-infected patients in that group to 47 and decreasing the number of HIV-uninfected women to 43 in the LEEP group. In addition, one HIV-uninfected person was inadvertently enrolled in the cryotherapy group, increasing the number of women to 46 in that group.

2.5 | HPV testing

Dry cervical swab specimens were transported to the AMPATH reference laboratory and stored at −80°C. The cervical swab

specimens were then transported on dry ice to the KEMRI-University of Massachusetts Medical School (UMMS) laboratory for processing and genotyping assays. Dry swab samples were eluted in 1 mL of 1× phosphate buffered saline and 250-μL aliquots of eluted samples were used for the extraction of DNA; the remaining eluted sample was stored at −20°C. Briefly, DNA samples were extracted following the Qiagen DNA extraction protocol (QIAamp® MinElute® Media Kit 50; Qiagen, Hilden, GmbH, Germany). The Roche PCR/Linear Array (LA-HPV) was used to determine types of HPV (Roche Molecular Systems, Inc., Branchburg, NJ, USA). HPV types included in the LA-HPV are HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73, 82, CP6108, and IS39. HPV 16 positive, negative, and human β-globin (used to assess adequacy and contamination of specimens) controls provided by the manufacturer were tested with each batch of samples.

Types of HPV were grouped into "high-risk" and "low-risk" (HR/LR-HPV) based on the designation in the LA-HPV instructions or HR-HPV types as defined by the International Agency for Research on Cancer (IARC). Types of HPV were also grouped into A9 and A7 types. IARC high-risk types include HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68.[16] A9 HPV types are HPV-16, 31, 33, 35, 52, and 58. A7 types are HPV 18, 39, 45, and 59.

2.6 | Statistical analysis

Descriptive statistics were summarized for demographic and behavioral characteristics of participants and compared between women receiving LEEP versus cryotherapy and stratified by their HIV status. The comparisons used Fisher exact tests, χ^2 tests, or Wilcoxon rank sum test, depending on the distributional properties of the data. A P value of <0.05 was considered statistically significant. Demographic and behavioral characteristics were also evaluated only among those individuals for whom data regarding type of HPV were available to evaluate for the introduction of unintentional bias. Statistical tests were chosen based on the distribution of the data and variable types. A first logistic regression analysis was conducted to quantify the association between type of HPV (outcome variable) and HIV status (predictor variable) with the HIV-negative status as the reference level. Both unadjusted odds ratios (OR) from univariable analyses and adjusted ORs from multivariable analyses were reported with HIV status as an independent variable and adjusting for the following variables: age; age of sexual debut; number of sexual partners (0 or >1); median number of pregnancies; marital status; having a medical condition in the past 12 months; and use of condoms in more than 75% of all coital events within the last 3 months. The second model reported the ORs from multivariable logistic regression analyses with type of HPV as the outcome variable and LEEP/cryotherapy as a predictor variable. Cryotherapy was used as the reference for reporting ORs and analyses were repeated stratified by HIV status. The multivariable analyses included the same variables as above with the exception of number of sexual partners, due to low cell counts. Data were analyzed using R Version 3.4.3 software.

3 | RESULTS

3.1 | Overall characteristics of participants

Out of 184 women with a positive VIA who were approached to participate in the present study, 175 (95%) agreed to be enrolled. Complete and valid results regarding type of HPV were available for 143/175 (82%) participants. Enrollment of participants and reasons for a lack of results of type of HPV in 32 (18.2%) participants are shown in Figure 1. Data collected in the initial interview are presented in Table 1, comparing HIV-infected/HIV-uninfected and LEEP/cryotherapy.

HIV-infected women were older (38.9 years vs 32.3 years, P<0.001), had a higher median number of pregnancies (4.0 vs 3.0, P=0.002), were less likely to have more than secondary education (7% vs 34.8%, P<0.001), were more likely to have no sexual partners in the previous 3 months (15.1% vs 2.2%, P=0.015), and were more likely to have used condoms in 75% or more coital events in the previous 3 months (33.7% vs 11.2%, P=0.002) compared to HIV-uninfected women. There were no differences in the other characteristics between HIV-infected and HIV-uninfected women. HIV-infected women had a mean CD4 count of 498.0 cells/mm^3 and 74.4% of HIV-infected women were receiving ART at enrollment. Ten (11.6%) HIV-infected women had a detectable viral load (>40 copies/mL) with a mean of 449.0 copies/mL. Among HIV-infected women, no significant difference was observed in use of ART, mean CD4 count, or mean viral load between the LEEP and cryotherapy groups. No other differences were observed between HIV-infected women undergoing LEEP versus cryotherapy. Among HIV-uninfected women, while those undergoing LEEP were older than those undergoing cryotherapy (36.1 vs 30.5 years, p=0.028), there were no significant differences in any other characteristics. Demographic and behavioral characteristics among the women for whom HPV type data were available were not significantly different from the demographic data for the entire cohort.

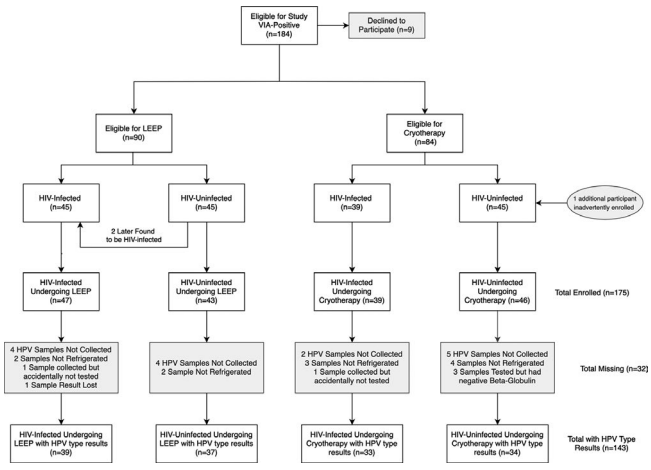

FIGURE 1 Enrollment of study participants.

TABLE 1 Characteristics of HIV-infected and HIV-uninfected women, stratified by treatment procedure.[a]

Characteristic	HIV-uninfected (n=89)				HIV-infected (n=86)				Total *P* value
	CRYO (n=46)	LEEP (n=43)	*P* value	Total (n=89)	CRYO (n=39)	LEEP (n=47)	*P* value	Total (n=86)	
Age (years)	30.5 (19.5–47.5)	36.1 (21–54.8)	0.028[b]	32.3 (19.5–54.8)	37.0 (19–52.6)	39.9 (22.9–56.4)	0.124[b]	38.9 (19–56.4)	<0.001[b]
Number of sexual partners in the last 3 months	1.0 (1–2)	1.0 (0–2)	0.331[b]	1.0 (0–2)	1.0 (0–1)	1.0 (0–2)	0.486[b]	1.0 (0–2)	0.009[b]
0	0 (0)	2 (4.7)	0.472[c]	2 (2.2)	7 (17.9)	6 (12.8)	0.874[c]	13 (15.1)	0.015[c]
1	27 (58.7)	23 (53.5)	—	50 (56.2)	23 (59)	26 (55.3)	—	49 (57)	—
2	1 (2.2)	1 (2.3)	—	2 (2.2)	0 (0)	1 (2.1)	—	1 (1.2)	—
Number of pregnancies	2.0 (0–6)	3.0 (1–10)	0.095[b]	3.0 (0–10)	3.5 (0–11)	4.0 (1–10)	0.235[b]	4.0 (0–11)	0.002[b]
Age at sexual debut (years)	19.0 (14–29)	17.5 (14–29)	0.159[b]	18.0 (14–29)	18.0 (9–24)	18.0 (12–26)	0.273[b]	18.0 (9–26)	0.354[b]
Marital status	33 (71.7)	31 (72.1)	0.97[d]	64 (71.9)	23 (59)	30 (63.8)	0.645[d]	53 (61.6)	0.149[d]
More than secondary school education	16 (34.8)	15 (34.9)	0.992[d]	31 (34.8)	1 (2.6)	5 (10.6)	0.215[d]	6 (7)	<0.001[d]
Condom use in >75% of all coital events within the last 3 months	5 (10.9)	5 (11.6)	1[c]	10 (11.2)	13 (33.3)	16 (34)	0.682[d]	29 (33.7)	0.002[c]
Use of ART at enrollment	—	—	—	—	31 (79.5)	33 (70.2)	0.326	64 (74.4)	—
CD4 count at enrollment (cells/mm^3)	—	—	—	—	536.5 (50–1213)	570.0 (124–1578)	0.877[b]	498.0 (388.0–663.0)	—
Viral load at enrollment (copies/mL)[e]	—	—	—	—	6469.0 (53–168088)	527.0 (239–4667)	0.676[b]	449.0 (127.0–888.0)	—

Abbreviations: ART, antiretroviral therapy; CRYO, cryotherapy; LEEP, loop electrosurgical excision procedure.

[a]Values are given as number (percentage) or median (range).

[b]*P* value from Wilcoxon rank sum test.

[c]*P* value from Fisher exact test.

[d]*P* value from χ^2 test.

[e]Viral load summary performed for all participants with viral load >40 (n=10).

3.2 | Distribution of type of HPV

Table 2 shows the distribution of type of HPV among participants who were treated with cryotherapy and LEEP, stratified by HIV status. Table 3 demonstrates unadjusted and adjusted ORs for types of HPV comparing HIV-infected and HIV-uninfected women. Table 4 shows adjusted ORs for detection of types of HPV among women receiving LEEP versus cryotherapy, stratified by HIV status. Data regarding typing of HPV were available for 143/175 (81.7%) participants (72 HIV-infected and 71 HIV-uninfected). Of the 32 participants for whom results of type of HPV were not available, 15 (46.8%) samples for HPV typing were not collected, 11 (34.3%) samples were not refrigerated due to equipment malfunction, 2 (6.25%) samples were collected but were accidentally not analyzed, data for 1 (3.12%) sample was lost, and 3 (9.4%) samples were tested but had negative β-globin.

Nearly 70% (n=50) of HIV-infected women and 52% (n=37) of HIV-uninfected women had detection of any type of HPV, although such a difference was not statistically significant after adjustment for demographic factors. Adjusted analysis showed that HIV-infected women were more likely to have any type of LR-HPV (OR 5.28, 95% confidence interval [CI] 1.75–18.1) and non-HPV-18 A7 type (OR 8.39, 95% CI 1.56–68.72) compared to HIV-uninfected women. No other differences were observed in the detected types of HPV between HIV-infected and HIV-uninfected women. Among HIV-infected women, women referred for treatment with LEEP were more likely to be infected with any type of HR-HPV (OR 6.67, 95% CI 1.65–33.19), an IARC type of HR-HPV (OR 4.51, 95% CI 1.23–18.98), an A9 HPV type (OR 4.87, 95% CI 1.23–24.56), and a non-HPV-16 A9 type (OR 5.23, 95% CI 1.17–32.65), and more likely to have two or more types of HPV detected (OR 7.79, 95% CI 1.51–57.95) compared to HIV-infected women eligible for cryotherapy. Among HIV-uninfected women, there was no difference observed in the detected types of HPV between women undergoing LEEP versus cryotherapy.

3.3 | Distribution of type of HPV by HIV status

Detection of types of HR-HPV by HIV status is shown in Figure 2. Overall, only the detection of HPV-39 was observed to be significantly higher among HIV-infected women compared with HIV-uninfected women. The five most frequently detected types of HR-HPV

TABLE 2 Distribution of type of HPV among cryotherapy and LEEP patients, stratified by HIV status.[a]

	Cryotherapy			LEEP		
HPV variable	HIV-negative (n=34)	HIV-positive (n=33)	Total (n=67)	HIV-negative (n=37)	HIV-positive (n=39)	Total (n=76)
Any HPV type	17 (50.00)	19 (57.58)	36 (53.73)	20 (54.05)	31 (79.49)	51 (67.11)
HR-HPV	16 (47.06)	13 (39.39)	29 (43.28)	17 (45.95)	29 (74.36)	46 (60.53)
IARC HR-HPV	12 (35.29)	12 (36.36)	24 (35.82)	16 (43.24)	27 (69.23)	43 (56.58)
A9 HPV	8 (23.53)	6 (18.18)	14 (20.90)	11 (29.73)	19 (48.72)	30 (39.47)
HPV 16	4 (11.76)	2 (6.06)	6 (8.96)	5 (13.51)	8 (20.51)	13 (17.11)
Non-HPV 16 A9	4 (11.76)	4 (12.12)	8 (11.94)	7 (18.92)	14 (35.90)	21 (27.63)
A7 HPV	4 (11.76)	7 (21.21)	11 (16.42)	10 (27.03)	14 (35.90)	24 (31.58)
HPV 68	1 (2.94)	2 (6.06)	3 (4.48)	1 (2.70)	1 (2.56)	2 (2.63)
Non-HPV 18 A7	2 (5.88)	5 (15.15)	7 (10.45)	6 (16.22)	10 (25.64)	16 (21.05)
Any LR-HPV	4 (11.76)	14 (42.42)	18 (26.87)	12 (32.43)	17 (43.59)	29 (38.16)
≥2 types of any HPV	6 (17.65)	10 (30.30)	16 (23.88)	13 (35.14)	17 (43.59)	30 (39.47)
Number of any HPV type	0.8 (0–4)	1.2 (0–7)	2 (0–7)	1.4 (0–18)	2.6 (0–11)	4 (0–11)
0	17 (50.00)	14 (42.42)	31 (46.27)	17 (45.95)	8 (20.51)	25 (32.89)
1	10 (29.41)	9 (27.27)	19 (28.36)	7 (18.92)	12 (30.77)	19 (25.00)
2	3 (8.82)	6 (18.18)	9 (13.43)	6 (16.22)	4 (10.26)	10 (13.16)
>2	4 (11.76)	4 (12.12)	8 (11.94)	7 (18.92)	15 (38.46)	22 (28.95)
≥2 Types HR-HPV	6 (17.65)	5 (15.15)	11 (16.42)	8 (21.62)	15 (38.46)	23 (30.26)
Number of HR-HPV types	0.7 (0–3)	0.6 (0–4)	1.3 (0–4)	0.9 (0–5)	1.6 (0–6)	2.5 (0–6)
0	18 (52.94)	20 (60.61)	38 (56.72)	20 (54.05)	10 (25.64)	30 (39.47)
1	9 (26.47)	8 (24.24)	17 (25.37)	9 (24.32)	14 (35.90)	23 (30.26)
2	5 (14.71)	3 (9.09)	8 (11.94)	5 (13.51)	5 (12.82)	10 (13.16)
>2	2 (5.88)	2 (6.06)	4 (5.97)	3 (8.11)	10 (25.64)	13 (17.11)

Abbreviations: ART, antiretroviral therapy; HR, high-risk; IARC, International Agency for Research on Cancer; LEEP, loop electrosurgical excision procedure; LR, low-risk.

[a]Values are given as number (percentage) or median (range).

TABLE 3 Unadjusted and adjusted ORs for results of HPV type versus HIV status (reference level).

HPV outcomes	Unadjusted ORs: HIV-infected vs HIV-uninfected	*P* value	Adjusted ORs: HIV-infected vs HIV-uninfected	*P* value
Any HPV type	2.09 (1.06–4.18)	0.034	2.29 (0.82–6.58)	0.116
HR-HPV	1.61 (0.83–3.14)	0.156	1.57 (0.56–4.43)	0.385
IARC HR-HPV	1.81 (0.94–3.55)	0.078	1.39 (0.5–3.86)	0.526
A9 HPV	1.46 (0.71–3.00)	0.302	0.93 (0.32–2.68)	0.893
HPV 16	1.11 (0.42–2.98)	0.831	0.81 (0.19–3.61)	0.775
Non-HPV 16 A9	1.82 (0.8–4.3)	0.157	1.47 (0.47–4.84)	0.51
A7 HPV	1.68 (0.78–3.7)	0.189	2.35 (0.72–8.51)	0.171
HPV 68[b]	—	—	—	—
Non-HPV 18 A7	2.07 (0.84–5.49)	0.127	8.39 (1.56–68.72)	0.023
Any LR-HPV	2.6 (1.27–5.47)	0.009	5.28 (1.75–18.1)	0.005
≥2 types of any HPV	1.72 (0.86–3.5)	0.127	2.55 (0.87–8.13)	0.098

Abbreviations: CI, confidence interval; HR, high-risk; IARC, International Agency for Research on Cancer; LEEP, loop electrosurgical excision procedure; LR, low-risk; OR, odds ratio.
[a]Values are given as OR (95% CI).
[b]Due to small sample size, logistic regression failed to produce a stable model for HPV 68.

in HIV-infected women were HPV 16 (13.9%), HPV 18 (11.1%), HPV 35 (8.3%), HPV 39 (8.3%), and HPV 51 (8.3%). Among HIV-uninfected women, the five most frequently detected types of HR-HPV were HPV 16 (12.7%), HPV 18 (11.3%), HPV 51 (7.0%), HPV 59 (7.0%), and HPV 35 (5.6%).

4 | DISCUSSION

Cervical cancer caused by types of HR-HPV contributes to a large burden of cancer-related mortality and morbidity in Kenya. Screening with VIA can identify premalignant cervical lesions and such lesions can be treated with cryotherapy or LEEP. Women infected with HIV are more likely to become infected with HPV and have greater risk of progression for cervical neoplasia. Although previous studies have compared types of HPV between HIV-infected and HIV-uninfected women, the present study demonstrates types of baseline HPV separated not only by HIV status but also by the severity of cervical lesions requiring either LEEP or cryotherapy.[7]

The population in the present study was divided nearly equally into four groups based on HIV status and treatment modality. It should be noted that there was difficulty recruiting HIV-infected women to the cryotherapy group given that most HIV-infected women presenting for screening had more advanced cervical lesions that were not amenable to treatment with cryotherapy. Such a discrepancy was not observed among HIV-uninfected women. Among HIV-infected women, those who were referred for treatment with LEEP were more likely to be infected with any type of HR-HPV and multiple types

TABLE 4 Risk for types of HPV detected among LEEP candidates, stratified by HIV status.[a,b]

HPV outcomes	Adjusted ORs: HIV-negative	*P* value	Adjusted ORs: HIV-positive	*P* value
Any HPV type	0.82 (0.17–3.92)	0.801	3.32 (0.86–14.41)	0.09
HR-HPV	0.75 (0.15–3.76)	0.726	6.67 (1.65–33.19)	0.012
IARC HR-HPV	0.83 (0.15–4.4)	0.825	4.51 (1.23–18.98)	0.028
A9 HPV	1.36 (0.2–9.65)	0.747	4.87 (1.23–24.56)	0.035
HPV 16	0.02 (0–1.9)	0.204	2.54 (0.33–28.37)	0.391
Non-HPV 16 A9	2.75 (0.41–24.77)	0.318	5.23 (1.17–32.65)	0.046
A7 HPV	3.18 (0.38–41.5)	0.315	2.56 (0.53–14.6)	0.255
Non-HPV 18 A7[c]	—	—	—	—
Any LR-HPV	3.4 (0.57–25.14)	0.196	1.91 (0.53–7.59)	0.331
≥2 types of any HPV	3.5 (0.78–18.73)	0.116	7.79 (1.51–57.95)	0.024

Abbreviations: CI, confidence interval; HR, high-risk; IARC, International Agency for Research on Cancer; LEEP, loop electrosurgical excision procedure; LR, low-risk; OR, odds ratio.
[a]Values are given as OR (95% CI).
[b]Cryotherapy was used as the reference level.
[c]Due to small sample size, logistic regression failed to produce a stable model for Non-HPV 18 A7.

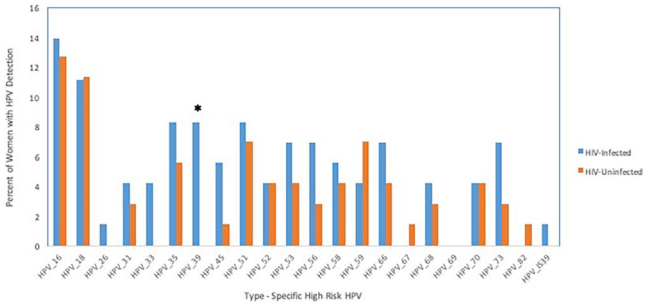

FIGURE 2 Detection of individual types of high-risk HPV in HIV-infected and HIV-uninfected women. * indicates, overall, only the detection of HPV-39 was observed to be significantly higher among HIV-infected women compared with HIV-uninfected women.

of HR-HPV compared to those treated with cryotherapy, even after adjusting for demographic factors. No such difference between treatment groups in the types of HR-HPV or multiple types of HR-HPV was observed among HIV-uninfected women. In the context of the present study, a patient's treatment group serves as a proxy for the severity of their cervical lesion. However, these data suggest that HIV-infected women infected with HR-HPV may be more likely to present with more advanced cervical lesions compared to HIV-uninfected women, which is consistent with previous research.[8,17] These findings also echo previous research demonstrating increased risk of HPV infection among women infected with HIV in spite of ART usage.[14,15,18–22] The literature further explains the finding that HIV-infected women were more likely to have types of LR-HPV identified compared to HIV-uninfected women.

These data are broadly consistent with previous analyses of prevalent types of HPV among HIV-infected women with cervical lesions and ICC.[8,9] HPV 16 and 18 continue to be the most commonly observed types of HR-HPV worldwide associated with cervical lesions and ICC.[6,7,14] In the present cohort, HPV 16 and 18 were the most prevalent types of HPV detected in both HIV-infected and HIV-uninfected women. In Clifford's 2017 meta-analysis[14] of carcinogenic types of HPV in HIV-infected women, HPV 45 was additionally identified as a particular concern among women in Africa living with HIV. While HPV 45 was not the most prevalent type of HR-HPV observed in the present study, it was observed in a higher proportion of HIV-infected women (5.6%) compared to HIV-uninfected women (1.4%). In addition, the data in the present study are consistent with Menon et al.'s[7] 2016 systematic review of HPV strains among HIV-positive women in Kenya, with HPV 35 similarly being identified among our cohort in a higher proportion of HIV-infected women compared to HIV-uninfected women (8.3% vs 5.6%) with abnormal cytology. A 2013 study by Maranga et al.[10] further identified HR-HPV types 52, 53, 58, 68, and 70 to be prevalent in higher proportion among HIV-infected women in Kenya compared to HIV-uninfected women. While the present data showed no difference in the proportion of women infected with HPV 52 and HPV 70, an increase was observed in the proportion of HIV-infected women infected with HPV 53 (6.9% vs 4.2%), HPV 58 (5.6% vs 4.2%), and HPV 68 (4.2% vs 2.8%) compared to HIV-uninfected women.

Based on the high burden of disease caused by HPV 16 and 18, there is clearly a role for HPV vaccination among the present cohort and, more broadly, HIV-infected women in Kenya. While the quadrivalent vaccine only additionally covers HPV 6 and 11, low-risk types that cause genital warts, the nonavalent vaccine covers the above types plus HPV 31, 33, 45, 52, and 58. Except for HPV 33, all of these additional types were identified among HIV-infected and HIV-uninfected women in the present cohort. It is thus expected that dissemination and uptake of the nonavalent HPV vaccine would lead to a decrease in HR-HPV infections and severity of identified cervical lesions among HIV-infected women in Kenya.

The present study is limited by a small sample size. While the aim was to recruit 45 individuals to each of the four groups, challenges were faced among many HIV-infected women with cervical lesions due to more advanced lesions, such as ineligibility for cryotherapy. Analysis of HPV type for 32 study participants was unavailable. Finally, the HIV-infected group overall had an almost normal CD4 count and high rate of undetectable viral load (88.4%). This may explain why no significant differences were found in the types of HPV identified between HIV-infected and HIV-uninfected women in the present cohort.

As the larger study progresses, the aim is to enroll more study participants and to incorporate these baseline data regarding HPV typing with further data on prevalence of HPV on semi-annual follow-up visits and to assess efficacy of cryotherapy and LEEP among HIV-infected and HIV-uninfected women. This will enable a better evaluation of optimal treatment modalities for cervical lesions in HIV-infected women in western Kenya and in other low-resource settings.

5 | CONCLUSION

The present study shows the baseline HPV characteristics of a population of HIV-infected and HIV-uninfected women who are VIA-positive in a rural Kenyan clinic setting. These data revealed that among HIV-infected women, those requiring LEEP versus cryotherapy had a higher prevalence of any type of HR-HPV and multiple types of HR-HPV, even after controlling for other factors. No such difference in types of HPV was identified among HIV-negative women. These data present implications for future screening, prevention, and treatment protocols for cervical lesions among HIV-infected and HIV-uninfected women in rural low-resource settings.

AUTHOR CONTRIBUTIONS

PJL is principal investigator of the U54 grant and PJL, SC-U, and TL conceived of and developed the study. SC-U, EOO, and TL supervised the study data collection and analysis. JPE conducted statistical analysis of the data, coordinated detailed statistical analysis with TL and VO, and wrote most of the manuscript text. ACE was responsible for collecting and supervising HPV typing and HPV data. JH, YT, and VO conducted data analysis and statistics. PMI and PKT performed cryotherapy and LEEP at clinical sites and compiled data on patients.

TM, DB, and AM performed HPV typing assays and HPV typing data management. JMO, SK, and KM managed the datasets. KM was program administrator. All authors contributed to writing portions of the manuscript and provided manuscript editing.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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