Long-term risk of recurrence of pre-cancerous cervical lesions among women living with HIV in Kenya

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Abstract

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Introduction

Women living with HIV (WLHIV) have a six-fold increased risk of developing cervical cancer compared to HIV-uninfected women. Despite this, limited data exists on the recurrence of precancerous cervical lesions among WLHIV following treatment with loop electrical excision procedure (LEEP) or cryotherapy. We sought to determine the long-term risk of recurrence of cervical intraepithelial neoplasia grade 2 or higher (CIN 2+) and associated risk factors among WLHIV with prior treatment for cervical disease.

Methods

We conducted a long-term follow-up study of WLHIV and CIN grade 2 or 3 previously randomized to LEEP or cryotherapy in Nairobi, Kenya between 2011 and 2013 Former trial participants were recontacted between January and August 2023 for cervical cancer screening using Papanicolaou (PAP) test and colposcopy-directed biopsy to determine presence of precancerous cervical lesions in the ≥9 years since initial treatment. Women with PAP results of low grade squamous intraepithelial lesions (LSIL), high grade squamous intraepithelial lesions (HSIL) or atypical squamous cells with the inability to exclude HSIL

(ASC-H) underwent colposcopy-directed biopsy. Primary and secondary outcomes were 1) recurrence of CIN 2+ (CIN 2, CIN 3, Carcinoma in-situ or invasive cancer) as determined by colposcopy-directed biopsy, measured ≥9 years after initial treatment, and 2) recurrence of HSIL+ (HSIL, ASC-H or invasive cancer) on PAP smear, measured ≥9 years after initial treatment, respectively. Log-binomial regression was used to estimate the relative risk of CIN 2+ and HSIL+ recurrence by treatment arm.

Results

Of the 400 former trial participants, 286 (71.5%) were recontacted of which 197 (68.9%) agreed to participate in this follow-up study. Five (4.7%) of 107 participants in the cryotherapy arm and 3 (3.3%) of 90 in the LEEP arm had recurrent CIN 2+ in this follow-up study. In addition, 10 (9.3%) participants in the cryotherapy arm and 4 (4.4%) in the LEEP arm had recurrence of HSIL+ in the ≥9 years since initial treatment. There was no difference in long-term risk of recurrence of CIN2+ and HSIL+ between treatment arms (RR=1.40, 95% Confidence Interval (95% CI), 0.34-5.71, p=0.64; and RR=2.10 95% CI, 0.68-6.48, p=0.18, respectively). Longer duration of antiretroviral therapy (≥10 years) was not significantly associated with recurrence of CIN2+ or HSIL2+. However, those with a nadir CD4 count of ≥500 cells/mm^3 were 6 times more likely to have a recurrence compared to those whose CD4 count of less than 500 cells/mm^3, a finding we postulate to be spurious (RR = 6.46 95% CI: 1.72, 24.26, p=0.01)

Conclusions

The long-term risk of recurrence of pre-cancerous cervical lesions among WLHIV was low.

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Abbreviations

AE	Adverse Events
ART	Antiretroviral therapy
CCSP	Cervical Cancer Screening Program
CD4	Clusters of differentiation 4
CIN	Cervical Intraepithelial Neoplasia
EMR	Electronic Medical Records
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
HSIL	High grade Squamous Intraepithelial Lesion
KNH	Kenyatta National Hospital
LSIL	Low-grade Squamous Intraepithelial Lesion
LEEP	Loop Electrical Excision Procedure
PAP	Papanicolaou
QA	Quality Assurance
QC	Quality Control
RCT	Randomized Clinical Trial
SSA	Sub-Saharan Africa
STI	Sexually Transmitted Infections
VIA	Visual Inspection with Acetic acid
WHO	World Health Organization
WLHIV	Women Living with HIV

Introduction

The World Health Organization (WHO) estimated 604,127 new cases and 341,831 deaths due to cervical cancer globally in 2020 (1). The highest incidence and one-quarter of cervical cancer deaths occur in sub-Saharan Africa (SSA) (1,2). HIV and cervical cancer present a significant double burden in SSA with increased cervical cancer morbidity and mortality (3). Despite the high burden of cervical cancer deaths in SSA, there is limited data on the rate of recurrence of precancerous cervical lesions among WLHIV following treatment with LEEP or cryotherapy (4).

Women living with HIV (WLHIV) have a six-fold increased risk of developing cervical cancer compared to women without HIV largely resulting from higher prevalence and persistence of high-risk human papillomavirus (HPV) infection and immunosuppression due to HIV (5). Improvements in CD4 count after initiating antiretroviral therapy (ART) are associated with increased HPV clearance and reduction in progression of precancerous lesions (5). However, despite ART, WLHIV continue to have more persistent high-risk HPV infection and unacceptably high cervical cancer incidence and recurrence rates compared to women without HIV (6,7).

In an effort to eliminate cervical cancer by 2030, the World Health Organization (WHO) launched the 90-70-90 targets where 90% of girls should receive HPV vaccination by age 15 years, 70% of women should be screening by age 45 years, and 90% of women with precancer undergo treatment (8). Kenya National guidelines recommend annual HPV testing among WLHIV as a primary screen for cervical cancer and visual inspection with acetic acid (VIA) where the former is unavailable (9). However, only half of WLHIV in Kenya have ever been screened for cervical cancer despite evidence suggesting high uptake among WLHIV when screening is offered (10,11). Barriers to cervical cancer screening include low health facility staffing, inadequate training of healthcare workers, supply shortages, and perceived discomfort of a speculum exam (12).

WHO recommends use of thermal ablation or cryotherapy in low and middle income countries (LMIC) using a screen-and-treat approach (13,14). While LEEP is preferred in high income settings, LEEP is largely inaccessible in LMIC due to lack of trained medical personnel,

limited electricity required for the wire loop, and the inability to treat rare but potentially fatal adverse events related to the procedure (15). Thus, most treatment programs in LMIC use cryotherapy or thermal ablation as it is cheaper than LEEP, requires less specialized training, and has been shown to be effective in treating cervical lesions (16).

A systematic review of eight studies comparing the efficacy of cryotherapy versus LEEP in HIV negative women with precancerous cervical lesions found 86% higher risk of disease recurrence in the cryotherapy group (17). Notably, only one of the eight studies was from SSA and six studies limited follow-up to ≤12 months after initial treatment. In a clinical trial in Kenya, WLHIV randomized to cryotherapy had higher recurrence risk in the 2-years following initial treatment and were less likely to clear high-risk HPV infection than WLHIV randomized to LEEP (18–20). Despite evidence that WLHIV are at increased risk of cervical disease recurrence (21), data on long-term outcomes among WLHIV in LMIC is limited. This study aimed to determine the long-term risk of recurrent cervical intraepithelial lesion grade 2 or higher (CIN 2+) and associated risk factors among WLHIV previously treated for CIN 2 or 3 with LEEP or cryotherapy.

Methods

Study Design and Participants

We conducted a cohort study among WLHIV previously randomized to LEEP or cryotherapy for treatment of CIN 2/3 and followed for two-years between June 2011 and September 2016 (22). The study was conducted at Coptic Hope Center for Infectious Diseases in Nairobi, Kenya, an urban HIV clinic that provides free, comprehensive HIV care including ART with support from the President's Emergency Plan for AIDS Relief (23). To be eligible for the parent treatment trial, participants had to be HIV positive, have biopsy confirmed CIN 2/3, be 18 years or older, sexually active, not pregnant, and have an intact cervix. Women were excluded if they had been previously been treated for cervical lesions (20). For this long-term follow-up study, we recontacted all WLHIV previously enrolled in the former trial, including those who had undergone hysterectomy (n=49) and those who had biopsy-confirmed CIN 2+ recurrence during the two-

years after initial treatment (n=95) (18,22). We did not contact participants who were reported as lost to follow-up at the Coptic Hope Center (n=14) or participants documented to have died (n=33). In addition, this long-term follow-up study excluded participants from the parent trial who were pregnant when recontacted, had a history of a bleeding disorder or those with known adverse outcomes to study intervention such as excessive hemorrhage after undergoing LEEP.

Procedures

Former trial participants were contacted by phone by study staff from February 2023 to August 2023 and invited to undergo cervical cancer screening including PAP testing at the Coptic Hope Center, free of charge after providing informed consent. During the clinic visit, study staff administered a questionnaire to collect data on medical and obstetric history, sexual history, contraceptive use, cigarette smoking and alcohol use, medical procedures such as hysterectomy, and sociodemographic characteristics. Other clinical data including history of cervical cancer screenings after exiting the parent trial, plasma HIV viral load, nadir CD4 cell count, ART regimen and duration were abstracted from the Coptic Hope Center Electronic Medical Record. All eligible participants underwent cervical examination by a trained study nurse. Women with STI symptoms or as indicated during clinical examination were offered syndromic management.

Clinical Procedures

PAP smear samples were collected by the study nurse using a cervex brush (Rovers Medical devices, The Netherlands) inserted into the endocervical canal and rotated to collect cells from the endocervix and ectocervix. Participants with low grade squamous intraepithelial lesions (LSIL), high grade squamous intraepithelial lesions (HSIL), atypical squamous cells with the inability to exclude HSIL (ASC-H) or atypical glandular cells were scheduled for a colposcopy directed biopsy. Participants had a pregnancy test prior to colposcopy. Women identified as pregnant were referred to Antenatal Clinic and followed up for cervical cancer screening at the Coptic Hope

Center. Colposcopy-directed biopsy was collected by the same study physician that performed colposcopy examinations in the parent trial.

Laboratory procedures

A PAP smear was prepared by smearing the brush on a clean glass slide and fixing immediately with 95% isopropyl alcohol. Specimens were transferred to the Coptic Hospital laboratory for staining and to a private laboratory in Nairobi (Hercules laboratory) for cytology. The fixed smear was stained at Hercules laboratory using the modified PAP smear method and mounted with permanent mounting medium (24).

Cervical samples and biopsies were fixed in a 10% buffered formaldehyde solution and transported to Hercules laboratory for haematoxylin-eosin staining and histopathology reading by a pathologist. Cytology was reported as CIN grade 1, 2 or 3 by the initial pathologist using the Bethesda classification system (25). Ten percent of cytology smears and colposcopy biopsy results were re-read by an independent pathologist at the Aga Khan University Hospital, Nairobi. If consensus cytology results were discordant, a third independent pathologist blinded to prior results acted as the tiebreaker. If alternative management was required based on these results, participants were notified for appropriate follow-up.

Participants with CIN 2/3 were referred for LEEP at the Coptic Hospital, paid by the study. Women with CIN 1 or normal biopsy results were referred for annual cervical cancer screening at the Coptic Hope Center Cervical Cancer Screening Program per national guidelines. Women with lesions that were not amenable to LEEP due to size or severity of disease, or anatomy did not allow proper access to the cervix, were referred to Kenyatta National Hospital for subsidized care.

Outcomes

The primary outcome was defined as recurrence of CIN 2+ (CIN 2, CIN 3, Carcinoma in-situ or invasive carcinoma) on colposcopy-directed biopsy, measured ≥9 years after initial treatment. The secondary outcome was defined as recurrence of HSIL+ (HSIL, atypical squamous

cells, cannot exclude HSIL or squamous cell carcinoma) on PAP smear, measured ≥9 years after initial treatment.

Statistical Analysis

The study required 300 former trial participants (150 per arm) to provide at least 80% power to detect a 15% difference in CIN 2+ recurrence between participants randomized to cryotherapy and LEEP arms at a two-sided alpha=0.05.

Descriptive statistics were used to summarize demographic and clinical characteristics of study participants by treatment arm. The primary analysis compared risk of CIN 2+ recurrence as measured in this follow-up study (≥9 years after initial treatment) by treatment arm. Secondary analysis compared recurrence of HSIL+ (HSIL, ASC-H or invasive cancer) on PAP smear as measured in this follow-up study. Log-binomial models were used to compare risk of recurrent CIN 2+ and HSIL+ between treatment arms, expressed as relative risk (RR) and 95% confidence intervals (CI).

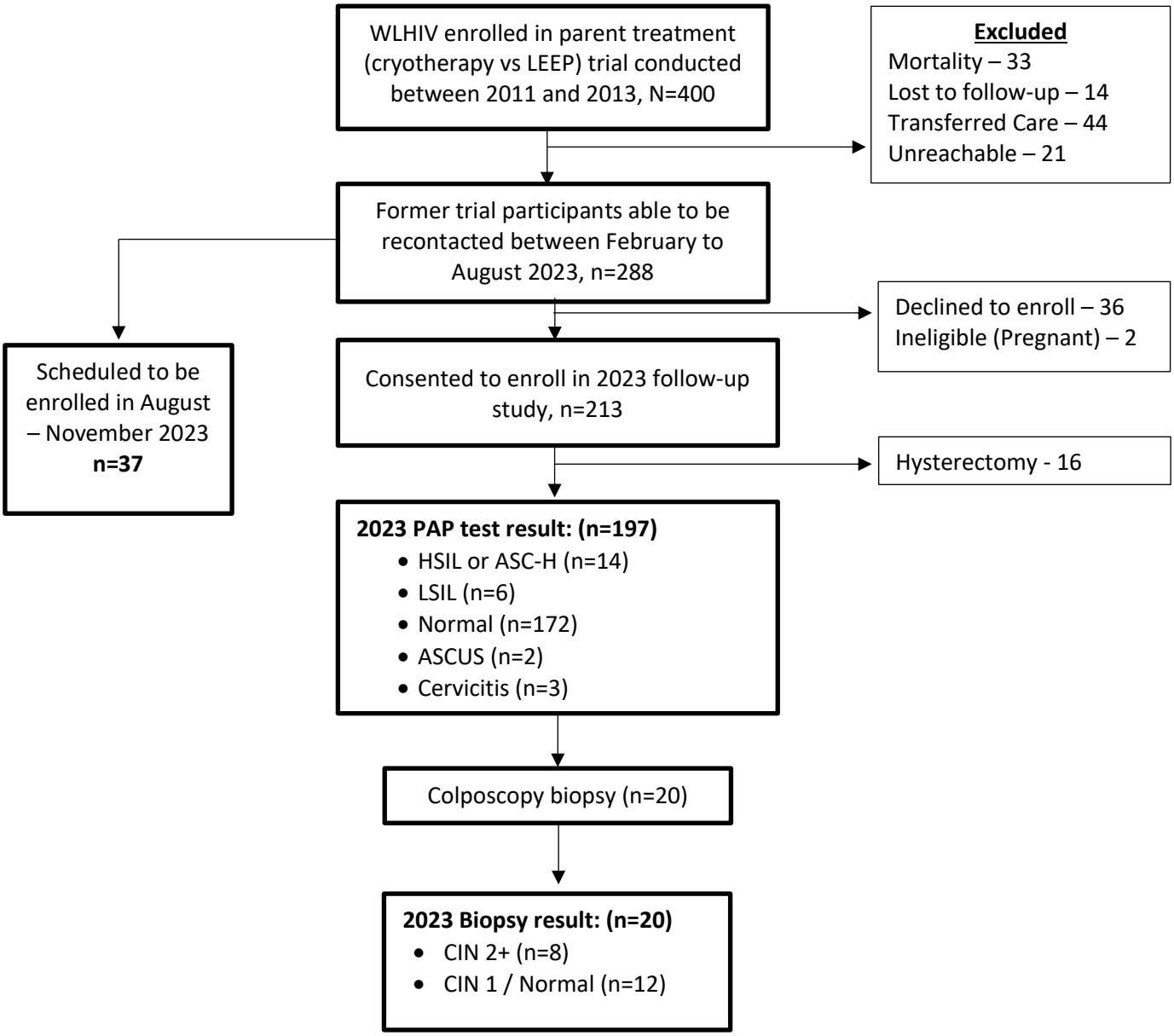
Based on *a priori* considerations, ART duration (≥10 years or <10 years), nadir CD4 count (<250, 250–499 and ≥500 copies per milliliter), and HIV viral suppression (<1000 copies/millimeter [ml]) were considered as potentially associated with disease recurrence. Multivariate models compared risk of recurrent CIN 2+ and HSIL+ by treatment arm adjusting for ART duration and nadir CD4 count. Due to small sample size, HIV viral suppression was not included in univariate analysis or multivariate models. Lastly, we evaluated whether ART duration, nadir CD4 count, and HIV viral suppression affected or modified treatment outcomes.

Ethical approval was obtained from Aga Khan University East Africa Medical College, Nairobi, and University of Washington Institutional Review Boards after which research approval was received from the Kenya National Commission for Science, Technology, and Innovation. Written informed consent was obtained from all participants prior to any clinical procedures or data collection.

Results

Of the 400 former trial participants, 33 (8.3%) were known to have died and 14 (3.5%) were lost to follow-up in the parent cryotherapy vs. LEEP trial. Of the remaining 353, 288 (81.6%) were able to be recontacted between February and August 2023. Of these, 213 (75.5%) agreed to participate in this follow-up study ≥9 years after initial treatment (**Figure 1**). Of these, 107 (50.2%) had previously been randomized to the cryotherapy arm and 90 (42.3%) to the LEEP arm. Thirteen (7.5%) former trial participants underwent total hysterectomy (TAH) since initial treatment in the parent trial; 11 of which were indicated by disease recurrence (6 in cryotherapy and 5 in LEEP arms) and 2 in the cryotherapy arm by uterine fibroids as self-reported. These thirteen women with a TAH were enrolled in the follow-up study to ascertain history of disease recurrence and indication for TAH, however, they did not undergo PAP testing and are excluded from the analysis.

Figure 1: Follow-up of study participants from the parent trial to 2023 follow-up study



Clinical and sociodemographic characteristics were similar between treatment arms **(Table 1)**. Fewer women in the LEEP arm (16.9%) had HIV viral suppression compared to women in the cryotherapy arm (23.5%). More women (16.7%) in the LEEP arm had nadir CD4 count ≥500 than those in cryotherapy arm (10.6%). Duration of ART was similar between treatment groups with an overall median of 10.9 years (Interquartile range [IQR] 9.7 – 11.5).

Table 1: Sociodemographic and clinical characteristics among participants measured at ≥9 years after initial treatment in parent cryotherapy vs. LEEP trial

	n (%) or median (IQR)	
	Cryotherapy (n=107)	**LEEP (n=90)**
Age (years)		
28-44	41 (38.3)	36 (40.0)
45-55	48 (44.9)	34 (37.8)
>55	18 (16.8)	20 (22.2)
Education Level		
None / Primary	41 (38.3)	27 (30.0)
Secondary	34 (31.8)	35 (38.9)
Tertiary	32 (29.9)	28 (31.1)
Married	41 (38.3)	35 (38.9)
Salaried Employment [b]	26 (24.3)	28 (31.1)
Monthly Income, Ksh. 15,000 and below	49 (59.0)	35 (56.5)
Ever Smoked Cigarettes	8 (7.5)	4 (4.4)
Age at sexual debut (median (IQR))	18 (16, 20)	18.5 (17, 20)
Lifetime number of sexual partners (median (IQR))	3 (2, 5)	3 (3, 5)
Consistent condom use preceding 1 month[c]	13 (31.0)	12 (33.3)
Hormonal Contraceptive use in the last year		
Yes	3 (15.0)	9 (33.3)
No	17 (85.0)	18 (66.7)
Number of prior pregnancies	3 (2, 4)	3 (2, 4)
Cervical Cancer Screening since parent trial		
Yes	81 (75.7)	67 (74.4)
No	22 (20.6)	18 (20.0)
Do not know	4 (3.7)	5 (5.6)
Cervical Cancer Screening Method since parent trial (n=148)		
PAP smear	11 (13.6)	10 (14.9)
VIA	67 (82.7)	56 (83.6)
HPV	1 (1.2)	0
Do not know	2 (2.5)	1 (1.5)
Unsuppressed HIV viral load (≥1000 copies/ml) [a]	24 (23.5)	15 (16.9)
Nadir CD4 count (cells/mm^3) [a]		
<500	93 (89.4)	75 (83.3)
≥500	11 (10.6)	15 (16.7)
Duration on ART (years) [d]	10.9 (9.9, 11.4)	10.9 (9.6, 11.6)
<10 years	27 (26.2)	28 (31.1)
≥10 years	76 (73.8)	62 (68.9)

[a]Missing data – 6 and 3 study participants had missing viral load and CD4 results
[b]Unsalaried includes those who are self-employed, housewife, unemployed and casual laborer's
[c]Consistent condom use refers to those that used condoms all of the time
[d]Four participants did not have ART initiation date

Primary Outcome

Overall, 8 (4.1%) participants had recurrent CIN 2+ at ≥9 years after initial treatment, of whom 5 (4.7%) were in the cryotherapy arm and 3 (3.3%) in the LEEP arm. Those whose prior treatment was cryotherapy had a 40% higher risk of recurrence compared to LEEP (RR = 1.40 (95% CI - 0.34, 5.71) (**Table 2**). Of the 8 participants with CIN 2+, 2 (25.0%; 1 in the cryotherapy arm and 1 in the LEEP arm) had a prior CIN 2+ recurrence in the two-years following initial treatment (during parent trial) (data not shown). Overall, 48 out of 197 participants enrolled had a recurrence during the initial trial but not during follow-up in 2023. Of these, 31 and 17 had been randomized to receive cryotherapy and LEEP respectively. There was no difference in risk of CIN 2+ recurrence at ≥9 years following initial treatment between cryotherapy and LEEP (RR=1.40, 95% CI, 0.34-5.71, p=0.64). In subgroup analysis, the effect of treatment on CIN 2+ recurrence did not vary by HIV viral suppression, nadir CD4 count, and ART duration.

Lower nadir CD4 count (<500) was associated with increased risk of recurrence of CIN2+ compared to higher nadir CD4 count (RR=1.15 (0.04, 0.58); p=0.01) (Table 3). There was no significant difference in CIN 2+ recurrence at ≥9 years after initial treatment by ART duration.

Secondary Outcome

Fourteen participants had the secondary outcome of recurrence of HSIL+ measured at ≥9 years after initial treatment: 10 (9.3%) in the cryotherapy arm and 4 (4.4%) in the LEEP arm (**Table 2**). Of these 14 WLHIV with HSIL+, 3 (21.4%; 2 in the cryotherapy and 1 in the LEEP arm) had a prior HSIL+ recurrence in the two-years following initial treatment (data not shown). There was no significant difference in risk of recurrence of HSIL+ at ≥9 years after initial treatment between cryotherapy and LEEP arms (RR= 2.10, 95% CI, 0.68-6.48; p=0.18)**.**

Table 2: Risk of recurrence of CIN 2+ or HSIL+ by HIV viral suppression, nadir CD4 count, and ART duration

	Cryotherapy (n=107)		LEEP (n=90)			
	No. of recurrences	% recurrence (95% CI)	No. of recurrences	% recurrence (95% CI)	Relative risk (95% CI)	P-value
CIN 2+ Recurrence						
Overall	5/107	4.67 (1.53, 10.57)	3/90	3.33 (0.69, 9.43)	1.40 (0.34, 5.71)	0.91
Viral Load (copies/mL)						
Suppressed (<1000)	5/78	6.41 (2.11, 14.33)	3/74	4.05 (0.84, 11.39)	1.58 (0.39, 6.38)	0.52
Unsuppressed (≥1000)	0/24	0	0/15	0	-	-
Nadir CD4 cell count (mm^3)						
<500	3/93	3.23 (0.67, 9.14)	1/75	3.45 (0.00, 17.76)	2.39 (0.25, 22.55)	0.43
≥500	2/11	18.18 (2.28, 51.78)	2/15	13.33 (1.66, 40.46)	1.36 (0.23, 8.24)	0.74
ART duration						
<10 years	2/27	7.41 (0.91, 24.29)	1/28	3.57 (0.09, 18.35)	2.07 (0.20, 21.56)	0.53
≥10 years	3/76	3.95 (0.82, 11.11)	2/62	3.23 (0.39, 11.17)	1.22 (0.21, 7.09)	0.82
HSIL + Recurrence						
Overall	10/107	9.35 (4.57, 16.52)	4/90	4.44 (1.22, 10.99)	2.10 (0.68, 6.48)	0.18
Viral Load (copies/mL)						
Suppressed (<1000)	7/78	8.97 (3.68, 17.62)	4/74	5.41 (1.49, 13.27)	1.66 (0.51, 5.44)	0.40
Unsuppressed (≥1000)	2/24	8.33 (1.03, 27.00)	0/15	-	-	-
Nadir CD4 cell count (mm^3)						
<500	7/93	7.53 (3.08, 14.90)	3/75	4.00 (0.83, 11.25)	1.88 (0.50, 7.03)	0.34
≥500	2/11	18.18 (2.28, 51.78)	1/15	6.67 (0.17, 31.95)	2.73 (0.28, 26.42)	0.36
ART duration						
<10 years	1/27	3.70 (0.09, 18.97)	0/28	0	-	-
≥10 years	8/76	10.53 (4.66, 19.69)	4/62	6.45 (1.79, 15.70)	1.63 (0.52, 5.17)	0.40

Missing data – 6 and 3 study participants had missing viral load and CD4 results

Table 3: Univariate and multivariate models evaluating factors associated with risk of recurrent CIN2+ and HSIL+ measured at ≥9 years after initial treatment

	Univariate		Multivariable Model #1		Multivariable Model #2	
	Relative Risk (95% CI)	P-value	Adjusted RR (95% CI)	P-value	Adjusted RR (95% CI)	P-value
Primary Outcome – CIN2+						
Cryotherapy (ref: LEEP)	1.40 (0.34, 5.71)	0.91	1.78 (0.44, 7.26)	0.21	1.49 (0.37, 5.99)	0.29
Nadir CD4 cells ≥500 (ref: <500)	6.46 (1.72, 24.26)	0.01	-	-	7.43 (1.87, 29.49)	<0.001
≥10 years on ART (ref: <10 years on ART)	0.66 (0.16, 2.69)	0.86	0.48 (0.12, 1.95)	0.15	-	-
Secondary Outcome – HSIL+						
Cryotherapy (ref: LEEP)	2.10 (0.68, 6.48)	0.18	2.05 (0.66, 6.40)	0.10	1.97 (0.63, 6.17)	0.14
Nadir CD4 cells ≥500 (ref: <500)	1.94 (0.57, 6.58)	0.52	-	-	1.67 (0.49, 5.68)	0.21
≥10 years on ART (ref: <10 years on ART)	4.78 (0.64, 35.91)	0.16	4.62 (0.59, 36.18)	0.74		
Model 1 and Model 2 are adjusted for nadir CD4 count and duration on ART respectively						

Discussion

This is among the first studies in SSA with long-term follow-up of recurrence of precancerous cervical lesions after LEEP or cryotherapy in WLHIV. At ≥9 years after initial treatment, 4.7% of WLHIV in the cryotherapy arm and 3.3% in the LEEP arm had recurrent cervical disease and there was no significant difference in risk of CIN 2+ recurrence by treatment arm.

The parent trial reported significantly higher risk of CIN 2+ recurrence in the cryotherapy arm with cumulative 2-year recurrence of 30% in cryotherapy and 19% in LEEP (22). These results were similar to treatment trials comparing CIN 2+ recurrence in the 12 months following LEEP or cryotherapy (26). Studies with longer follow up indicate that most recurrences of cervical disease occur within three years of initial treatment (27). This could perhaps explain the low incidence of recurrent lesions in our follow-up study. In addition, women who had prior recurrence during the RCT, had undergone re-treatment with LEEP (22).

We were unable to assess association between viral suppression and cervical disease recurrence due to inadequate sample size. However, other studies have reported an association between HIV viral suppression and recurrence of cervical disease (28). Among WLHIV, longer optimal HIV control has been associated with lower cervical disease recurrence (27) . Lower CD4 counts have been shown to elevate the risk of high-risk HPV infection and subsequently, increase the rate of precancerous cervical lesions and invasive cervical cancer (29). However, in our study we see the opposite. This is likely a spurious finding. A retrospective cohort study in Nigeria demonstrated that a lower CD4 count was associated with a higher risk of disease recurrence following thermoablation (30). Low nadir CD4 count at ART initiation or unsuppressed HIV viral load despite ART may be associated with increased risk of cervical disease recurrence and inform the treatment offered. Studies comparing treatment modalities for HSIL recommend excisional methods for WLHIV with unsuppressed HIV viral load and ablative therapy for women with both undetectable HIV viral load and CD4 count >500 cells/mm^3 (31).

The major limitation of our study is the limited sample size. We were unable to enroll the required 300 former trial participants and therefore, not adequately powered to detect a difference in disease recurrence between cryotherapy and LEEP. Selection bias could have affected our study results if those former trial participants that were unable to be recontacted or refused to participate differ in regard to HIV associated exposures (ART duration, nadir CD4 or viral suppression) or outcome status. In addition, due to budgetary constraints, we were unable to conduct HPV co-testing which would have increased the sensitivity and specificity of cervical cancer screening at enrollment into our follow-up study (32). However, this study used the same PAP and colposcopy-biopsy outcomes as the parent trial and thus, outcomes are similarly defined. Most participants in the long-term follow-up study did not undergo annual cervical cancer screening after exiting the parent trial. However, 75% self-reported having at least 1 screening since completion of the RCT. Based on EMR abstraction, only 15% of those screened in this follow-up study had a PAP test between 2016 and 2023. Thus, we are limited in differentiating the timing of cervical disease recurrence and unable to present incidence rates. Finally, this study was conducted in a single large HIV clinic in urban Nairobi and may not be generalizable to other settings.

In our cohort of WLHIV, long-term recurrence of precancerous cervical lesions was low (4%). Long-term outcomes following treatment of precancerous lesions with cryotherapy offers benefits that are not significantly different from LEEP. We recommend a larger cohort study to evaluate this further.

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