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Outcomes up to Twelve Months after Treatment with Loop Electrosurgical Excision Procedure for Cervical Intraepithelial Neoplasia Among HIV-Infected Women

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Abstract

Introduction—HIV-infected women may have higher rates of recurrent cervical precancer after treatment. Knowledge about rates and predictors of recurrence could impact guidelines and program planning, especially in low-resource settings.

Methods—In this prospective cohort study in Western Kenya, we followed HIV-infected women at six and twelve months after treatment for cervical intraepithelial neoplasia two or greater (CIN2+) after treatment with loop electrosurgical excision procedure (LEEP). All women underwent follow-up colposcopy with biopsy as indicated for diagnosis of CIN2+. We calculated the incidence and predictors of primary disease recurrence after treatment.

Results—Among the 284 women who underwent LEEP and had at least one follow-up visit, there were 37 (13%) cases of CIN2+ detected by twelve-month follow-up. Four (10.8%) of the recurrences were invasive cancer, all Stage IA1. The 6 and 12-month rates of recurrence were 13.7 and 12.8 cases/100 person-years of follow-up, respectively. Antiretroviral therapy (ART) use did not significantly impact the rate of recurrence (Hazard Ratio 1.24, 95% CI 0.59, 2.79). The only significant predictor of recurrence in the multivariate analysis was CD4+ nadir < 200 cells/mm^3 (Adjusted Hazard Ratio 3.14, 95% CI 1.22, 8.08).

Discussion—The overall rate of treatment failure within a year of LEEP was low in this cohort of HIV-infected women. Among the women with recurrence, there was a significant amount of invasive cancer. The relatively high rate of cancer after treatment suggests that HIV-infected women merit continued close follow-up after treatment.

Keywords

Cervical cancer screening; cervical intraepithelial neoplasia; HIV-infection; Kenya

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Introduction

The burden of cervical cancer is highest in less developed regions, where it is a leading cause of cancer-related mortality among women. Of the estimated 266,000 deaths from cervical cancer worldwide in 2012, nearly nine out of ten occurred in less-developed regions.[1] Such disparities can be largely explained by the lack of population-level screening programs in low-resource settings that have been successful in the United States and Western Europe.[2] Many areas with the highest cervical cancer rates, such as sub-Saharan Africa (SSA), are also among those with the highest HIV prevalence,[3] which is known to increase the risk of developing cervical cancer. Studies comparing HIV/AIDS and cancer registries have shown a 2- to 22-fold increase in the incidence of invasive cervical cancer among women living with HIV compared to the general population.[4-6]

The immunosuppression that accompanies HIV has been linked to increased susceptibility to human papillomavirus (HPV) infection – the cause of nearly all cases of cervical cancer – as well as infection with multiple strains and persistence of HPV over time.[7-9] The inability to clear HPV due to impaired immune response is likely the cause of increased incidence, progression and recurrence of cervical neoplasia found in HIV-positive women.[10] Cervical lesions in HIV-positive women have been found to be nearly twice as likely to progress in severity compared to women without HIV.[11] Studies in HIV-positive women have reported post-treatment recurrence rates of 20% to 75.6% for the cervical cancer precursor cervical intraepithelial neoplasia 2+ (CIN2+) compared to rates of 8.4% to 16% in HIV-negative women.[12-14] The wide range in these values reflects the variability in study design, including criteria for treatment, definition of treatment failure versus recurrence and use of cytology with and without histology to define the outcome.[15] A number of studies have reported a higher prevalence and recurrence of cervical lesions when CD4+ counts are low, [16-18] yet evaluations of the impact of antiretroviral therapy (ART) have been inconsistent,[19-21] with some studies suggesting that the inherent biologic relationship between HPV and HIV will mitigate the impact of ART on HPV-related cervical lesions. [22, 23] While ART use has not led to a clear improvement in cervical cancer outcomes, the extended lifespans of women on ART leave them at increased risk for development and recurrence of CIN2+ and invasive cancer.

In 2010, half of the 34 million people living with HIV globally were women, and SSA has the largest proportion of HIV-positive women of reproductive age in the world.[24] The excess cervical cancer risk experienced by HIV-positive women who are now living longer highlights the urgent need for effective cervical cancer prevention programs that take into account potential biologic differences in risk for HIV-infected women, in SSA and elsewhere. Although access to regular screening tests and treatment for CIN2+ would greatly reduce cervical cancer mortality in these settings, screening guidelines that seek to take into cost and infrastructure barriers, such as the single lifetime screening model, may be inadequate for HIV-positive women due to their differently biologic risk for cervical precancer and cancer, including a higher risk of disease recurrence. It is critical to understand and take into account the unique needs of women living with HIV in order to develop effective cervical cancer prevention programs in low-resource settings with high HIV prevalence.

To inform cervical cancer screening protocols for HIV-positive women, we evaluated the 12-month recurrence rate and factors associated with recurrence for biopsy-confirmed CIN2+ after treatment with loop electrosurgical excision procedure (LEEP) in a cohort of HIV-positive women in rural Western Kenya.

Materials and Methods

We conducted a prospective cohort study among HIV-infected women undergoing primary treatment for biopsy-confirmed CIN2+ between March 2008 and December 2012 at the Family AIDS Care and Education Services program (FACES) in Kisumu, Kenya.[25] Women were identified through the cervical cancer screening program offered to all women enrolled into care. Screening was performed with Visual Inspection with Acetic Acid, followed immediately by colposcopy for women who screened positive. All CIN2+ cases were determined by colposcopically-directed biopsy. We sought to consecutively enroll the first 300 eligible women, with a 2:1 ratio of ART users to non-users. ART users were defined as women who had been on ART for at least three months and reported at least 90% adherence during the past three months. ART use was defined as a triple antiretroviral drug regimen prescribed for clinical or immunologic indications. Non-users were defined as women not on ART at the time of their LEEP, who did not meet clinical or immunologic criteria to initiate ART and had not received antiretrovirals for prevention of mother-to-child transmission (PMTCT) within the past six months. Exclusion criteria included pregnancy, <90% ART adherence and plans to move out of the clinic area or become pregnant during the 24-month follow-up period.

The LEEP was performed in the clinic by trained and certified clinical officers. Specimens were removed in one to three passes using the “blend” setting of cut and coagulation.[26] Women who underwent LEEP were given an appointment to return to the clinic at four to six weeks post-treatment. At that visit, they were offered enrollment in the follow-up study and signed a written informed consent. Women who enrolled in the study participated in a post-LEEP questionnaire to assess their experience with the LEEP, including any post-LEEP symptoms or adverse events. [27] They were then scheduled to come back for colposcopy at six, twelve and twenty-four months post-procedure. Colposcopy was performed by study staff (a nurse and clinical officer) who had each been trained and certified, and had performed over 50 colposcopies prior to the study initiation. Colposcopy was performed per standard guidelines, with biopsy performed for any lesions suggestive of CIN2+.[28] Biopsy specimens were immediately placed in 10% buffered formalin and stored at room temperature until they were sent to the Kenya Medical Research Institute (KEMRI) pathology laboratory in Nairobi. Final diagnoses were based on the histopathology results, except in cases in which the colposcopist identified a normal cervix or no lesions greater than CIN1. Results were categorized as negative (normal squamous epithelium), inflammation, CIN1, CIN2/3 or invasive cancer. For specimens with more than one diagnosis, the outcome was defined as the most severe diagnosis. Because the coagulation setting was used for the procedure, margins were not assessed histologically. Repeat LEEP was offered to women who had recurrence of CIN2/3, and they were exited from the cohort.

Statistical Methods

Information from the cervical cancer screening visit was collected on a paper form and entered into an Access database (Microsoft,™ Redmond, WA). Clinical and demographic variables from the FACES clinical encounter closest (within six months) to the time of the LEEP were obtained through the electronic medical record system (OpenMRS). Clinical variables that were likely to change between enrollment and the six-month follow-up visit, including CD4+ cell count, World Health Organization (WHO) stage, family planning method and any ART initiation or regimen change were collected from patient interviews and through review of clinical data in OpenMRS.

Sample size calculations were based on an assumption of at least 10% recurrence, defined as CIN2+ (CIN2/3 or invasive cancer) within 12-months of treatment. We calculated that a sample size of 270 was needed to determine a difference in recurrence rates of 15% between women on ART and not on ART. We modeled time to recurrence using Cox regression due to individual variation in exact time of follow-up; we assessed each model to ensure the assumption of proportional hazards was not violated. Age-adjusted associations were calculated for both static characteristics described at baseline (age, site, education level, partner status, use of contraceptives, pathology on LEEP specimen, lesion size, lowest recorded CD4+ nadir and time since HIV-diagnosis) and clinical variables that changed between baseline and follow-up (using ART at follow-up visit, ART regimen change between visits and CD4+ count at follow-up). We modeled ART and CD4+ jointly adjusting for age and site. Sensitivity analysis of the association of ART with recurrent CIN2+ was performed using marginal structural modeling in order to account for time-dependent confounding by CD4+.[29] Probability of ART at each time point was modeled as a function of age, pre-ART (or pre-LEEP) CD4+ nadir, CD4+ count, WHO stage and duration of time in study. Observations were weighted by the inverse probability of ART based on this model; weights were stabilized by multiplying them by baseline probability of ART. The analytic model included adjustment for age, site, and pre-treatment CD4+ nadir. Censoring weights were not estimated due to the small number of censored observations; bias-corrected 95% confidence intervals (CI) were generated based on 10,000 bootstrap resamples. All statistical analyses were performed in Stata 11 (StataCorp LP, College Station, TX).

Ethical approval was obtained from the University of California San Francisco Committee for Human Research and the KEMRI Ethical Review Committee.

Results

Two hundred and ninety seven women underwent LEEP for CIN2+ and consented for enrollment in the study. At baseline, the mean age was 32.6 years (SD 6.3), average CD4+ count was 419 cells/mm^3 (SD 252), 94 (32.5%) had a CD4+ nadir < 200 cells/mm^3, 52% were WHO clinical stage 1 or 2 and 194 (68.3%) were on ART (Table 1). Among the 284 women who a twelve-month follow-up visit and were included in the outcome analysis, an additional 23 (8.1%) women initiated ART in the study period. In the vast majority of cases, LEEP confirmed the CIN2+ diagnosis (255 women, or 89.8%), while in 11 (6.7%) cases the specimen showed cervicitis, 8 (2.8%) were inadequate, 5 (1.8%) were CIN1 and 5 (1.8%)

were negative. Complete baseline demographic data on the cohort are presented elsewhere.[30]

Thirty-seven (13.0%) participants had a treatment failure, i.e. CIN2+ on repeat biopsy within twelve months of treatment by LEEP. Twenty of these occurred by the six-month follow-up visit and 17 women had CIN2+ detected at their twelve-month visit. Between six and twelve months 13 additional women were dropped from the study, leaving 251 twelve-month follow-up visits. Six (50%) were lost-to-follow-up at FACES, 1 (8.3%) transferred to another HIV clinic, 1 (8.3%) died of tuberculosis and 4 (33.3%) were actively receiving care at clinic, but did not attend their follow-up colposcopy within three months of the scheduled visit.

The total follow-up time for the cohort was 289.4 woman-years, median 12.2 months. The incidence of recurrence at six months was 13.7 per 100 woman-years and the six to 12 month incidence was 11.9 per 100 woman-years. These rates were not significantly different (IRR 0.87, 95% CI 0.43, 1.76). The cumulative incidence of recurrence at twelve-months was 12.8 per 100 woman-years. Although not counted in the analysis of primary recurrence, 5 of the 20 (25%) women who had recurrence of CIN2/3 and were treated with repeat LEEP at six months had a second recurrence at their twelve-month visit.

Rates of recurrence at 12 months did not differ significantly by ART status at baseline (IRR 1.24, 95% CI 0.59, 2.79) or at the time of follow-up (IRR 1.98, 95% CI 0.81, 5.79). The adjusted analysis using a marginal structural model similarly did not indicate a significant relationship of ART with CIN2+ recurrence (Adjusted Hazard Ratio [AHR] 3.41, 95% CI 0.35, 170.22). After adjusting for age, higher gravidity (AHR 0.71, 95% CI 0.54, 0.94) was associated with a lower hazard of recurrence (Table 2). Evidence of microinvasion on the primary LEEP specimen (AHR 13.91, 95% CI 1.6-120.14), WHO stage 4 (AHR 5.44, 95% CI 1.72, 17.23), CD4+ count <200 cells/mm^3 at the time of LEEP (AHR 4.85, 95% CI 2.13, 11.05) and CD4+ nadir (AHR 3.15. 95% CI 1.48, 6.71) were all associated with an increased hazard of recurrence in an age-adjusted model. In the final multivariate model, CD4+ nadir was the only variable associated with an increased rate of recurrence (AHR 3.14, 95% CI 1.22, 8.08).

Among the 37 women with recurrent disease, there were four (10.8%) cases of invasive cancer diagnosed with biopsy, two at six months and two at twelve months (1.34 cases per 100 woman-years), with no difference in incidence between the two time intervals. All of these women had Stage IA1 disease and were referred for treatment at the Provincial Hospital.

Discussion

This study of almost 300 HIV-infected women followed after treatment with LEEP for CIN2+ showed a cumulative incidence of recurrence at twelve months of 12.8 per 100 woman-years for CIN2+ and 1.3 per 100 woman-years for invasive cancer. Compared to the six-month outcome rates and predictors of recurrent disease previously reported for this cohort,[30] we sought to examine whether the low early recurrence rate was predictive of a

lower 12-month rate, and to further explore factors associated with recurrence in HIV-positive women. While these findings may not be generalizable to populations with regular lifetime screening, they will help guide post-treatment follow-up protocols for HIV-positive women, particularly in low-resource settings similar to Kenya implementing a “screen-and-treat” approach.

The fact that the rates of recurrence of CIN2+ are lower than has been previously reported may be related to the relatively healthy status of the cohort.[6, 12] While the high average CD4+ count likely reflects the majority of women on ART, over half of women were WHO Stage 1 or 2, suggesting limited clinical evidence of immunosuppression. Interestingly, in the final model, the only predictor of recurrent CIN2+ was CD4+ nadir < 200 cells/mm^3 prior to ART initiation. Although this is not a modifiable risk factor once CIN2+ has been diagnosed, it adds to the increasingly robust body of literature supporting the early initiation of ART, regardless of CD4+ cell count. Potential other reasons for the lower than previously reported recurrence rate is that the threshold for biopsy was colposcopic impression of CIN2+, rather than random biopsies for all participants, and our design limited the outcome to biopsy-confirmed disease. Other studies have looked at cytological abnormalities or CIN1+, both of which may reflect transient HPV infection with a high likelihood of spontaneous clearance.[15, 31]

The lack of association between ART and improved treatment outcomes could be due to the overall lower than expected number of outcomes, the fact that the ART influence on cervical disease is mediated by immune status, reflected in CD4+ count rather than solely ART status, or the selection-by-indication bias. The latter bias, meaning sicker women are the ones assigned to ART, even after controlling for WHO Stage and CD4+ count, may dampen the positive effect of treatment. This type of bias has plagued the study of ART's effect on slow-progressing opportunistic diseases such as cervical cancer and its precursors, HPV and CIN2+. Although there is certainly biologic plausibility for a benefit of ART on preventing disease development or recurrence, findings in the literature examining the relationship between ART and cervical disease remain mixed. [5, 6, 32-35] A recent review of the literature on HPV-related immunity in immunocompetent individuals suggests that once HPV-induced lesions are established, they fail to trigger an immune response to clear them. [23] This would suggest that the main biologic mechanism for disease prevention lies in avoiding or clearing the initial HPV infection before integration into the host-cell DNA; therefore HAART use would not be expected to show any benefit for disease clearance or prevention of recurrence.

This study builds on other studies by looking at a larger number of HIV-infected women undergoing treatment for biopsy-confirmed CIN2+. We had a very high follow-up rate, and colposcopy was performed for outcome ascertainment at all follow-up visits. In addition, all women underwent a single treatment modality, so we are able to directly comment on the performance of LEEP. In spite of the strengths, there were a number of limitations. These include a lack of an HIV-negative comparison group, so we cannot comment on how these recurrence rates compare to HIV-negative women in our setting. Another limitation is the lack of differentiation between CIN 2 and CIN 3 in our outcome analysis. Because this was done in a clinical setting, we requested a combined diagnosis of CIN2/3 from the pathologist

to simplify the interpretation of results for treatment and follow-up planning. Although this may limit comparison to some other studies, it is reflective of the real-world setting and may make our findings more generalizable. Finally, there was no HPV testing done, so we cannot assess the impact of persistent or type-specific HPV infection on the risk of recurrence, or the possibility that post-treatment disease detection is due to a new vs. recurrent vs. persistent HPV infection.

We found that treatment of HIV-infected women with CIN2+ with LEEP in an outpatient setting was effective up to one year, with only 13% of women experiencing treatment failures, similar to what was seen in HIV-negative women in previous studies. [12-14] The observed incidence of invasive cancer (1.3 per 100 woman-years) within the one-year follow-up period, although substantially lower than what has been reported as a baseline risk,[6] suggests that HIV-infected women remain at high-risk after treatment and merit close follow-up with histological evaluation after treatment. While this is certainly feasible and considered standard of care in resource-replete settings, in resource-poor settings the move toward “screen-and-treat” with techniques such as cryotherapy that do not include specimen sampling may mean that cases of invasive disease may be missed, especially among HIV-infected women.[8, 36] While not discounting the overall benefit that these programs provide to populations that may not have had access to any cervical cancer prevention in the past, this analysis suggests that HIV-infected women remain at increased risk for invasive disease. This warrants the continued investigation into the most cost-effective and feasible strategies for prevention of invasive disease in low-resource settings, specifically in terms of determining the risk of missed invasive cancers in screen-and-treat programs and defining the optimal post-treatment follow-up strategy for women with more severe immunosuppression. After over 50 years of planning and implementing successful cervical cancer screening programs in resource-replete settings, it is time to extend the benefits of screening and treatment of dysplasia throughout the world, and ensure that HIV-infected women in these regions have access to effective prevention.

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Table 1

Baseline characteristics of HIV-infected women undergoing Loop Electrosurgical Excision Procedure for Cervical Intraepithelial Neoplasia 2 or greater (N=297)

	Mean (+/- SD) or n (%)
Demographics	
Age (yrs)	32.6 (6.2)
Education (n=241)	
Attended primary school	131 (54.4%)
Attended secondary school	86 (35.7%)
Attended university	24 (10.0%)
Relationship Status (n=127): *	
No current partner	58 (45.7%)
At least one current partner	69 (54.3%)
Reproductive History	
Number of pregnancies (n=221)	2.7 (1.8)
Contraception (n=287)	
Oral contraceptives	9 (3.1%)
Injectable (Depo Provera)	64 (22.3%)
Implant (Jadelle)	13 (4.5%)
Intrauterine Device in-situ †	2 (0.7%)
Female Sterilization	8 (2.8%)
Condom only	36 (12.5%)
No contraception reported	155 (54.0%)
HIV-related Characteristics	
Time since first HIV-diagnosis (mo)	24.8 (+/- 22.3)
Time enrolled in HIV-care	13.7 (+/- 16.2)
Most Advanced WHO Stage (n=295)	
1	59 (20.0%)
2	97 (32.9%)
3	101 (34.2%)
4	38 (12.9%)
CD4+ at LEEP (n=276)	419 (+/- 252)
CD4+ nadir prior to LEEP, mean cells/dL (n=276)	
<200	94 (32.5%)
201-350	74 (25.6%)
351-500	55 (19.1%)
>500	66 (22.8%)
On HAART at Study Initiation (n=297) ††	194 (65.3%)
Duration on HAART at time of LEEP (mo)	15.3 (+/- 16.2)

	Mean (+/- SD) or n (%)
Time in care before HAART initiation (mo)	10.9 (+/-14.7)
Cervical Cancer Screening Characteristics	
Screening performed at FACES enrollment visit	109 (36.7%)
Histopathology on LEEP specimen (n=284)	
CIN2+	255 (89.8%)
CIN1	5 (1.8%)
Cervicitis	11 (6.7%)
Negative	5 (1.8%)
Inadequate Specimen	8 (2.8%)
Lesion greater than 2.5 cm	39 (13.1%)

*Women were defined as having a current partner if they reported living with a spouse or unmarried partner

†At the time of this analysis, levonorgestrol-releasing IUDs were not available in western Kenya. Therefore, IUDs are not classified under hormonal contraception

††First line HAART regimens consisted of a triple drug combination of either zidovudine or stavudine + lamivudine + either nevirapine or efaviranz

Table 2

Demographic and clinical characteristics associated with CIN2+ recurrence at 12-months

	Age-adjusted Models (N=284)		Multivariate Model: HAART and predictors (N=227)	
	HR (95% CI)	**p-value**	**AHR (95% CI)**	**p-value**
Time-Independent Variables (Baseline)				
Demographics				
Age	1.90 (0.97, 3.72)	0.061	2.05 (1.02, 4.12)	0.045
Site[1]				
Lumumba	1.00 (REF)		1.00 (REF)	
Kisumu District Hospital	1.77 (0.85, 3.68)	0.125	1.68 (0.78, 3.39)	0.191
Study Referral	2.32 (0.79, 6.80)	0.125	8.19 (1.65, 40.69)	0.010
Education				
Some primary	1.00 (REF)			
Some secondary	0.80 (0.36, 1.77)	0.588		
College	1.30 (0.44, 3.89)	0.637		
Has current partner	1.06 (0.44, 2.54)	0.900		
Reproductive Characteristics				
Combined oral contraceptive	0.84 (0.20, 3.50)	0.807		
Injectable (Depomedroxyprogesterone acetate)	0.95 (0.44, 2.01)	0.884		
Implant (Jadelle)	0.32 (0.04, 2.36)	0.265		
Intrauterine device in place	NA			
Number of past pregnancies	0.71 (0.54, 0.94)	0.017		
LEEP Characteristics				
Pathology on LEEP specimen				
Less than CIN2+	1.00 (REF)			
CIN2+	5.02 (0.68, 37.02)	0.114		
Microinvasive cancer	13.91 (1.61, 120.14)	0.017		
Lesion size >2.5 cm	1.77 (0.83, 3.80)	0.142		
HIV-related characteristics				

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	Age-adjusted Models (N=284)		Multivariate Model: HAART and predictors (N=227)	
	HR (95% CI)	**p-value**	**AHR (95% CI)**	**p-value**
Time since HIV diagnosis (months)	1.00 (0.98, 1.02)	0.645		
Most advanced WHO stage				
Stage 1	1.00 (REF)			
Stage 2	2.05 (0.66, 6.39)	0.213		
Stage 3	1.48 (0.46, 4.72)	0.510		
Stage 4	5.44 (1.72, 17.23)	0.004		
Time-Dependent HIV-Related Variables				
On ART at follow-up visit	1.93 (0.80, 4.65)	0.141	2.54 (0.64, 10.15)	0.187
ART regimen switch prior to recurrence (in those on ART)	1.21 (0.28, 5.18)	0.800		
CD4+ count/mm^3 at visit				
<200	4.85 (2.13, 11.05)	<0.001		
201-350	2.14 (0.98, 4.65)	0.055		
>350	1.00 (REF)			
CD4+ count/mm^3 nadir[2]				
<200	3.15 (1.48, 6.71)	0.003	3.14 (1.22, 8.08)	0.018
201-350	0.73 (0.25, 2.14)	0.564	1.15 (0.23, 2.52)	0.664
>350	1.00 (REF)		1.00 (REF)	

[1] Participants were recruited from three sites within the FACES program: Lumumba Health Center, Kisumu District Hospital and from a couples HIV-prevention study. Clinical and demographic characteristics did not differ among study sites (data not shown).

[2] CD4+ nadir defined as lowest CD4+ recorded prior to recurrence visit and/or prior to initiation on ART among ART users