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Factors Associated With Recurrence of Cervical Intraepithelial Neoplasia 2+ After Treatment Among HIV-Infected Women in Western Kenya

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Abstract

HIV-infected women are at increased risk for recurrence of cervical dysplasia after treatment. Short-term recurrence rates may reflect treatment efficacy and therefore impact screening protocols and follow-up planning. We conducted a prospective study of 297 HIV-infected women undergoing loop electrosurgical excision procedure for cervical intraepithelial neoplasia 2+ (CIN2+) in an HIV clinic in Kisumu, Kenya. By 6 months after the procedure, 20 (7.1%) of women had recurrent CIN2+. Recurrence was significantly associated with $CD4^+$ nadir but not with highly active antiretroviral therapy use. Longer-term follow-up of this cohort will illustrate the potential impact of highly active antiretroviral therapy and immune status on CIN2/3 disease recurrence.

Keywords

cervical cancer prevention; HIV; women's global health; Kenya; loop electrosurgical excision procedure; treatment recurrence

Introduction

The global burden of both cervical cancer and HIV is borne by women in low- and middle-income countries, where health care infrastructure is limited.[1,2] In addition to the lack of cervical cancer prevention programs in these settings, HIV infection increases women's risk for cervical cancer through an increase in the prevalence of human papillomavirus infections and development of human papillomavirus–related pre-cancerous and cancerous lesions.[3,6] Cervical cancer risk and outcomes worsen with increasing immune dysfunction.[7,8] HIV-

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infected women also have increased rates of recurrence after treatment for cervical intraepithelial neoplasia 2+ (CIN2+), the immediate cervical cancer precursor.[9,10] Although access to highly active antiretroviral therapy (HAART) in many countries has dramatically increased over the past decade, the impact of HAART on the development of cervical precancer and recurrence after treatment remain unclear.[1115] This means that an increasing number of HIV-infected women are living longer with a potentially higher risk for cervical cancer.

Risk for cervical cancer can be greatly reduced if women have access to screening programs with effective treatment for precancerous lesions. Efforts to implement screening programs in low- and middle-income countries focus on cost and infrastructure requirements, and often aim to achieve a single lifetime screening, with treatment as needed.[16] For HIV-infected women, the high risk of disease recurrence may make the single lifetime screening model inadequate. Estimates for the incidence of disease recurrence after treatment vary widely from 25% to 55% at 12 months in HIV-infected women[1719] compared with 5%–16% in HIV-negative women.[20,21] There are very few studies focusing on early posttreatment outcomes (6 months) in HIV-infected women.[18] Disease identified at 6 months or less may represent either treatment failure or disease recurrence, both of which necessitate additional follow-up and possibly retreatment. Identification of clinical and demographic factors that may put HIV-infected women at increased risk for early posttreatment recurrence of CIN2+ are also important, as they may potentially impact clinical care decisions and posttreatment follow-up guidelines.

Cervical cancer prevention strategies must be modified to address the increased risk of disease in HIV-infected women. To inform cervical cancer prevention programs offered to HIV-infected women, we sought to examine the early recurrence rate and factors associated with recurrence, for biopsy-confirmed CIN2+ after treatment with loop electrosurgical excision procedure (LEEP) among HIV-infected women attending a cervical cancer screening program in Kisumu, Kenya.[22]

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). We sought to enroll 300 women, with a 2:1 ratio of HAART users to nonusers. HAART users were defined as women who had been on HAART for at least 3 months and reported at least 90% adherence during the past 3 months. HAART use was defined as a triple antiretroviral drug regimen prescribed for clinical or immunologic indications. Non-users were defined as women not on HAART at the time of their LEEP, who did not meet clinical or immunologic criteria to initiate HAART and had not received antiretrovirals for prevention of mother-to-child transmission within the past 6 months. Exclusion criteria included pregnancy, HAART use less than 3 months, or (for nonusers) in the past, <90% HAART adherence and plans to move out of the clinic area during the 24-month follow-up period.

LEEP was performed by trained and certified clinical officers in the clinic in 1–3 passes using the coagulation setting.[23] Women who underwent LEEP for CIN2+ were given an appointment to return to the clinic at 4–6 weeks posttreatment. 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.[24] They were then scheduled to come back for colposcopy at 6, 12, and 24 months postprocedure. Colposcopy was performed by trained and certified providers with biopsy performed for any lesions suggestive of CIN2+ on colposcopy during those follow-up visits.[25] Biopsy specimens were immediately placed in 10% buffered formalin and stored at room temperature until they were sent to the Kenya Medical Research Institute pathology laboratory in Nairobi. Final diagnoses were based on the colposcopy, and if taken, histopathology results. Results were categorized as negative (normal squamous epithelium), inflammation, CIN1, CIN2/3, or invasive cancer. For specimens with more than 1 diagnosis, the outcome was defined as the most severe diagnosis. Repeat LEEP was offered to women who had recurrence of CIN2/3.

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 6 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 6-month follow-up visit, including $CD4^+$ cell count, World Health Organization (WHO) stage, family planning method, and any HAART initiation or regimen change were collected from patient interviews as well as review of clinical data in OpenMRS.

Sample size calculations were based on an assumption of at least 10% recurrence defined as CIN2+. We calculated that a sample size of 270 was needed to determine a difference in recurrence of 15% between women on HAART and not on HAART. We modeled time to recurrence using Cox proportional hazards models because of individual variation in exact time of follow-up; clinical variables that changed between baseline and follow-up were included as time-varying covariates. We implemented 2 sets of models: (1) individual assessment of each predictor adjusting for age and (2) regressing HAART on time to recurrence controlling for $CD4^+$ nadir and covariates that were significant at $P < 0.10$ in the first model. We selected $CD4^+$ nadir as the best available indicator of pre-HAART immune dysfunction out of recent $CD4^+$ nadir, most recent $CD4^+$ count, and worst WHO stage. Sensitivity analyses were performed without HAART in the model and excluding women who initiated HAART between enrollment and the 6-month follow-up visit. We performed an additional sensitivity model including CIN1 as an outcome. 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 Subjects Research and the Kenya Medical Research Institute Ethical Review Committee.

Results

Two hundred ninety-seven women with CIN2+ underwent LEEP at FACES between March 2008 and December 2012 and enrolled in the follow-up study, of whom 283 (95.2%) contributed a total of 1758 months (mean: 6.2 months) of valid follow-up time. Among the 15 (5.1%) women without follow-up data, 4 were lost-to-follow-up at FACES, 1 died of other opportunistic infections, 1 sought a second opinion and had a hysterectomy, 5 were missing results, and 4 came in for follow-up within 3 months or after 12 months of LEEP and thus were not included in this analysis. At the time of LEEP, the average age of participants was 32.6 years (±6.3), average $CD4^+$ count was 418 (±252), 52% were WHO clinical stage 1 or 2, and 194 (65.3%) were on HAART (Table 1).

Twenty [7.1%, 95% confidence interval (CI): 4.4 to 10.7] women had CIN2+ and 8 (2.8%, 95% CI: 1.2 to 5.5) had CIN1 detected at their 6-month follow-up. Among the CIN2+ cases, there were 2 invasive cancers diagnosed on biopsy. The incidence of recurrent CIN2+ over follow-up period was 13.7 per 100 person-years. Rates of recurrence did not differ significantly by HAART status. The incidence rate ratio for recurrence among women on HAART compared with HAART naive women was 2.25 (95% CI: 0.7 to 12.0). On bivariate analysis controlling for age, significant predictors of recurrence were gravidity, $CD4^+$ count before the 6-month visit <350 cells per cubic millimeter $CD4^+$ nadir <200 cells per cubic millimeter and WHO stage 4 (Table 2; column 1). HAART use was not significantly associated with recurrence, even when adjusting for $CD4^+$ nadir and other covariates (Table 2; column 2) and after restricting to prestudy HAART use (data not shown). Gravidity remained associated with reduced recurrence in the adjusted model, although this association became insignificant in both sensitivity analyses (data not shown). $CD4^+$ nadir remained associated with recurrence in all models.

Discussion

This prospective cohort of HIV-infected women undergoing LEEP for CIN2+ showed a lower than expected rate of disease recurrence (7.1%) at 6 months based on earlier reports.[18,26] In a final multivariable model, women with a lower $CD4^+$ nadir had an increased risk of disease recurrence at 6 months. We did not find a difference in recurrence rates among women on HAART compared with those not on HAART, even after controlling for clinical variables reflective of disease status and restricting analysis to women on HAART before LEEP.

This study has several strengths. This is a primary data analysis from a relatively large number of HIV-infected women followed prospectively, so we were able to determine incidence and incidence ratio of disease recurrence, which can be more universally applied across populations. We studied a single treatment modality, LEEP, which can be safely performed in a low-resource setting[23]; others studied a combination of LEEP and cold knife cone.[18,26] Another strength of this study is that we defined recurrence as biopsy-proven CIN2+, in contrast with other studies that have included CIN1 and/or abnormal cytology results as recurrence.[17] We chose this outcome because it is the most clinically relevant in terms of guiding decisions about additional treatment. Finally, because this study took place

within the FACES-supported HIV care clinic, we had a high rate of follow-up and were able to use laboratory and medical record data to update clinical and demographic variables throughout the study.

There were also several limitations in this study. We did not see a significant difference in recurrence rates between women on HAART and not on HAART. This could be due to a true lack of biological difference, or insufficient power to detect a true difference because of low numbers of women not on HAART, and/or a lower than expected CIN2+ recurrence rate. In addition, we were not able to look at the impact of specific HAART regimens or classifications on recurrence risk. This was due to both sample size and limited availability of different HAART regimens in our settings (less than 10% of participants were on protease inhibitor–containing regimens). Finally, although we were able to look at the size of the LEEP specimen, we were not able to comment on margins at the time of treatment because LEEP was performed using the coagulation function. Because disease margin status has been shown to be predictive of recurrence in the past,[21] we considered altering the LEEP protocol. However, optimizing the procedure to reduce the risk for postprocedure bleeding in this outpatient setting was thought more important.

Although HAART was not significantly associated with recurrence outcomes, our cohort had an overall better immune status than previous studies, reflected in a higher proportion of women on HAART, greater mean $CD4^+$ count and less advanced WHO stage.[26] It is possible that our overall lower rate of recurrence is related to the better immune status, and that HAART would have a greater impact in women who have more immune dysfunction. It will be important to evaluate CIN2+ prevalence at 12 and 24 months postprocedure to see if the 6-month outcomes are predictive of lower rates of recurrence in the long term and to further explore factors associated with recurrence at later time points. These findings will help define the need for follow-up after treatment for CIN2+ in HIV-infected women, especially in settings implementing a “screen & treat” protocol. Low rates of early recurrence as seen in this study suggest that it may be safe to lengthen the first post-LEEP follow-up in selected populations and support the new WHO recommendations for a 1-year post-treatment follow-up among HIV-infected women in resource-limited settings.[27]

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Table 1

Baseline Characteristics of Women Undergoing Loop Electrosurgical Excision Procedure for CIN2+, N = 297

	Mean (6±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 1 current partner	69 (54.3)
Reproductive history	
No. 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 (IUD) in place†	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 before 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 the time of LEEP (mo)	15.3 (616.2)
Time in care before HAART initiation (mo)	10.9 (±14.7)
Screening performed at FACES enrollment visit	109 (36.7%)

[*] 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 6 Months

	Age-Adjusted Models		Multivariate Model: HAART and Predictors (N = 206)	
	HR (95% CI)	***P***	**AHR (95% CI)**	***P***
Time-independent variables (baseline)				
Demographics				
Age	1.70 (0.70 to 4.15)	0.24	1.79 (0.78 to 4.11)	0.17
Site*				
Lumumba	1.00 (Ref)		1.00 (Ref)	
Kisumu district hospital	2.31 (0.93 to 5.75)	0.073	2.26 (0.72 to 7.11)	0.16
Study referral	1.54 (0.19 to 12.22)	0.681	4.25 (0.38 to 47.52)	0.24
Has current partner	1.20 (0.39 to 3.69)	0.75		
Reproductive characteristics				
Combined oral contraceptive	0 (n/a)	n/a		
Injectable (Depo Provera)	1.06 (0.38 to 2.93)	0.91		
Implant (Jadelle)	0 (n/a)	n/a		
Intrauterine device in place	0 (n/a)	n/a		
No. past pregnancies	0.60 (0.39 to 0.91)	0.02	0.66 (0.43 to 1.00)	0.05
LEEP characteristics				
Pathology on LEEP specimen				
Less than CIN2+	1.00 (Ref)			
CIN2+	2.21 (0.29 to 16.86)	0.45		
Microinvasive cancer	4.00 (0.36 to 44.31)	0.26		
Lesion size >2.5 cm	2.04 (0.74 to 5.64)	0.17		
HIV-related characteristics				
Time since HIV diagnosis (mo)	1.00 (0.97 to 1.02)	0.99		
Most advanced WHO stage				
Stage 1	1.00 (Ref)			
Stage 2	2.73 (0.54 to 13.72)	0.22		
Stage 3	1.91 (1.65 to 9.89)	0.44		
Stage 4	7.96 (1.64 to 38.54)	0.01		
Time-dependent HIV-related variables				
On HAART at follow-up visit	2.66 (0.78 to 9.12)	0.12	0.57 (0.10 to 3.31)	0.53
HAART regimen switch before recurrence	1.22 (0.16 to 9.62)	0.85		
$CD4^+$ count at visit				
<200	4.81 (1.85 to 12.52)	<0.01		
201–350	1.39 (0.37 to 5.19)	0.63		
>350	1.00 (Ref)			
$CD4^+$ count nadir†				
<200	4.08 (1.31 to 12.68)	0.01	8.32 (1.22 to 56.87)	0.03

	Age-Adjusted Models		Multivariate Model: HAART and Predictors (N = 206)	
	HR (95% CI)	***P***	**AHR (95% CI)**	***P***
201–350	2.26 (0.56 to 9.14)	0.25	3.19 (0.42 to 24.35)	0.26
>350	1.00 (Ref)		1.00 (Ref)	

*Participants were recruited from 3 sites within the FACES program: Lumumba health center HIV, Kisumu District Hospital, and from a couples HIV prevention study. Clinical and demographic characteristics did not differ among study sites (data not shown).

†$CD4^+$ nadir defined as lowest $CD4^+$ recorded before recurrence visit and/or before initiation on HAART among HAART users.

AHR, adjusted hazard ratio; HR, hazard ratio.