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Outcomes after an excisional procedure for cervical intraepithelial neoplasia in HIV-infected women

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Abstract

Objective—To determine predictors of treatment failure and recurrence after surgical excisional procedures for CIN in HIV-infected women.

Methods—A retrospective cohort study was conducted in which 136 eligible HIV-infected women treated for CIN between 1999 and 2005 were included. Data were abstracted from charts and computer databases. Treatment failures were defined as the presence of CIN 1+ at initial follow-up. Recurrences were defined as the presence of CIN 1+ subsequent to initial normal follow-up.

Results—Treatment failure at initial follow-up was common, occurring in 51% of CIN 1 and 55% of CIN 2+. Most lesions detected at treatment failure were high grade (>70%), regardless of the grade of initial lesion. Significant risk factors for treatment failure were loop electrosurgical excision procedure (LEEP) compared to cold knife conization (RR=1.76; 95% CI: 1.15–2.64), and low CD4+ count ($p = 0.04$). Among those with an initial normal clinical evaluation, 55% eventually recurred. As with treatment failure, most lesions detected at recurrence were high grade. Risk factors for recurrence included use of LEEP (hazard ratio [HR] = 3.38; 95% CI: 1.55–7.39), higher HIV RNA level, and the presence of positive margins at treatment (HR = 6.12; 95% CI: 1.90–19.73).

Conclusions—Most CIN treatment of HIV-infected women studied either failed or resulted in recurrence. Of particular concern, many of these subsequent lesions were high grade. Conization, however, was associated with significantly less failure/recurrence than LEEP. Clinicians treating CIN in HIV-infected women should avoid raising expectations of cure and instead focus on the achievable goal of cancer prevention until there are better therapies for this patient population.

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Conflicts of interest statement

The authors declare that there are no conflicts of interest.

Keywords

Cervical intraepithelial neoplasia; HIV; Cervical conization; Loop electrosurgical excision procedure; LEEP

Introduction

Compared with immunocompetent women, HIV-infected women have high risk of cervical cancer [1] and cervical intraepithelial neoplasia (CIN) [2–5], as well as infection by human papillomavirus (HPV), the viral cause of cervical cancer and most CIN [6,7]. Further, the treatment of CIN in HIV-infected women often fails, and even after successful treatment of CIN in HIV-infected women, the lesions frequently recur [7–14]. This is in contrast to the high success of LEEP in immunocompetent women, where cure is common, not just cancer prevention. There are surprisingly limited data regarding the risk factors for CIN treatment failure and recurrence in HIV-infected women, and few data regarding the grade of neoplasia of the subsequent lesions after LEEP or cold knife conization in HIV-infected women.

In the few prior studies of HIV-infected women, the significant predictors of CIN treatment failure and recurrence included lowCD4⁺ T-cell count [10,13,15,16] and the presence of positive margins [4,13,16,17]. Only one study to our knowledge examined the grade of neoplasia detected at treatment failure and recurrence, and it reported that most of these lesions were low grade [8]. However, most of these early reports were based on observational or clinical cohorts, and the extent to which such data can be generalized to the broader population of HIV-infected women is unclear. In the current study, therefore, we conducted a retrospective study of unselected, sequential HIV-infected patients who presented for CIN treatment at either of two hospital systems, serving the same surrounding community, in the Bronx, NY.

Materials and methods

Study participants

After IRB approval, we searched electronic records to identify all HIV-infected women who had an extirpative procedure for CIN between 1999 and 2005, using the computerized database and informatics systems at Montefiore Medical Center (MMC) and Jacobi Medical Center (JMC); hospitals that serve an ethnically and racially diverse Bronx population. Relative to the United States as a whole, New York City has a high proportion of women infected with HIV [18], with similarly high rates of CIN and cervical cancer. Follow-up data were then obtained through further review of the medical records documented in the electronic medical records and patient charts.

Histopathologic, cytologic, and colposcopic follow-up data were recorded to assess associations with CIN treatment failure and recurrence. Abstracted data also included demographic, as well as known risk factors for cervical disease, such as smoking status, parity, use of hormone contraceptives, and diagnosis of other sexually transmitted infections. Use of highly active anti-retroviral therapy (HAART) was classified based on the medications listed in patients' chart upon review.

CD4 T-cell count and HIV RNA level in our models were the most recent values documented within ± 8 weeks from procedure date. Consistent with prior studies, we stratified CD4⁺ T-cell count >500 cells/ μ L, 201–500 cells/ μ L, and ≤ 200 cells/ μ L. HIV RNA

level was also divided into three previously reported categories, namely, undetectable, detectable at 20,000 copies/mL, and detectable at >20,000 copies/mL.

The LEEP or cone specimens were used to define initial patient diagnosis. The choice of procedure, LEEP versus cone was based on provider preference and standard clinical factors such as lesion size and concerns for margins. Included subjects were all who had LEEP or cone biopsies during this defined time period. Currently, treatment guidelines for persistent CIN 1 in HIV are not clearly defined; there is some debate as to the appropriateness of treating CIN 1 in HIV-positive patients. However, in this patient population, treatment for persistent CIN 1 in HIV occurred and was thus included in this analysis. We conservatively defined treatment failure and recurrence as the presence of CIN 1+. Exclusions included women who underwent a hysterectomy and patients with a second procedure immediately following the first due to concerns for a microinvasive or invasive cervical cancer. Other exclusions included women who had no signs of CIN on procedure biopsy and women lacking follow-up data after the procedure. Also, women who required more aggressive management such as those diagnosed with adenocarcinoma in situ, invasive squamous cell carcinoma, or adenocarcinoma diagnosed from their LEEP or cone were excluded.

Statistical analysis

Log-binomial regression was used to evaluate the association of each patient characteristic (age, etc.) and risk factor (CD4 count, viral load, etc.) separately with treatment failure, in which treatment failure was conservatively defined as the presence of CIN 1+ at initial follow-up after the procedure [8,19]. In most cases, the time from initial follow-up to failure occurred within 1 year after the procedure.

Multivariate log-binomial regression was used to include multiple patient characteristics and risk factors in the regression model. The final multivariable model was constructed using variables that had an association of $p < 0.1$ in the univariate analysis while controlling for age at procedure. Data are presented as relative risks with 95% confidence intervals (for categorical and ordinal variables) or as p values (for continuous variables). Ordinal variables (e.g., CD4⁺ T-cell strata) were evaluated for linear trend by parameterizing these strata as a continuous variable in the model. For example, 1 = CD4⁺ T-cell count >500 cells/ μ L, 2 = CD4⁺ 201–500 cells/ μ L, and 3 = CD4⁺ $\leq$ 200 cells/ μ L.

Recurrence of CIN was defined as the presence of CIN 1+ subsequent to an initial normal follow-up. The time to recurrence was calculated as the period between the date of CIN treatment and the date the recurrence of CIN 1+ was first detected. However, because patients were followed every several months, the exact time of the recurrence was not observed. We only know that the recurrence happened during a particular interval if recurrence was diagnosed on the latter of consecutive visits. To address this issue, a lifetime regression model allowing interval censoring and right censoring, in which patients who did not recur during follow-up were right censored, was used; assuming a Weibull distribution for time to CIN recurrence [20]. Covariates in recurrence analysis were assigned their value at time of procedure. A $p < 0.05$ was considered statistically significant in all analyses. All statistical analyses were performed using SAS version 9.1.3 (SAS Institute, Cary, NC).

Results

The electronic records included 191 HIV-infected women who had an extirpative procedure for CIN at either Montefiore Medical Center or Jacobi Medical Center during 1999–2005. Of these women, 136 were eligible based on our defined inclusion criteria. Exclusions included women who had a hysterectomy ($n=13$), women classified as having a normal histopathology at the time of their LEEP or cone ($n=10$), women with adenocarcinoma in

situ, squamous cell carcinoma, or adenocarcinoma from their LEEP or cone ($n=5$), and patients who underwent a second procedure immediately following the first due to concern for microinvasive or invasive cancer ($n=9$). An additional 18 women with no documented follow-up were excluded from the analyses. Patient characteristics are shown in Tables 1a and 1b. A similar number of subjects were obtained from both medical centers, and the rate of CIN treatment failure was also similar at these two sites ($p=0.45$). The mean age at the time of CIN treatment was 39 years, with the majority of women classified as African American (47.5%). Of note, most of the women had previously reported having had a sexually transmitted infection (STI) other than HIV (55%).

Initial treatment failure

Treatment failure occurred in 31 (51%) of 61 CIN 1 (see Fig. 1) and 41 (55%) of 75 CIN 2+ (see Fig. 2). As might be expected, women with >6 months until their initial follow-up appeared to have a higher rate of treatment failure (55% of CIN 1 and 76% of CIN 2+) compared with those assessed in ≤ 6 months (49% and 56%, respectively). Time to first follow-up, therefore, was a variable incorporated into our multivariate models (see Table 2).

CIN treatment failure occurred in 27 (71%) of 38 women with CD4 ≤ 200 cells/ μ L, 32 (57%) of 56 with CD4 201–500, and 4 (20%) of 20 with >500 cells/ μ L. Most of the lesions detected at treatment failure were high grade (>70%), regardless of the grade of lesion at the time of treatment. In multivariate models, CD4 ≤ 200 cells/ μ L (relative risk [RR]=2.93; 95% confidence intervals [CI]: 1.06–8.11) was associated with significantly increased risk of CIN treatment failure compared with CD4 >500 cells/ μ L, and the risk increased monotonically with diminishing CD4 count ($p_{\text{trend}} < 0.001$). HAART use, however, was not significantly associated with risk of treatment failure, even in univariate analysis. The only other significant variable was the use of LEEP versus conization (RR=1.76; 95% CI: 1.17–2.64). Positive tissue margins following treatment and race/ethnicity were significant risk factors in univariate but not in multivariate models.

Recurrence after initial treatment success

Of the 56 women who initially had treatment success, 31 (55%) experienced recurrence of CIN (see Figs. 1 and 2). Eight patients had no further follow-up after their initial postprocedure follow-up. Among the 26 CIN 1 and 30 CIN 2+ patients with an initial normal clinical evaluation and appropriate follow-up, 65% and 47% recurred, respectively. In both groups, recurrence was high grade (CIN 2+) in 22 (71%) of 31 patients. Even among women with clear margins (data not shown), there was an overall higher recurrence rate among the CIN 2+ population.

The risk of recurrence was significantly associated with host immune status as measured by HIV RNA level. Specifically, the hazard ratio (HR) for recurrence among women with HIV RNA level >20,000 copies/mL (hazard ratio [HR]=6.32; 95% CI: 2.22–17.94; Table 3) was higher compared with those who had undetectable levels. However, there was no monotonic trend to these results, nor was CD4 T-cell count or use of HAART associated with risk of recurrence. Significant risk factors included the presence of positive tissue margins involving both the endocervical and ectocervical tissue (HR=6.12; 95% CI: 1.90–19.73) and the use of LEEP versus conization (HR=3.38; 95% CI: 1.55–7.39). Women who underwent a LEEP had a median recurrence time of 33 months, whereas women who underwent a conization had a median time of recurrence of 81 months.

Discussion

Failure and recurrence following excisional procedures in our retrospective cohort of HIV-infected women with CIN were very high and were particularly high in patients with poorly controlled HIV, women who had a LEEP instead of conization, and women with positive tissue margins following treatment. The rates of treatment failure were similar to those reported in other captured patient cohort studies, but our rates of recurrence was higher [7,8,11,13,15,16,21]. Moreover, most lesions diagnosed in our patient population that were detected at treatment failure or recurrence were high-grade CIN. This is in contrast to findings of a recent observational cohort study, which found most treatment failures and recurrences were low grade [8]. The reason for these differences is unknown. However, a difference in the characteristics of the unselected subjects in the current study and those of the volunteer subjects in that prior observational cohort (e.g., a higher rate of concurrent STI) [8] is one possible explanation. In any event, the high rates of CIN 2+ at the time of treatment failure and recurrence we observed are concerning and provide a rationale for careful and frequent follow-up of HIV-infected women after treatment of CIN. This frequency should also likely increase, or continue to remain frequent with worsening HIV status. Also, even CIN 1 is relevant in the setting of HIV since this requires regular, frequent follow-up. Until better therapies are available, clinicians who treat cervical dysplasia in HIV-infected women should avoid raising expectations of cure and instead focus on the achievable goal of cancer prevention.

The other major finding was the superiority of cervical conization to LEEP in treatment of CIN in our population. This included lower risk of treatment failure as well as a lower risk of recurrence over time. It is possible the lower risk is due to an often smaller resection in a LEEP when compared to a cone, but the size of the biopsy was not available for this analysis. Previous studies have shown that the length and weight, as well as the general size of specimen, are often less in a LEEP than in a conization [22,23]. In our population, negative endocervical and ectocervical margins were found in 60% of conizations versus 31% of LEEPs, suggesting less of the lesion was completely removed in a LEEP than in a conization. In women who underwent a LEEP, but had positive endocervical and ectocervical margins, only 32% of the positive margins were positive for CIN 2+. Most of these positive margins were found to be koilocytosis, low-grade dysplasia, or CIN 1, as is typical for an general HPV effect in these often persistently HPV-infected women. Fewer short-term side effects and office availability without the need for an operating room have prompted surgeons to choose a LEEP over a conization; however, women may ultimately have to return for re-treatment. In prior studies, researchers found no significant differences between excisional treatments [24,25], and in a population of HIV-infected women, researchers also found no difference between treatment type [13]. A recent study found similar results as ours where loop excision was inferior to conization; however, the investigators saw no difference in margin positivity between the two treatment types [21]. Because of the potential importance of these results, further study of LEEP versus conization in this patient population is warranted.

Given that type of procedure is provider-directed, bias was potentially introduced. However, generally cones have been chosen or were preferred to a LEEP for lesions that were larger, to ensure complete excision or due to margin concerns. Thus, our analysis should not have been affected by provider preference and further supports that LEEPs are an inefficient excisional procedure in the setting of HIV. Since LEEPs often fail and/or recur even when there are smaller lesions, or persistent CIN 1. Additional bias could have been introduced with the number of women who were lost to follow-up; however, we feel that given the similarity in diagnosis and histopathology between those women and the subjects remaining in the cohort, the chance of these patients affecting the overall analysis is slight. Along with

loss to follow-up, another limitation of our study is that the time between follow-up visits varied for each woman, as is typical in observational cohorts. The interval analysis, however, allowed us to take these follow-up variations into account.

It is worth noting that the relationship of CD4 T-cell count with treatment failure was stronger than its relationship with CIN recurrence. This helps point to an important limitation of the current study. Both the CD4 and HIV RNA levels were based on the values obtained at time of procedure. Therefore, these values may be less representative of each patient's immune status over increasing time of follow-up. When longer follow-up periods are involved, this aspect is more likely to affect our analysis of recurrence. These same concerns probably affected our analysis of HAART use. Further, since the HAART use data found in patients' records was based on self-report, our analysis of HAART was also subject to misclassification. Recently, reported data regarding adherent HAART use suggest that HAART has a beneficial effect on control of both HPV and cervical dysplasia [26].

Despite these weaknesses, our study has an important strength that cannot be addressed in carefully followed voluntary prospective cohorts where subjects usually have more time with providers, more support staff, and are often reimbursed for added time and travel expenses. Our study may provide results that are more representative of outcomes in the real-world situation that clinicians face with HIV-infected women with dysplasia. This includes barriers to regular follow-up, variation in patient compliance, including treatment for sexually transmitted infections, as well as other high-risk behaviors that may be less prevalent in subjects who remain in long-term cohort studies.

Overall, the current study reports provocative results suggesting that in HIV-infected women who are not volunteers in long-term observational or clinical cohorts: treatment of CIN often fails; even after initial successful treatment of CIN often recurs; and that a substantial fraction of CIN at treatment failure and recurrence may be high grade. Furthermore, cold knife conization may be more effective than a LEEP in treating CIN in HIV-infected women. Larger, more comprehensive retrospective cohort studies of high-risk HIV-infected women are, therefore, greatly needed.

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Fig. 1.
Time to failure and recurrence among 61 HIV-infected women treated for CIN 1 who came for initial follow-up before (top group) or after (bottom group) 6 months.

Fig. 2.
Time to failure and recurrence 75 HIV-infected women treated for CIN 2+ who came for initial follow-up before (top group) or after (bottom group) 6 months.

Table 1**Table 1a Characteristics of 136 patients in our population-based study.**

Characteristics	N/Total	%
Montefiore Medical Center	57/136	41.9
Jacobi Medical Center	79/136	58.1
Age at procedure		
<30	24/136	17.7
30–45	80/136	58.8
>45	32/136	23.5
Race		
Black	56/118	47.5
White	10/118	8.5
Hispanic	36/118	30.5
Other	16/118	13.6
Current smoker		
Yes	71/106	67.0
No	35/106	33.0
Intravenous drug use		
Yes	21/99	21.2
No	78/99	78.8
Parity		
Multiparous	44/48	91.7
Nulliparous	4/48	8.3
Ever had an STD		
Yes	67/121	55.4
No	54/121	44.6
Current hormone contraceptive use		
Yes	6/29	20.7
No	23/29	79.3
Missed appointments		
Rarely (0–3)	39/89	43.8
Frequently (3+)	50/89	56.2
Current HAART use		
Yes	57/111	51.4
No	54/111	48.7

Table 1b Procedure and pathologic information for population-based study.

Characteristics	N/Total	%
First procedure type		
LEEP	93/136	68.4
Cone	43/136	31.6
Procedure biopsy		
CIN 1	61/136	44.9

Table 1b Procedure and pathologic information for population-based study.

Characteristics	N/Total	%
CIN 2	47/136	34.6
CIN 3	28/136	20.6
Margin status (endo- and ectocervical)		
Both positive	20/117	17.1
Either positive	49/117	41.9
Both negative	48/117	41.0
CD4 count at time of procedure (± 8 weeks)		
≤ 200 cells/ μ L	38/114	33.3
201–500 cells/ μ L	56/114	49.1
> 500 cells/ μ L	20/114	17.5
Viral load at time of procedure (± 8 weeks)		
Undetectable	55/122	45.1
Detectable –20,000 copies/mL	35/122	28.7
$> 20,000$ copies/mL	32/122	26.2

Table 2

Univariate and multivariate analyses of failure after extirpative procedure.

Characteristics	Univariate analysis			Multivariate analysis		
	RR	95% CI	p	RR	95% CI	p
Age at procedure (years)						
<30	1.05	(0.70–1.57)	0.81	0.94	(0.60–1.47)	0.79
30–45	1.17	(0.72–1.89)	0.53	1.01	(0.73–1.40)	0.94
>45	1.00	–	–	1.00	–	–
Ethnicity						
African American	1.78	(1.11–2.87)	0.02	1.47	(0.93–2.34)	0.10
Caucasian	1.94	(1.07–3.51)	0.03	1.63	(0.94–2.85)	0.08
Hispanic	1.00	–	–	1.00	–	–
Other	1.73	(0.97–3.08)	0.06	1.50	(0.79–2.82)	0.21
Current smoker	0.75	(0.54–1.05)	0.09			
Intravenous drug use	1.09	(0.71–1.66)	0.70			
Parity (multiparous vs. nulliparous)	1.09	(0.39–3.01)	0.87			
Ever had an STI	1.16	(0.83–1.63)	0.37			
Current hormone contraceptive use	0.82	(0.35–1.95)	0.66			
Missed appointments						
Rarely (0–3)	1.00	–	–			
Frequently (3+)	1.23	(0.86–1.75)	0.26			
Current HAART use	0.98	(0.71–1.35)	0.89			
Time to first follow-up						
≤6 months	1.00	–	–	1.00	–	–
>6 months	1.44	(1.07–1.96)	0.02	1.13	(0.82–1.54)	0.46
Result of LEEP/cone specimen						
<CIN 2	1.00	–	–			
≥CIN 2	1.08	(0.78–1.48)	0.66			
Procedure type						
LEEP	1.39	(0.94–2.05)	0.10	1.76	(1.17–2.64)	0.007
Conization	1.00	–	–	1.00	–	–
Margin status (endo- and ectocervical)						

Characteristics	Univariate analysis			Multivariate analysis		
	RR	95% CI	p	RR	95% CI	p
Both positive	1.98	(1.23–3.19)	0.01	1.23	(0.77–1.91)	0.35
Either positive	1.73	(1.11–2.69)	0.02	0.99	(0.66–1.48)	0.97
Both negative	1.00	–	–	1.00	–	–
CD4 count at time of procedure (± 8 weeks)						
≤200 cells/ μ L	3.55	(1.44–8.74)	0.006	2.93	(1.06–8.11)	0.04
201–500 cells/ μ L	2.86	(1.16–7.07)	0.02	2.23	(0.79–6.29)	0.13
>500 cells/ μ L	1.00	–	–	1.00	–	–
Viral load at time of procedure (± 8 weeks)						
Undetectable	1.00	–	–			
Detectable –20,000 copies/mL	1.12	(0.76–1.65)	0.56			
>20,000 copies/mL	1.17	(0.79–1.72)	0.44			

All significant *p*-values (*p*<0.05) were italicized.

Table 3

Univariate and multivariate analyses of recurrence after extirpative procedure.

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	p	HR	95% CI	p
Age at procedure (years)						
<30	1.39	(0.46–4.18)	0.56	0.28	(0.10–1.29)	0.07
30–45	1.33	(0.52–3.37)	0.55	1.84	(0.36–1.98)	0.77
>45	1.00	–	–	1.00	–	–
Ethnicity						
Black	0.63	(0.23–1.71)	0.34			
Caucasian	0.70	(0.14–3.62)	0.66			
Hispanic	–	–	–			
Other	1.00	(0.28–3.53)	1.00			
Current smoker	0.49	(0.22–1.11)	0.09			
Intravenous drug use	0.49	(0.10–2.29)	0.34			
Parity (multiparous vs. nulliparous)	1.04	(0.09–11.70)	0.97			
Ever had an STI	1.74	(0.80–3.77)	0.16			
Current hormone contraceptive use	2.74	(0.41–18.30)	0.28			
Missed appointments						
Rarely (0–3)	1.00	–	–			
Frequently (3+)	1.49	(0.78–2.86)	0.21			
Current HAART use	0.84	(0.38–1.84)	0.67			
Time to first follow-up						
≤6 months	1.00	–	–			
>6 months	0.81	(0.36–1.81)	0.61			
Procedure type						
LEEP	3.26	(1.52–7.00)	0.005	3.38	(1.55–7.39)	0.02
Conization	1.00	–	–	1.00	–	–
Margin status (endo-and ectocervical)						
Both positive	3.85	(1.22–12.27)	0.03	6.12	(1.90–19.73)	0.03
Either positive	2.07	(0.94–4.60)	0.09	2.58	(0.16–6.16)	0.12
Both negative	1.00	–	–	1.00	–	–

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	p	HR	95% CI	p
CD4 count at time of procedure (±8 weeks)						
≤200 cells/μL	1.47	(0.44–4.95)	0.53			
201–500 cells/μL	0.74	(0.30–1.86)	0.52			
>500 cells/μL	1.00	–	–			
Viral load at time of procedure (±8 weeks)						
Undetectable	–	–	–	–	–	–
Detectable –20,000 copies/mL	0.56	(0.21–1.50)	0.28	0.62	(0.26–1.48)	0.43
>20,000 copies/mL	1.89	(0.79–4.52)	0.18	6.32	(2.22–17.94)	0.01

All significant *p*-values (*p*<0.05) were italicized.