

Cervical Intraepithelial Neoplasia in a Cohort of HIV-positive Women at the University Hospital of the West Indies: Management and Outcome

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ABSTRACT

Objective: To determine the rate of recurrence of cervical intraepithelial neoplasia (CIN) in HIV-positive women evaluated at the University Hospital of the West Indies (UHWI).

Method: A chart review of all non-pregnant HIV-positive women who attended the gynaecologic and colposcopic clinics between January 1994 and December 2004 identified 21 such women. Fifteen of these patients who had CIN and had at least one follow-up Pap smear were the main subjects of this study. These patients were compared to 21 HIV-negative controls who were seen during the same period and who also had at least one follow-up Pap smear. Treatment modalities for the groups included cold coagulation and large loop excision of the transformation zone (LLETZ). Cox proportional hazards analysis was used to determine the effect of HIV status on the time to first recurrence of CIN.

Results: The mean ages of the subjects were 32.7 ± 8.0 and 33.2 ± 8.1 years, respectively. With a mean follow-up period of 1.7 years, the rate of recurrence of CIN in patients with and without HIV was 66.24 (95% CI 27.6, 159.1) and 3.0 (95% CI 1.3, 7.3) per 100 person years. The hazards rate ratio for recurrence in subjects with HIV after adjusting for age and CIN stage was 19.1 (95% CI 4.4, 82.1).

Conclusion: HIV increases the risk of recurrence of CIN.

Keywords: Cervical cancer, cervical intraepithelial neoplasia, HIV

Neoplasia Intraepitelial Cervical en una Cohorte de Mujeres VIH-positivas en el Hospital Universitario de West Indies: Manejo y Resultados

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RESUMEN

Objetivo: Determinar la tasa de recurrencia de la neoplasia intraepitelial cervical (NIC) en las mujeres VIH-positivas evaluadas en el Hospital Universitario de West Indies (HUWI).

Método: Una revisión de las historias clínicas de todas las mujeres VIH-positivas no embarazadas que asistieron a la clínica ginecológica y la clínica colposcópica entre enero de 1994 y diciembre de 2004, identificó 21 de estas mujeres. Quince de estas pacientes que tenían NIC y habían tenido al menos una prueba de Papanicolaou de seguimiento, fueron los sujetos principales de este estudio. Estas pacientes fueron comparadas con 21 controles de VIH-negativos que fueron vistos durante el mismo período y que también tuvieron al menos una prueba de Papanicolaou de seguimiento. Las modalidades de tratamiento para los grupos incluyeron coagulación fría y escisión con asa grande de la zona de transformación (LLETZ). El modelo de análisis de riesgos proporcionales de Cox fue utilizado para determinar el efecto del estatus de VIH al momento de la primera recurrencia de CIN.

Resultados: Las edades promedios de los sujetos fueron 32.7 ± 8.0 y 33.2 ± 8.1 años, respectivamente. Con un período de seguimiento promedio de 1.7 años, la tasa de recurrencia de NIC en pacientes con y sin VIH fue 66.24 (95% IC 27.6, 159.1) y 3.0 (95% IC 1.3, 7.3) por 100 persona/años. El cociente de tasas de riesgo de recurrencia en pacientes con VIH después de ajustar por edad y etapa de CIN fue 19.1 (95% IC 4.4, 82.1).

Conclusión: El VIH aumenta el riesgo de recurrencia de la NIC.

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Palabras claves: Cáncer de cuello uterino, neoplasia intraepitelial cervical, VIH

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INTRODUCTION

Women infected with HIV are at increased risk of developing pre-invasive cervical lesions and invasive cervical cancer (1) and they may have higher grades of cervical intraepithelial neoplasia (CIN) than HIV-negative women. As a result, in 1993, invasive cervical cancer was designated an AIDS-defining disorder by the US Centers for Disease Control and Prevention (2). The treatment of pre-invasive cervical disease in HIV-infected women is among the most challenging and frustrating tasks, as they often experience higher rates of recurrence (3).

OBJECTIVE

The objective of this study was to review the presentation, risk factors, treatment and rate of recurrence of CIN in HIV-positive women evaluated at the University Hospital of the West Indies (UHWI) colposcopic unit and gynaecology clinic, and to compare them with a group of HIV-negative women.

SUBJECTS AND METHOD

Charts for all non-pregnant female patients with HIV treated at the UHWI colposcopy clinic from 1994 to 2004 with cervical abnormalities were reviewed. For each subject, demographic data, social and sexual history, time of diagnosis of HIV, gynaecologic presentation for Pap smear, time of diagnosis of cervical abnormalities, presence of human papillomavirus virus (HPV) infection, use of antiretroviral therapy and CD4 counts were extracted.

Twenty-one HIV-positive women were identified; 15 of these patients were seen for cervical disorders and were the focus of this paper. These patients were matched according to stage of CIN, age and, when possible, parity, to women who were HIV negative. HIV infection was defined serologically from enzyme-linked immunosorbent assay (ELISA) and Western blot tests criteria (4). Cervical intraepithelial neoplasia and invasive cervical lesion were diagnosed by colposcopic biopsy and histology. Recurrence of CIN was determined by follow-up Pap smears and defined as low-grade or high-grade using the Bethesda System of Classification.

Statistical analysis

Statistical analysis was performed using Stata 8. Proportional hazards models were used to determine the effect of HIV status on the risk of recurrence of cervical lesions. Subjects were included in a prospective analysis if they had at least one follow-up visit. Subjects were followed up to the time of their first recurrence.

RESULTS

Age, parity, age at first sexual intercourse, HPV infection on Pap smear and history of cigarette smoking did not differ by much between women infected and not infected with HIV (Table 1).

Table 1: Sociodemographic characteristics and potential risk factors for CIN for HIV-positive women and controls (HIV-negative)

Sociodemographic characteristics	HIV-positive women n = 15	HIV-negative controls n = 21
Mean age \pm SD (years)	32.7 \pm 8.0	33.2 \pm 8.1
Mean age of coitarche \pm SD (years)	16.3 \pm 1.9	16.8 \pm 3.0
Parity (mean)	2	2
> 5 sexual partners (%)	10 (48)	9 (60)
Smoke	1 (6.7)	1 (4.8)
Antiretroviral (HAART) (%)	3 (20)	—
CD4 count < 200 (%)	3 (20)	—
CD4 count 200–500 (%)	3 (20)	—
Invasive disease (%)	1 (6.7)	1 (4.8)
HPV infection (%)	15 (100)	19 (90.5)
Recurrence of disease after treatment (%)	5 (26)	1 (4.8)
Died (%)	1 (6.7)	—

CIN – cervical intraepithelial neoplasia, SD – standard deviation, HAART – highly active antiretroviral therapy

The majority of the patients in each group were asymptomatic at presentation (67% and 81%) and cervical disease was discovered by a routine Pap smear. Other presentations are as seen in Table 2. One HIV-positive woman with ab-

Table 2: Gynaecologic presentation of the patients

Presentation	HIV-positive women (%) n = 15	HIV-negative controls (%) n = 21
Routine Pap smear	10 (67)	17 (81)
Vaginal discharge	2 (13)	1 (4.8)
Vulval warts	2 (13)	1 (4.8)
Abnormal vaginal bleeding	1 (6)	2 (9.5)

normal vaginal bleeding had invasive disease. Of the HIV-negative women with abnormal vaginal bleeding, one had cervical cancer and the other had CIN 1.

The most common cervical lesion was CIN 1 (60% and 52%) and abnormal Pap smear was the most common presentation for this lesion (62% and 72%). The incidence of high-grade lesions was not different between the groups (40% and 48%) [Table 3]. The mean age by CIN types was similar in both groups.

Table 3: Frequency and types of cervical abnormalities and age distribution

Cervical abnormality	HIV-positive (%) n = 15	Mean \pm SD age	HIV-negative (%) n = 21	Mean \pm SD age
CIN 1	9 (60)	32 \pm 9.0	11 (52)	30.6 \pm 8.6
CIN 2	2 (13)	33 \pm 2.6	4 (19)	33.6 \pm 4.3
CIN 3	3 (20)	38 \pm 9.6	5 (24)	39.5 \pm 8.0
Invasive lesion	1 (7)	34	1 (5)	36

HIV INFECTION AND CIN

HIV-positive women were analysed separately in a model that included date of HIV diagnosis to CIN presentation, antiretroviral therapy and CD4 lymphocyte count. The date of diagnosis of HIV was known for 13 of the 15 subjects who had chart review. The mean age at which a diagnosis of HIV was made was 30 \pm 7.9 years. Eight (62%) of the cohort were diagnosed with HIV prior to presentation. The mean time between HIV diagnosis and presentation was 4.2 \pm 2.3 years. Five (33.3%) were diagnosed with HIV at a mean of six months after presentation. The majority of the patients presented within two years of HIV diagnosis with CIN 1 (Table 4).

Table 4: Subjects by cervical intraepithelial neoplasia (CIN) diagnosis at presentation and relationship to HIV diagnosis (n = 13)

Cervical abnormality	Diagnosed with HIV prior to referral		Diagnosed with HIV after referral	
	Number of subjects	Time from diagnosis to presentation (years)	Number of subjects	Time from diagnosis to presentation (years)
CIN 1	4	4.5 \pm 2.5	3	0.2 \pm 0.2
CIN 2	2	3.9 \pm 2.6	1	0.6
CIN 3	2	4.1 \pm 3.7		
Invasive			1	1.1

Only three (20%) of the 15 patients were known to be on highly active antiretroviral therapy (HAART). Two patients had mild cervical dysplasia (CIN 1), the other had CIN 3. Most of the patients with low-grade lesions were not on antiretroviral therapy.

The CD4 count was known for six of the subjects. The CD4 count for three women was < 200 cells/ μ L; two had CIN 1 and one had CIN 2. For those with CD4 counts of 200–500 cells/ μ L, one subject each had CIN 1, CIN 2 and CIN 3.

The treatment options for both HIV-positive and controls were similar. These consisted mainly of cold coagulation (local ablative therapy) and large loop excision of the transformation zone [LLETZ] (Table 5).

Thirty subjects (11 HIV-positive and 19 HIV-negative) had at least one follow-up Pap smear. The mean follow-up time was 1.7 years. Five (45.5%) HIV-positive subjects had CIN recurrence (low-grade lesions) following therapy. One patient who had cold coagulation had recurrence of the same lesion in seven months and four patients who had LLETZ

Table 5: Treatment by cervical intraepithelial neoplasia (CIN) and HIV status

Treatment	HIV-positive n = 15	HIV-negative controls n = 20
Cold coagulation	4 (26.7%)	8 (38%)
LLETZ	9 (60%)	11 (52.4%)
Hysterectomy	2 (13.3%)	1 (4.8%)

LLETZ – large loop excision of the transformation zone

procedure had recurrence within 3–25 months. The rate of CIN recurrence was 66.2 per 100 person years in the HIV-positive women and 3.0 per 100 person years in the control group. The hazards rate ratio for recurrence in subjects with HIV after adjusting for age and CIN stage was 19.1 (95% CI 4.4, 82.1) [Figure].

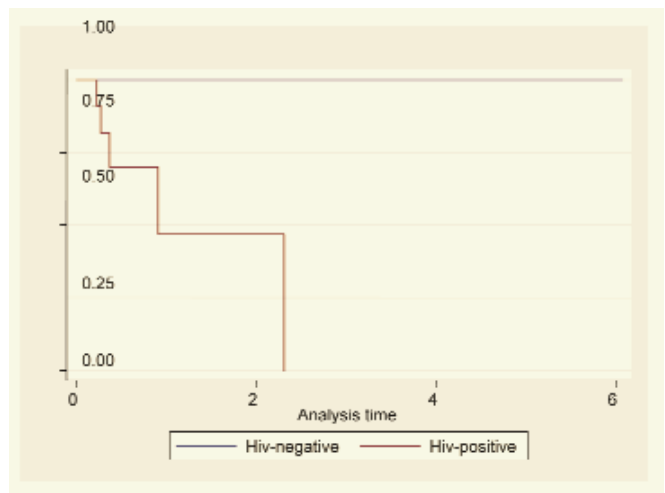


Figure: Kaplan-Meier survival curves of recurrence by HIV status.

The mortality rate for the HIV-positive subjects was 13.3% (2/15). One patient with CIN 3 and a three-year history of HIV infection died two years after treatment. The exact cause of her death was not ascertained from the chart. The second death occurred in a patient who was diagnosed with HIV one year after she was discovered to have invasive cervical cancer. She had radical hysterectomy performed, but died four years after presentation. There were no deaths recorded for the controls during the follow-up period.

DISCUSSION

It has been reported that HIV-positive women have as much as a 10-fold increased rate of abnormal cervical cytology, including a wide range of cellular and inflammatory changes, such as hyperkeratosis parakeratosis, trichomonas, herpes, inflammatory atypia, HPV-related changes and varying degrees of cervical neoplasia (4). Higher rates of abnormalities have been demonstrated after seroconversion than before seroconversion. Studies from several centres have shown that women who are immunodeficient from HIV infection have cytological abnormality rates between 30% and 60% (5) and Pap smears consistent with dysplasia from 15% to 40% (6). In this study, 71% of the HIV-infected women seen at the clinics had cervical dysplasia. Most studies have consistently demonstrated that the prevalence of these abnormalities increases as immunodeficiency becomes more severe. As a result, the Centers for Disease Control and Prevention (CDC) recommend Pap smear screening in women with HIV every six months (7).

Given the large number of women living with HIV/AIDS in Jamaica, it is interesting to note that very few patients were referred to the UHWI colposcopy clinic. This could possibly be due to the low rate of Pap smear screening done on these patients. In the present study, the majority of the HIV-positive subjects were seen with cervical dysplasia after a routine Pap smear and the degree of dysplasia was mild, although this presentation was not statistically different from the controls.

There were statistical differences between the groups and associated risk factors for CIN. However, patients who had more sexual partners had more severe dysplasia than those with less sexual partners across the groups and this was independent of HIV status. This relationship between sexual partners and severity of dysplasia correlated with the findings of Bazuaye *et al* (8). In their study, which looked at lifestyle factors and sexual practices and the development of cervical dysplasia in women with abnormal Pap smear (236) and those without cervical abnormality (102), they found that parity and number of sexual partners were independent risk factors for high-grade cervical dysplasia. In their multivariate analysis, after controlling for age, number of sexual partners remained significant. The present study did not find parity to be a risk factor but this could be related to the sample size. Smoking and early age at first intercourse are associated with the disease in other populations (9). Both the cases and controls had similar rates of HPV infection on Pap smear. Natural history studies examining the biologic behaviour of cervical HPV and CIN strongly suggest that the disease is more aggressive in HIV-positive patients.

The median time of presentation of CIN after HIV diagnosis was similar to the finding of Conley *et al* (10). In their study, they found a median time of 25 months (range 5–68 months) to develop cervical lesions after follow-up of HIV subjects twice yearly with a mean follow-up time of 3.2 years.

The present study only found one HIV-positive patient with invasive cervical cancer (stage 1B), who had radical hysterectomy but died four years after diagnosis. The patient with invasive cervical lesion in the control group is still alive after four years of diagnosis. Although much of the data so far have been limited to case reports and single institution studies, it seems apparent that in some HIV-infected women, the disease characteristics may take a more aggressive clinical course (11). In the largest study to date at the SUNY-Health Science Center, Brooklyn in the United States of America, comparing 16 seropositive to 68 seronegative women, significantly more advanced disease was found in the HIV-positive women (11). Half of the seropositive patients presented with stage 3 or 4 diseases, compared with 19% in seronegative controls. Most importantly, the majority of the patients died of cervical cancer before they died of AIDS and were usually asymptomatic with regard to HIV. In that same study, the median time to death was found to be 10 months in seropositive women compared with 23 months in seronegative patients.

The treatment of CIN was similar for both cases and controls. However, the HIV-positive patients had recurrences compared to one in the controls. Treatment of pre-invasive cervical disease in HIV-positive women is among the most challenging tasks faced by the gynaecologists. Excisional methods are preferred over ablated therapy. Del Priore *et al* (12) reported that colposcopically directed biopsies may be poor predictors of histology on excisional cone specimens in HIV-seropositive women since 47% with CIN 2–3 on cone biopsy had only CIN 1 or HPV on punch biopsy compared with only 9% in HIV-negative patients. Even though some subjects in the present study with CIN were treated by excisional therapy in cases where there were discrepancies between the colposcopy findings and histology of the punch biopsy, the recurrence rate was almost twice as high for those treated by excisional methods than those treated by ablative methods. This is contrary to findings in other populations. In one study, 48% of HIV-infected women with low-grade CIN developed recurrence compared with 1% of seronegative women (13). The only confounder in the present study was the CD4 T lymphocyte counts, as 27% of those with counts less than 200 cells/mm³ and who had LLETZ procedure had recurrences. Recurrence rate for CIN in HIV-positive women with standard therapies have been reported to be as high as 40% at one year and 60% with longer follow-up (13). Wright *et al* (14) and Del Priore *et al* (15) reported recurrences of 39% and 40%, respectively, compared with 9% and 10% in seropositive controls. Fruchter *et al*, at 36 months, reported a 62% failure rate compared with 18% in control subjects, and an 87% failure rate in patients with CD4 less than 200/mm (3).

In response to the high rates of treatment failures for pre-invasive cervical disease in HIV-positive women, the AIDS Clinical Trials Group (ACTG) is investigating novel therapeutic approaches (16). For patients with high-grade

dysplasia, ACTG recommends the use of topical vaginal fluorouracil cream as maintenance therapy and prophylaxis against recurrent CIN.

The limitations of this study were largely related to the sample size and therefore trends were difficult to pick up. The evaluation of risk factors was limited to the data available in the charts reviewed; a larger cohort of patients and longer follow-up would allow further evaluation of factors related to recurrences and survival.

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