International Journal of Women's Health

Dovepress
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ORIGINAL RESEARCH

Prevalence and risk factors for cervical squamous intraepithelial lesions among women infected with HIV-1 in Makurdi, Nigeria

This article was published in the following Dove Press journal:
International Journal of Women's Health
13 February 2012
Number of times this article has been viewed

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Background: The purpose of this study was to determine the prevalence and risk factors for cervical squamous intraepithelial lesions (SIL) among women infected with human immunodeficiency virus type 1 (HIV-1) receiving care at the Federal Medical Center Makurdi, Nigeria.

Methods: Between March and December 2009, a total of 253 women infected with HIV-1 had cervical smears taken for cytology. HIV-1 RNA viral load and CD4 counts were also measured.

Results: Of the 253 women, cervical SIL were present in 45 (17.8%). However, abnormal cervical cytology was noted in 146 (57.7%). Of those with abnormal cervical cytology, 101 (39.9%) women had atypical squamous cells of undetermined significance, 16 (6.3%) had low-grade SIL, and 29 (11.5%) women had high-grade SIL. The median CD4 lymphocyte count was lower in participants with cervical SIL compared with those without (132 versus 184 cells/mm^3; $P = 0.03$). The median HIV-1 RNA viral load was higher in women with cervical SIL (102,705 versus 64,391 copies/mL; $P = 0.02$). A CD4 lymphocyte count of <200 cells/mm^3 and an HIV-1 RNA viral load of $<10,000$ copies/mL were found to be significantly associated with cervical SIL.

Conclusion: A high prevalence of cervical SIL was found among HIV-1-infected women in Makurdi, Nigeria. Increased immune suppression and HIV-1 viremia are significantly associated with cervical SIL.

Keywords: cervical squamous intraepithelial lesions, human immunodeficiency virus, risk factors, immunosuppression, cervical dysplasia, Nigeria

Introduction

Cancer of the uterine cervix is the second most common cancer among women worldwide, with an estimated 493,000 new cases in 2002[1,2] and over 250,000 deaths in 2005.[3] Without urgent action, deaths from cervical cancer are projected to rise by almost 25% over the next ten years.[3] Therefore, cervical cancer presents a serious global problem.[2] Over 80% of cases of cervical cancer occur in developing countries where it represents the commonest malignancy affecting women.[4,5] In Nigeria, it is the commonest cancer of the female genital tract.[6] Most women who die from cervical cancer, particularly in developing countries, are in the prime of their life. They may be raising children, caring for their family, and contributing to the social and economic life of their town or village. Their death is both a personal tragedy and a sad and unnecessary loss to their family and their community.[3]

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Invasive cancer of the cervix is considered to be a preventable condition, given that it is associated with a long preinvasive stage, making it amenable to screening and treatment as long as it is detected early and managed effectively.[3,7] Cancer of the cervix has been classified as an acquired immune deficiency syndrome (AIDS) defining cancer by the US Centers for Disease Control and Prevention.[8] Unfortunately, the global human immunodeficiency virus (HIV) epidemic continues to expand, with about five million people becoming infected each year and an estimated 39.5 million people living with HIV at the end of 2006.[9,10] With an estimated 2.95 million people living with HIV in Nigeria in 2008, Nigeria ranks as one of the countries with the highest burden of HIV infection in the world, next only to India and South Africa.[11] Over the decades, the epidemic, once dominated by infected males, has become progressively feminized. In sub-Saharan Africa, where about two-thirds of the global disease burden occurs, 57% of adults living with HIV are women.[12] As more women contract the virus, the risk of cervical squamous intraepithelial lesions (SIL) or cervical intraepithelial neoplasia and ultimately cervical cancer increases.[13]

Despite the fact that HIV infection and cervical cancer constitute a major reproductive health challenge in Nigeria and Africa, only a few studies have investigated the relationship between HIV infection and cervical SIL. Both CD4 lymphocyte count and HIV RNA viral load are independent predictors of the course of HIV/AIDS, and the frequency of occurrence and severity of cervical SIL in HIV-infected women increase as the CD4 count declines.[14] However, the role of HIV RNA viral load and antiretroviral therapy regarding the risk of cervical SIL has not been satisfactorily established. This study aimed to determine the prevalence of cervical SIL among a cohort of women infected with HIV-1 and to identify its relationship with risk factors, CD4 cell count, and HIV-1 RNA levels in Makurdi, north central Nigeria.

Materials and methods

The Federal Medical Center Makurdi, is situated in Benue State, a low resource setting with the highest burden of HIV infection (seroprevalence 10.6%) in the Nigerian federation.[11] The HIV care clinic of the center, located on the banks of the River Benue, is a regional reference center for comprehensive treatment and support of people living with HIV. This study was approved by the research ethics committee of the Federal Medical Center Makurdi in October 2008. After detailed explanation of the study and clinical procedures, all 253 participants provided their written consent in English and pretested translations of the local languages for illiterate women. Consecutive nonpregnant clients were recruited into the study between March and December 2009. Other eligibility criteria included documented evidence of HIV-1 infection by Western blot (Immunetics Inc, Boston, MA) and current absence of acute illness. Excluded from the study were clients who declined to participate, pregnant women (from menstrual history), women in the puerperium, women with obvious genital tract lesions and infection (referred for appropriate treatment), and those with a prior history of treatment for preinvasive and invasive cervical neoplasia.

Demographic data were collected using a pro forma, and included age, parity, marital status, number of lifetime sexual partners, history of tobacco smoking, and previous sexually transmitted infection. History of use of highly active antiretroviral therapy (HAART) was obtained and verified from client records. All study participants on HAART during the study period were on a regimen consisting of two nucleoside reverse transcriptase inhibitors (stavudine or zidovudine and lamivudine) and one non-nucleoside reverse transcriptase inhibitor (nevirapine or efavirenz). All patients on HAART were receiving first-line drugs according to national guidelines. None of the clients recruited were on second-line drugs.

The CD4 count was measured using flow cytometry (Cyflow; Partec, Germany) and reported as cells per cubic milliliter of blood (cells/mm^3). HIV-1 RNA viral load was determined by nucleic acid amplification (Roche-Ampliclor HIV-1 monitor test, version 1.5; Roche Molecular Systems Inc, Branchburg, NJ). Results were expressed as the number of RNA copies per milliliter of plasma (copies/mL). Values of 400 copies/mL and below were regarded as undetectable. Blood samples for CD4 count and viral load were taken on the same day as the Papanicolaou smear.

All pelvic examinations were performed by a gynecologist or a trained gynecology resident. The clients were placed in the lithotomy position and a Cusco's speculum applied. Following visual inspection with a good light source, the cervix was assessed for gross lesions and abnormal discharge. Cervical smears were obtained using the Ayre's spatula from both the ectocervix and endocervix. Smears were made at two points on prelabelled glass slides and then fixed immediately in 95% (v/v) alcohol in coupling jars. These were delivered to the cytopathology laboratory for staining and microscopic examination. All the slides were stained using the Papanicolaou staining technique. The fixed slides were stained in Harris hematoxylin. The smear was decolorized

with acid alcohol and rinsed in Scott's tap water. They were then stained in orange G stock solution and finally stained with Eosin Azure 50. The slides were further rinsed in two changes of 95% alcohol, cleared in xylene, and mounted in a neutral synthetic resin medium. To ensure unbiased reporting, the cytopathologist was blinded to the clinical profile of the samples. Cytology was reported using the Bethesda system of classification by an experienced cytologist/pathologist. The smears were reported as normal, inflammatory, atypical squamous cells of undetermined significance, low-grade SIL, or high-grade SIL. Women with initial "inflammatory" Papanicolaou smear results were treated appropriately and reconsidered afresh for recruitment into the study. With the exception of patients with a normal report, all others were referred to the gynecology clinic for further evaluation.

Statistical analysis

All data were entered and the analysis was performed using the Epi-info version 3.3.2 (CDC Atlanta, GA) computer software program. The *t*-test was used to compare differences in normally distributed continuous variables between subjects with and without cervical SIL. Non-normally distributed variables were compared using the Mann-Whitney test. Univariate analysis using the Chi-square (χ^2) statistic was performed to identify risk factors associated with cervical SIL. Multivariate logistic regression was used to identify independent risk factors for cervical SIL. Variables were entered into the model if their *P* value on univariate analysis was 0.25 or less. $P < 0.05$ was considered to be statistically significant.

Results

The mean age of the 253 participants was 34.2 ± 6.4 (range 20–60) years. The median number of lifetime sexual partners was five (range 0–60), and 107 (42.3%) women had a prior history of sexually transmitted infection (Table 1). A total of 104 (41.1%) participants in the study were on HAART, with a mean duration of use of 16 ± 2 (range 1–36) months. The predominant HAART regimen was lamivudine, stavudine, and nevirapine (67.3%), while zidovudine, lamivudine, and nevirapine was the regimen used by 26% of the patients. Other regimens were being taken by 6.7% of the patients. The median CD4 count was 174 (range 12–1468) cell/mm^3. HIV-1 RNA levels were detectable in 205 (81.0%) women, with a median detectable level of 64,786 (range 426–1,854,296) copies/mL. There were 146 (57.7%) women with abnormal cervical cytology. Of these, 101 (39.9%) women had atypical squamous cells of undetermined significance. SIL was present in 45 (17.8%) women. Among the women with SIL, low-grade SIL and high-grade SIL was present in 16 (6.3%) and 29 (11.5%) of cases, respectively. No case of invasive cervical cancer was identified.

Table 1 Key sociodemographic characteristics and risk factors for squamous intraepithelial lesions in 253 women in Makurdi, Nigeria, infected with HIV-1[a]

Characteristic	Value
Age (years)	34.2 (±6.4)
Parity	2 (±2)
Educational status	
None	69 (27.3)
Primary	19 (7.5)
Secondary	107 (42.3)
Tertiary	58 (22.9)
Married	134 (53.0)
Previous sexually transmitted infection	107 (42.3)
Tobacco smoking	28 (11.0)
Number of lifetime sexual partners	5 (±4)
Use of HAART	104 (41.1)
CD4 count, cells/mm^3	
≤200	125 (49.4)*
201–499	105 (41.5)
≥500	23 (9.1)
HIV-1 RNA, copies/mL	
≥400	205 (81.0)
≤400	48 (19.0)
Cervical cytology	
Normal	107 (42.2)
ASCUS	101 (39.9)
LSIL	16 (6.3)
HSIL	29 (11.5)

Notes: [a]Values are given as mean ± standard deviation or number (percentage); *21 naive women were having CD4 estimation for the first time.

Abbreviations: ASCUS, atypical squamous cells of undetermined significance; HAART, highly active antiretroviral therapy; LSIL, low-grade squamous intraepithelial lesions; HSIL, high-grade squamous intraepithelial lesions; HIV-1, human immunodeficiency virus type 1.

The mean age of participants with SIL was 36 ± 7 years compared with 33 ± 5 years for women without SIL ($P = 0.009$; Table 2). However, the parity of participants was similar in the two groups. Women with SIL did not have a greater number of lifetime sexual partners and had rates of history of sexually transmitted infections similar to that of the women without SIL. Likewise, tobacco smoking and mean duration on HAART were similar in women with and without SIL (Table 2). Women with SIL had a median CD4 cell count of 132 cells/mm^3 compared with 184 cells/mm^3 for those without SIL ($P = 0.03$). The HIV-1 RNA viral load was also significantly higher in women with SIL compared with that in women without SIL (102,705 versus 64,391 copies/mL, respectively; $P = 0.002$, Table 2).

The results of the multivariate analyses are presented in Table 3. Having adjusted for other determinants, the risk

Table 2 Demographic characteristics and selected risk factors for HIV-1 infected women with and without squamous intraepithelial lesions in Makurdi, Nigeria[a] (n = 253)

Characteristic	SIL (n = 45)[b]	No SIL (n = 208)[c]	*P* value
Age, years	36 ± 7	33 ± 5	0.009
Parity	2 ± 7	2 ± 3	0.34
Lifetime sexual partners	5 ± 4	5 ± 3	0.84
Mean duration on HAART (months)	17 ± 6	15 ± 6	0.32
Tobacco smoking, %	9.3	7.1	0.47
Previous sexually transmitted infection, %	41.7	36.5	0.43
Median CD4 count, cell/mm^3	132	184	0.03
Median HIV-1 RNA, copies/mL	102,705	64,391	0.002

Notes: [a]Values are given as the mean ± standard deviation, percentage, or median, unless otherwise indicated; [b]SIL group consists of those with low-grade squamous intraepithelial lesions (n = 16) and high-grade squamous intraepithelial lesions (n = 29); [c]no SIL group consists of those with normal smears (n = 107) and those with atypical squamous cells of undetermined significance (n = 101).
Abbreviations: HAART, highly active antiretroviral therapy; SIL, squamous intraepithelial lesions; HIV-1, human immunodeficiency virus type 1.

of all types of SIL was significantly associated with a CD4 count < 200 cells/mm^3 and HIV-1 RNA viral load >10,000 copies/mL. Low CD4 count <200 cells/mm^3 and HIV-1 RNA viral load >10,000 copies/mL remained significantly associated with SIL when the variables were analyzed for risk of either low-grade SIL alone or high-grade SIL alone.

Discussion

During the early days of the HIV epidemic, HIV-infected women who had cervical human papillomavirus infection and SIL frequently died of AIDS well before developing invasive cervical cancer. However, following the introduction of HAART, the clinical course of HIV has been substantially prolonged, making HIV-infected women a clinically significant group of patients who have an increased risk of acquiring human papillomavirus infection and developing SIL and invasive cervical cancer.[15] This study provides the first comprehensive analysis of the prevalence of cervical SIL, the precursor to invasive cervical cancer, in this population in Makurdi, Nigeria.

The prevalence of SIL among the HIV-1 infected women in this study was 17.8%. Anorlu et al[6] recently reported a lower prevalence of 10.9% in HIV-positive women in Lagos, Nigeria. The reported prevalence in this study is also higher than the 2.9% and 13.3%, respectively, reported by Kapiga et al[16] among HIV-seropositive pregnant women in Tanzania and Chalermchockcharoenkit et al[17] among HIV-infected women by postpartum Papanicolaou smear in Thailand. The fact that the other studies were conducted among pregnant and postpartum women may have contributed to the observed variation. However, other researchers have reported higher prevalences in Africa involving HIV-positive women in Jos, Nigeria (29%),[14] commercial sex workers in Kenya (26%),[18] and sexually transmitted disease clinic attendees in Zambia (56%).[19] The difference between the findings of this study and those of other researchers may be attributed to the different populations sampled and possibly the different stages of HIV infection. Elsewhere, Lehtovirta et al[20] found a prevalence of 33% in a cohort of HIV-infected women in Helsinki, Finland. The prevalence of SIL in the general Nigerian population ranges from 4.1% to 11.8%.[14] These rates in the general population are less than the 17.8% reported in this study.

Previous studies have not satisfactorily established a protective effect of antiretroviral treatment on the risk of SIL. HAART showed some potential effect in the Women's Interagency HIV study.[21] Heard et al[22] showed that HAART had a positive impact on regression of SIL, and this was associated with increasing CD4 cell counts. In other studies, the effect of HAART on the prevalence of SIL has not been significant[14,20] or the prevalence of SIL has remained unchanged.[23] Similarly in this study, the use of HAART was not associated with a significant reduction in the risk of SIL.

Immunosuppression by HIV infection is a strong risk factor for SIL. In this study, 49.4% of HIV-positive women had CD4 counts <200 cells/mm^3, which is diagnostic of immunologic AIDS. In a recent review in Jos, Nigeria, Agaba et al[14] found that 60.9% of their 369 HIV-positive women had CD4 counts <200 cells/mm^3. The lower percentage of women

Table 3 Multivariate analysis of risk factors for cervical SIL among HIV-1 infected women in Makurdi, Nigeria

	Variable all SIL			Low-grade SIL			High-grade SIL		
	AOR 95%	CI	*P* value	AOR 95%	CI	*P* value	AOR 95%	CI	*P* value
Age > 35 years	1.29	0.68–2.34	0.35	1.29	0.68–2.34	0.35	1.02	0.63–2.17	0.79
CD4 count < 200 cells/mm^3	3.64	1.40–5.17	0.04	3.63	1.39–5.16	0.05	4.95	2.16–7.83	0.002
HIV-1 RNA > 10000 copies/mL	2.58	1.08–3.87	0.03	2.58	1.08–3.87	0.03	3.67	1.73–6.39	<0.001

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; HIV-1, human immunodeficiency virus type 1; SIL, squamous intraepithelial lesions.

with immunologic AIDS in this study may partly explain the lower prevalence of SIL of 17.8% in this study as compared with 29% in the Jos study. This study also showed that the CD4 count was inversely associated with SIL, and women with a CD4 count <200 cells/mm^3 were at greater risk of SIL compared with women with CD4 counts >200 cells/mm^3. This finding is in accordance with several other studies involving HIV-positive women.[8,14,16,17,20,24] Davis et al[13] reported that the strongest predictor of genital dysplasia was a nadir CD4 and CD4 count <200 cells/mm^3. Prolonged CD4 lymphopenia in patients infected with HIV results in defective T-cell proliferation regardless of the current CD4 count or viral load.[14] The CD4 count was independent of HAART use and HIV-1 RNA viral load as a risk factor for SIL in this study.

HIV-1 RNA levels have been directly correlated with a higher risk of SIL.[25] In this study, the median HIV-1 RNA viral load was significantly higher in patients with SIL than in those without SIL. Furthermore, an HIV-1 RNA viral load >10,000 copies/mL was associated with SIL in multivariate analysis. However, a high level of HIV/RNA does not always predict the risk of SIL, because some studies have failed to show a positive association.[13] For instance, Agaba et al[14] observed that although the HIV viral load was higher in patients with SIL, it was not predictive of SIL in multivariate analysis.

This study is not without important limitations. First, it was essentially a cross-sectional study, with a Papanicolaou smear taken only once at recruitment. Follow-up with multiple Papanicolaou smears over a period of time would have been ideal. Another limitation was the fact that SIL was determined using only cytology without histologic confirmation. There was also no end-of-study colposcopy to seek occult lesions. This leaves the possibility of underestimation of the endpoints of low-grade SIL and high-grade SIL.

In conclusion, a high prevalence of cervical SIL was found among HIV-1 infected women in Makurdi, Nigeria. Decreased CD4 cell counts and increasing HIV-1 RNA viral load were associated with cervical SIL. CD4 cell counts <200 cells/mm^3 and HIV-1 RNA viral loads >10,000 copies/mL were significantly associated with cervical SIL. Accordingly, HIV treatment programs and clinics must as a matter of policy institute comprehensive reproductive health care services for this high-risk group, including routine Papanicolaou smear screening.

Disclosure

The authors report no conflicts of interest in this work.

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