Determinants of Cervical Cytological Abnormalities among HIV-positive Women Receiving Care in a Tertiary Health Facility in Southeast Nigeria

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Abstract

Background: HIV infection is associated with increased risk of precancerous and cancerous lesions of the cervix. There is a need to identify the women mostly at risk to guide cervical cancer screening efforts. The objective of this study was to evaluate the determining factors for premalignant lesions of the cervix among HIV-positive women attending the adult HIV clinic in Nnamdi Azikiwe University Teaching Hospital, Nnewi, Nigeria. **Materials and Methods:** The Pap smears of 110 HIV-positive women were selected through purposive sampling and evaluated for premalignant lesions of the cervix using the Bethesda system of classification. STATA software, version 12.0 SE (Stata Corporation, TX, USA; 1985), was used to analyze the data, and multiple logistic regression models were employed to determine the risk factors of premalignant lesions. $P = 0.05$ at 95% confidence interval was taken as statistically significant. **Results:** The prevalence of premalignant lesions of the cervix was 28.2%, and these constitute mainly of atypical squamous cells of undetermined significance (56.5%). Women with cervical cytological abnormalities have significantly lower mean age (35.39 vs. 38.89; $P = 0.04$), lower mean CD4 count (325.3 vs. 648; $P < 0.01$), and lower mean age of coitarche (15.89 vs. 19.9; $P < 0.001$). On bivariate analysis, the significant determinants of abnormal cervical cytology include CD4 count <300 cells/mm^3 (odds ratio [OR] = 0.037; $P < 0.001$), age <30 years (OR = 0.26; $P < 0.01$), duration of illness of <5 years (OR = 0.34; $P < 0.05$), and the use of highly active antiretroviral therapy (HAART) for <5 years (OR = 0.09; $P < 0.001$). On multivariate analysis, CD4 count <300 cells/mm^3 (adjusted OR [aOR] = 0.018; $P < 0.001$) and the use of HAART for <5 years (aOR = 0.13; $P < 0.05$) significantly predicted the presence of premalignant lesions. **Conclusion:** The determinants of cervical cytological abnormalities among the women were CD4 count <300 cells/mm^3 and the use of HAART for <5 years. We recommend routine screening for cervical cancer among this class of women.

Keywords: Developing countries, gynecological malignancies, HIV infection, premalignant lesions, screening

Introduction

In sub-Saharan Africa, the burden of cervical cancer-related morbidity and mortality is still high.[1-4] This is as a result of ignorance, poverty, and deprivation as well as lack of organized cancer of the cervix screening program in the subregion. In a bid to scale up screening for cervical cancer, the visual inspection methods were introduced, and reports show that the methods are effective in improving access to screening and treatment of premalignant lesions of the cervix in the developing countries.[5-7]

Women living with HIV are at an increased risk of developing infection with high-risk human papillomavirus (HPV) and invasive cancer. This is as a result of immune suppression associated with the condition. Published reports show a high prevalence of premalignant lesions of the cervix among women infected with HIV.[8-11] This high prevalence underlines the need for establishing effective and robust screening program among this high-risk group to reduce progression to invasive

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lesions with the attendant reduction in cancer-related morbidity and mortality.

However, instituting an effective cervical cancer screening program within the developing countries including Africa has proved quite a challenging and daunting task mainly because of the requirement for skill, finance, and facilities. It is important, therefore, to define the population at most risk to be able to carry out targeted screening and treatment.

HIV is endemic in Nigeria, and at present, it is estimated that about 3.2 million Nigerian women are living with HIV infection.[12] In addition to providing antiretroviral therapy, the care for these women should include the detection and treatment of gynecological diseases, especially preinvasive and invasive cancers of the cervix. Screening for premalignant lesions of the cervix among this large cohort of women is not feasible based on resource constraints. However, targeted screening focusing on the groups that are mostly at risk may be feasible.

At present, only a few studies have examined the risk factors for cervical cytological abnormalities among HIV-positive women in Nigeria.[13,14] None of the studies was done in the southeast part of the country. This study, therefore, aims to determine the risk factors for cervical cytological abnormalities among a cohort of HIV-positive women in southeastern Nigeria.

Aim

The aim of this study is to determine the risk factors for premalignant lesions of the cervix among HIV-positive women attending the adult HIV clinic in Nnewi, southeast Nigeria.

Materials and Methods

Study design

This is a cross-sectional descriptive study that was carried out among HIV-positive women who were attending the adult HIV clinic in Nnamdi Azikiwe University Teaching Hospital (NAUTH), Nnewi.

Study area

NAUTH, Nnewi, is a tertiary health institution with a catchment area of the five states of the southeast geopolitical region of Nigeria. These are Anambra, Enugu, Abia, Imo, and Ebonyi states.

Study population

The study population comprised 110 HIV-positive women attending the HIV clinic in the hospital. All HIV-positive women attending the clinic were included while those with a history of cervical cancer, previously treated premalignant lesions of the cervix and those that were pregnant were excluded from the study.

Sample size determination

The prevalence of abnormal cervical cytology among HIV-positive women in Nnewi of 6.8% reported by Ugboaja and Monago[15] in Nnewi, Nigeria, was used as a reference value for the calculation of sample size. The minimum sample size for a statistically meaningful deduction was determined using the statistical formula of Fisher for calculating sample size (WHO):[16]

$Z^2 P (1 - p)/d^2$

Where N is the minimum sample size for a statistically significant survey, Z is normal deviant at the portion of 95% confidence interval (CI) = 1.96, P is prevalence value of cervical cytological abnormalities among HIV-positive women in Nnewi, Nigeria = 6.8%, and d is margin of error acceptable or measure of precision = 0.05.

Using this formula, minimum sample size (N) is 100. Therefore, the study of 100 women will give meaningful statistical deductions. However, the sample size was increased to 110 to compensate for 10% attrition. Therefore, 110 women were recruited for the study.

Data collection

Consecutive HIV-positive women attending the adult HIV clinic in NAUTH, Nnewi, were educated on purpose, value, and the nature of the study and those that gave consent for the study were recruited.

Data on sociodemographic, sexual, and reproductive characteristics as well as the use of highly active antiretroviral therapy (HAART) and duration of use were obtained with a coded pro forma by trained assistants.

Sample collection

After completion of the pro forma, 5 ml of venous blood was obtained from the cubital fossa for measurement of CD4 count in the laboratory while cervical smear was obtained for Pap smear screening. The Pap's smear was collected with Ayre's spatula and smeared evenly on a slide which was immersed instantly in 95% alcohol. The samples were sent to the histopathology laboratory to be read by cytopathologist using the Bethesda classification.

Data analysis

The data collected was analyzed with STATA software, version 12.0 SE (Stata Corporation, TX, USA; 1985). Continuous variables were expressed as means and standard deviations and categorical variables as percentages. Logistic regression models were developed to explore the association of selected variables with cervical cytological abnormalities among the women. Three levels of analysis were done.

The first level analysis was a descriptive analysis to determine the overall prevalence and pattern of cervical cytological abnormalities among the women. The second level analysis was bivariate logistic regression analysis performed to assess the association between selected sociodemographic, clinical, sexual, and reproductive characteristics as well as the use of HAART and the prevalence of premalignant lesion. The third level analysis was a multivariate logistic regression analysis involving all the factors that were significantly associated with cervical cytological abnormalities at the second level analysis

which were considered as confounding variables using the presence of cervical cytological abnormality as the outcome variable. $P < 0.05$ at 95% CI was considered as statistically significant. The results are presented as odds ratios (ORs) or adjusted ORs and their 95% CI.

Ethical considerations

Ethical approval for the study was obtained from NAUTH ethical committee, and the study protocol was made to conform to the ethical guidelines of the Declaration of Helsinki (1975). As much as possible, the rights of the patients were fully protected in this research work. Only women who gave consent were recruited for the study. The patients were required to fill the informed consent form. As much as possible, confidentiality was maintained at all stages of the research work. Every participating patient had the right to privacy and could withdraw from the study at any time after counseling. Patients also had the right to anonymity.

Results

Sociodemographic characteristics of the women

As shown in Table 1, majority of the women were married (61.8%; $n = 68$) and were mainly traders (67.3%; $n = 74$) who had attained at least secondary education (85.5%; $n = 94$). The age of the women ranged from 20 to 61 years with a mean of 37.7 ± 9.5 years. The mean parity of the women was 2.8 ± 2.3.

Sexual, reproductive, and sexual characteristics of the women

The sexual, reproductive, and disease characteristics of the studied women are presented in Table 2. The mean age of menarche was 14.3 ± 1.4 years, and most (52.7%, $n = 58$) of the women had their first birth between the age of 20 and 30 years (mean age of first birth = 24.3 ± 6.2). Majority (60.9%, $n = 67$) of the women had been diagnosed for more than 5 years (mean duration of disease 5.5 ± 3.2 years) and 89.1% ($n = 98$) of them were on HAART. The mean CD4 count 557.1 ± 26 cells per ml and 82.7% of the women had a CD4 count of more than 300 cells per ml in at the time of the study.

Prevalence and pattern of cervical cytological abnormalities among the women

Thirty-one of the women had abnormal cervical cytological abnormalities giving a prevalence of 28.2%. Atypical squamous cells of undetermined significance constituted the highest class of abnormality accounting for 51.6% ($n = 16$) of all cases of abnormal cytology. This is shown in Table 3.

Comparative descriptive statistics of some variables among the women

This is presented in Table 4 and shows that among other factors, the mean age (35.39 vs. 38.89; $P = 0.04$), the mean CD4 count (325.3 vs. 648; $P < 0.01$), and the mean duration of illness (4.55 vs. 5.89; $P = 0.04$) were significantly lower among the women with cervical cytological abnormalities than their counterparts. The mean age of coitarche was also significantly lower among women with cervical cytological abnormalities than their counterparts (15.89 vs. 19.9; $P < 0.001$).

Table 1: Sociodemographic characteristics of the women living with HIV/AIDS

	Frequency (%)
Sociodemographic characteristics of the women	
Age	
20-24	5 (4.5)
25-29	16 (14.5)
30-34	17 (15.5)
35-39	22 (20.0)
40 and above	50 (45.5)
Parity	
0-1	41 (37.3)
2-4	45 (40.9)
5 and above	24 (21.8)
Marital status	
Married	68 (61.8)
Widowed	31 (28.2)
Single	7 (6.4)
Divorced	3 (2.7)
Separated	1 (0.9)
Highest educational level	
No formal education	3 (2.7)
Primary	13 (11.8)
Secondary	65 (59.1)
Tertiary	29 (26.4)
Other sociodemographic characteristics of the women	
Occupation	
Trading	74 (67.3)
Public service	21 (19.1)
Artisans	9 (8.2)
Student	5 (4.5)
Unemployed	1 (0.9)
Religion	
Catholic	54 (49.1)
Anglican	31 (28.2)
Pentecostal	25 (22.7)
Social class	
2	10 (13.0)
3	47 (61.0)
4	19 (24.7)
5	1 (1.3)

Factors associated with premalignant lesions of the cervix among of the women

The predictive factors for premalignant lesions of the cervix among of the women as explored with a logistic regression model are presented in Tables 5 and 6.

On bivariate analysis, CD4 count < 300 (C. OR = 0.037, $P = 0.00$), age 30 years and above (C. OR = 0.26, $P < 0.01$), duration of illness of more than 5 years (C. OR = 0.34, $P = 0.02$), and the use of HAART for more than 5 years (C. OR = 0.09, $P < 0.001$) predicted the occurrence of the cytological abnormalities of the cervix while inconsistent use

of condom (C. OR = 0.78, *P* = 0.69) and having multiple sexual partners in the preceding 6 months (C. OR = 0.37, *P* = 0.15) were not significantly associated with premalignant lesions of the cervix among the women. On multivariate analysis, after controlling for confounders, only CD4 count 300 cells/ml and above (a OR = 0.02, *P* < 0.000) and the use of HAART for more than 5 years (aOR = 0.13, *P* <=0.03) significantly reduced the odds for premalignant lesions of the cervix.

Table 2: Sexual, reproductive and disease characteristics of the women living with HIV/AIDS

Sexual, reproductive and disease characteristics of the women	Frequency (%)
Age of coitache	
<15	12 (10.9)
≥15	98 (891)
Age of first birth	
<20	22 (20.0)
20-30	58 (52.7)
30 and above	30 (27.3)
Number of sexual partners in the last 6 months	
2 and less	107 (97.3)
>2	3 (2.7)
Duration of illness (diagnosis)	
<5 years	43 (39.1)
5-10 years	55 (50.0)
>10 years	12 (10.9)
Use of HAART	
Yes	98 (89.1)
No	12 (10.9)
CD4 count	
<300	19 (17.3)
300 and above	91 (82.7)

HAART: Highly active antiretroviral therapy

Table 3: The pattern of cervical cytological abnormalities of women living with HIV/AIDS attending a clinic in Nnewi

Grade of abnormality	Frequency (%)
ASCUS	16 (51.6)
LGSIL	7 (22.6)
HGSIL	7 (22.6)
Inflammatory	1 (3.2)
Total	31 (100.0)

ASCUS: Atypical squamous cells of undetermined significance, LGSIL: Low grade squamous intraepithelial lesion, HGSIL: High grade intraepithelial lesion

Discussion

Targeted screening for cancer of the cervix among HIV-positive women in Africa requires the identification of the risk factors. The risk factors of cervical cytological abnormalities among HIV-positive women differ according to reports. Our study found a significant association between CD4 counts <300 cells/mm^3, age <30 years, use of HAART for <5 years, and duration of illness <5 years with increased risk of cervical cytological abnormalities. The presence of cytological abnormalities was also significantly associated with lower mean age at sexual debut, lower mean age, and lower mean CD4 count. A history of multiple sexual partners and inconsistent use of condom though increased the odds for premalignant lesions of the cervix did not have significant effects.

The association of low CD4 count with a significant risk for cervical cytological abnormality among HIV-positive women has been severally reported in previous accounts.[17,18] One of those earlier reports was the account of Kreitchmann *et al*.[17] who studied 898 HIV-positive women to identify the risk for cervical cytological abnormalities and found a significant association between cervical cytological abnormalities and CD4 count <200 cells/mm^3. This observation was very similar to our own findings. A similar finding was also recently reported by Sansone *et al*.,[18] and CD4 count reflects the immunologic status of the patients infected with HIV which correlates with the clinical status of the patient. The lower the CD4 count the higher the viral load and consequently the worse the clinical status of the patient. Our finding strongly indicates the assessment of cervical cytology for premalignant lesions among the HIV-positive women receiving care in our facility.

This study also found a significant association of age <30 years with the presence of premalignant lesions of the cervix which is similar to the account of Kreitchmann *et al*.[17] and Obiri-Yeboah *et al*. in Ghana.[19] The younger women are more likely to involve in more risky sexual

Table 4: Comparative descriptive statistics of selected variables of women living with HIV/AIDS in Nnewi

Variables	Cervical cytological abnormality		*T*-statistic	*P*
	Positive	Negative		
Parity (mean±SD)	2.39±2.03	3.00±2.4	1.26	0.20
Age (mean±SD)	35.39±9.18	38.89±8.67	1.97	0.04*
CD4 count (mean±SD)	325.30±164.00	648.00±239.70	6.88	<0.001*
Duration of disease (years) (mean±SD)	4.55±0.92	5.89±1.23	2.02	0.04*
Number of sexual partners in the last 6 months (mean±SD)	1.10±0.83	0.88±0.52	1.63	0.11
Duration of use of HAART (mean±SD)	2.96±1.91	5.01±1.30	3.83	<0.001*
Age of coitache (mean±SD)	15.87±2.4	19.90±4.00	5.33	<0.001*

*Significant. SD: Standard deviation, HAART: Highly active antiretroviral therapy

Table 5: Logistic regression (bivariate) analysis for the predictors of premalignant lesions of the cervix among the women

Variable	cOR	95% CI	*Z*-statistic	*P*
CD4 count (cells per mm^3)				
<300	1.00	Reference	N/A	N/A
300 and above	0.037	0.01-0.14	−4.78	0.0004**
Age (years)				
<30	1.00	Reference	N/A	N/A
30 and above	0.26	0.10-0.71	−2.64	<0.01*
Use of HAART				
No	1.00	Reference	N/A	N/A
Yes	0.76	0.21-2.7	−0.42	0.68
Duration of use of HAART (years)				
<2	1.00	Reference	N/A	N/A
2-5	0.28	0.09-0.9	−2.1	0.03*
>5	0.09	0.02-0.36	−3.4	<0.001**
Duration of illness (years)				
5 and less	1.00	Reference	N/A	N/A
>5	0.34	0.14-0.84	−2.35	0.02*
Consistent use of condom				
No	1.00	Reference	N/A	N/A
Yes	0.78	0.23-2.65	−0.39	0.69
Sexual partners				
2 and less	1.00	Reference	N/A	N/A
>2	0.38	0.1-1.41	−1.45	0.15

*Significant. cOR: Crude odd ratio, HAART: Highly active antiretroviral therapy, CI: Confidence interval, N/A: Not available

Table 6: Multivariate analysis for independent predictors of cervical cytological abnormalities among the women

Variable	aOR	95% CI	*Z*-statistic	*P*
CD4 count (cells per mm^3)				
<300	1.00	Reference	N/A	N/A
300 and above	0.018	0.00-0.15	−3.6	0.0006
Age (years)				
<30	1.00	Reference	N/A	N/A
30 and above	0.65	0.15-0.29	−4.2	0.57
Duration of use of HAART (years)				
<2	1.00	Reference	N/A	N/A
2-5	0.34	0.07-1.7	−1.32	0.19
>5	0.13	0.02-0.85	−2.13	0.03*
Duration of illness (years)				
5 and less	1.00	Reference	N/A	N/A
>5	0.87	0.14-5.5	−0.15	0.88

*Significant. aOR: Adjusted odd ratio, HAART: Highly active antiretroviral therapy, CI: Confidence interval, N/A: Not available

behavior including having more sexual partners.[20,21] Therefore, these women require closer surveillance and sensitization about healthy sexual habits including the need for consistent use of condoms and should be targeted for cervical cancer screening.

An important finding from this study is the significant reduction in the risk of premalignant lesions with the use of HAART for more than 2 years. Women who had used HAART for more than 2 years were associated with three times reduction in the odds for cytological abnormalities and this reduction increases to about 11 times when HAART was taken for more than 5 years. This finding agrees with the previous account of many authors, and it is not surprising as HAART improves the immune status of HIV-infected people.[14,22,23] The effect of HAART on cervical cytological abnormalities is traceable to the immune reconstitution effect of HAART allowing the body immune system to clear the HPV infection which is the precursor for premalignant changes of the cervix. This effect is expected to develop gradually at commencement of therapy. This may explain, therefore, the finding in our study of the increasing reduction in risk as the duration on HAART increased.

A surprising finding from our work was the finding of no significant association between cervical cytological abnormalities and the history of multiple sexual partners in the preceding 6 months among the women. The precursor of premalignant lesions is HPV which is mainly sexually transmitted, and previous studies have demonstrated the increased prevalence of cervical premalignant lesions among women with multiple sexually partners.[10,24] Our finding may be a reflection of the small number of women who gave the history of multiple sexual partners. It is also possible that we may not have had the true picture with respect to the number of women who actually had multiple sexual partners as most of the women are married and may be constrained to accepting having multiple sexual partners. A study using a larger number of women will give a more reliable report with respect to the association of multiple sexual partners and premalignant lesions of the cervix among HIV-infected women in our environment.

Conclusion

This study found a high rate of cervical cytological abnormalities among HIV-positive women attending the HIV clinic in Nnewi. CD4 count <300 cells/mm^3 and the use of HAART for <2 years were the true determinants of cervical cytological abnormalities. Routine screening of this set of women for premalignant lesions of the cervix at the first visit is, therefore, recommended.

Limitations

This is a hospital-based study, and therefore, the findings may not be a true representation of those in the general population. However, it provided us with very useful evidence and guidance with which to manage the HIV-positive women receiving care in our hospital. In addition, some of the women may not have given us the correct information, especially with respect to having multiple sexual partners.

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Conflicts of interest

There are no conflicts of interest.

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