Original Article

Cervical cytology pattern and human immunodeficiency virus serostatus of women seen in Ahmadu Bello University Teaching Hospital, Zaria, Nigeria

Umma Sulaiman Bawa, Abimbola Omolara Kolawole, Nana Hauwa Madugu, Sani Mohammed Shehu[1]

Departments of Obstetrics and Gynaecology and [1]Pathology, Ahmadu Bello University Teaching Hospital, Shika, Zaria, Nigeria

Abstract

Background: Cervical cancer is the second most common cancer in women worldwide. Human immunodeficiency virus (HIV) has been suggested to be a cofactor in the association between human papillomavirus and cervical intraepithelial neoplasia (CIN).

Aim: To determine the pattern of cervical cytology changes in women of different HIV status and characterise the sociodemographic factors that confound the changes seen.

Methods: This was a cross-sectional comparative study. This study was conducted in Gynaecology Clinic of Ahmadu Bello University Teaching Hospital, Zaria, Nigeria. Following informed consent, 272 HIV-positive (HIV+) and 275 HIV-negative (HIV−) women had questionnaires administered and Papanicolaou smears were taken.

Results: The average age of the respondents was 32.6 ± 6.8 years (range: 15–49 years). Mean parity for HIV+ women was 3.28 and 3.36 for HIV− women while 70.8% of HIV+ women were married comparable with 72.7% in HIV− women. Twenty-nine per cent of HIV+ women had positive smears for CIN compared with 16.4% in those that were HIV−. This was statistically significant (odds ratio = 2.05, $P = 0.001$). The high-grade lesions (CIN II and CIN III) tended to be higher in the HIV+ women (11.4%) than the HIV− women (0.7%).

Conclusion: HIV+ women in Zaria, Northern Nigeria, are at higher risk of severe cervical dysplasia compared with their counterparts who are HIV−. It is recommended that greater effort should be made to have an integrated reproductive healthcare service which includes cervical cytology within the HIV clinics.

Keywords: Cancer, cervical, cervical intraepithelial neoplasia, cytology, dysplasia, human papillomavirus, Papanicolaou smear, squamous intraepithelial lesion

Address for correspondence: Dr. Abimbola Omolara Kolawole, Department of Obstetrics and Gynaecology, Ahmadu Bello University Teaching Hospital, Shika, Zaria, P. O. Box 7062, Kaduna, Nigeria.
E-mail: kolabimbo@yahoo.com

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INTRODUCTION

Cervical cancer is an important reproductive public health problem. It is the second most common cancer in women worldwide with over 450,000 new cases and 300,000 deaths annually. Over 80% of these deaths occur in the developing countries where it is said to be the most common cancer

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in women.[1-3] In Sub-Saharan Africa, about 190,000 deaths occur each year from cancer of the cervix.[4,5] The incidence and mortality in England and Wales is approximately 9.3 and 3.7/100,000 women.[2] In the United States of America, the age-adjusted incidence rate of 8.1 per 100,000 with a mortality rate of 2.6 per 100,000[6-9] was reported. However, in Nigeria, the incidence rate of approximately 24.1 per 100,000 was reported from the Ibadan cancer registry.[7]

Cancer of the cervix is a slowly developing tumour that takes about 8 to 10 years to develop from the pre-cancer stage; thus, it is a suitable disease for screening.[1,7] There are various methods used in assessing changes in the cervical cells with the most common being the Papanicolaou smear (Pap Smear) smear. Others include visual inspection with acetic acid (VIA) and visual inspection with Lugol's iodine (VILI) which is very useful in low-resource settings. The 'ThinPrep Pap' which is a modification of the conventional Pap smear though expensive produces better quality smears and results. HPV-DNA testing is also used to improve the efficiency of screening.

Cancer of the cervix has close to 100% cure rate if detected early at the pre-invasive stage through cytological screening.[8] The high-risk human papillomavirus (HPV), especially types '16, 18, 31 and 45', are central to the development of cervical cancer and its precursors. Primary prevention is aimed at reducing HPV infection, and following years of research, the bivalent Cervarix^{R}, quadrivalent Gardasil^{R} and the Nonavalent Gardasil 9 vaccine have been developed and have proven to be efficacious in preventing infection with HPV.[3] These are administered to girls and women between the ages of 9–26 years in three doses within 6 months.[9] Secondary prevention using cervical cytology, VIA or VILI has to continue for the other high-risk strains, 31, 35 and 45 and for older unvaccinated women in the populace.

The association between HPV and human immunodeficiency virus (HIV) is an important one. The prevalence of both viruses in a population is strongly related to sexual behaviour pattern.[10-12] Nonetheless, data from Africa, America and Europe till date are conflicting on whether or not there is increased risk of cervical cancer in HIV-positive (HIV+) women.[13-15]

More than one-third of the 38 million persons infected with the HIV worldwide are women.[14] Over 25.8 million adults and children are living with HIV/AIDS in Sub-Saharan Africa and 13.5 million are women.[15] The first case of AIDS in Nigeria was reported in 1986, and since then, the HIV prevalence has been increasing from 1.8% in 1991 to 5.8% in 2001.[16,17] However, the report of 2008 national HIV sentinel survey reported a reduced prevalence of 4.6%.[18] The first HIV-seropositive patient was detected at the Ahmadu Bello University Teaching Hospital (ABUTH), Zaria, in 1987, and increasing numbers have since emerged.[18]

The 1993 Centre for Disease Control revised classification for HIV added moderate or severe cervical dysplasia as a 'category B' AIDS defining condition and invasive cervical cancer as an AIDS or 'category C' defining condition.[10]

HIV-seropositive women were shown in separate studies to be at an increased risk of developing squamous intraepithelial lesions (SILs) and invasive cancer of the cervix, vagina, vulva, anus and perianal regions.[12,19] HIV is suggested to be a cofactor in the association between HPV and cervical intraepithelial neoplasia (CIN), and this effect seems to vary with level of immune function.[10,14,19] Studies have also shown that standard modalities of screening and treatment as applicable to the general 'at risk' population for these cervical conditions may suffice for HIV/AIDS-positive women.[10,11] In a study from Senegal, both HIV I and HIV II were found to be associated with SILs.[18] In women with HIV, untreated CIN I is likely to persist and the likelihood is higher than that in HIV-seronegative women.[20]

Currently, the use of highly active antiretroviral (ARV) agents has prolonged the life expectancy and improved the quality of life of people living with HIV; the increasing population of these women may then be faced with another dilemma of cancer of the cervix which is better prevented than managed.

The justification for this study is to know if a relationship exists between CIN and HIV in this centre since studies done in other centres in North East and North Central Nigeria found a strong association between HIV positivity and cervical dysplasia in women. Moreover, there was also some association between levels of immune suppression and severity of dysplasia.

The aim of this study is to assess the pattern of cervical cytology amongst HIV+ women attending clinics in ABUTH, Zaria.

Objectives

To determine:

1. The prevalence of abnormal cervical smears amongst HIV+ women in Zaria
2. The association between abnormal cervical smears and HIV serostatus

3. The sociodemographic factors associated with abnormal cervical smears in HIV+ women.
4. The pattern of CIN changes present.

METHODS

This was a cross-sectional, case–control study to investigate cervical smear patterns amongst HIV+ and HIV negative (HIV−) women conducted in the Virology Clinic and the Gynaecology Clinics of ABUTH, Shika-Zaria, Nigeria. HIV+ women aged 15–49 years attending these clinics were enrolled after giving informed consents. A control group consisting of HIV− women matched for age was recruited from the reproductive health clinics following pre-test HIV counselling, a negative HIV screening test and a post-test counselling.

The sample size was determined using the formula:

$n = (z^2pq)/d^2$

Where

z = standard normal deviate for a normal distribution and is taken as 99% confidence interval (CI) = 1.96 from the z table.

P = proportion or prevalence is taken as 0.23[19]

q = 1–p

d = degree of precision which is taken as 0.05 (precision limit = 0.05)

272 was the minimum sample size that could be used.

The respondents were administered questionnaires to collect information on their sociodemographic characteristics, obstetric history, contraceptive, sexual history and history of smoking. Their Pap smears were then taken; with the patient in the dorsal position, the vulva was parted with the left hand and a bivalve speculum inserted into the vaginal cavity exposing the cervix. The ectocervix was cleansed using a sterile swab and the wooden Ayre's spatula inserted into the cervix and rotated 360° to abrade the surface slightly and to pick up cells from the squamocolumnar area of the cervical ostium. The specimen was smeared on the slide and put in a container of 95% alcohol for fixation. This was then analysed in the histopathology department of the hospital. The slides were then reported by a consultant pathologist. Patients who had abnormal smears were referred to the gynaecology clinic for further management. The Pap smears were collected over a period of 1 year.

The information obtained was coded and recorded on data sheets designed for the study and analysed using SPSS statistical software version 15. Produced by SPSS Inc., current versions (2015) named IBM SPSS Statistics. 24.0/ March 15, 2016, USA. Test of significance was based on $P < 0.05$ using the appropriate tests.

RESULTS

The mean age of the respondents was 32.6 ± 6.8 years (range: 15–49 years). The mean parity in the HIV+ women was 3.28 ± 1.90; this was not significantly different from that for HIV− women with 3.36 ± 1.62 ($P = 0.598$). In the unmarried HIV+ women, 27.3% had positive smears; there was no statistically significant difference in the occupational status of the HIV+ and the HIV− women where 28.0% and 23.6% were civil servants. ($P = 0.385$). The greater majority in both groups were housewives 33.6% and 34.5%, respectively. The HIV+ women had a lower level of education (25.6%) than those that were HIV− 17.8% though it was not statistically significant ($P = 0.057$). The mean number of sexual partners (1.66 ± 1.074 and 1.65 ± 0.968 CI: 157–188) in HIV+ and HIV− was not significantly different.

Table 1 shows the prevalence of positive smears in HIV+ women was 28.7% and was significantly higher than 16.4% found in HIV− women ($P = 0.001$, odds ratio = 2.05).

Table 2 showed how HIV status relates to the severity of cervical changes. The high-grade lesions (CIN II and CIN III) tended to be higher in the HIV+ women (11.4%) than HIV− (0%) women. There were 20 (7.4%) HIV+ women with CIN II and 11 (4.0%) with CIN III both constituting high-grade lesions. None of the HIV− women had

Table 1: Prevalence of squamous intraepithelial lesions in human immunodeficiency virus-positive and human immunodeficiency virus-negative women

Cytological result	HIV positive, *n* (%)	HIV negative, *n* (%)	Total, *n* (%)
Negative smear	194 (71.3)	230 (83.6)	424 (77.5)
Positive smear	78 (28.7)	45 (16.4)	123 (22.5)
Total	272 (100)	275 (100)	547 (100)

$\chi^2=11.9$, df=1, $P=0.001$. HIV: Human immunodeficiency virus

Table 2: Relationship between cervical intraepithelial neoplasias and human immunodeficiency virus status

Cytology result	HIV positive, *n* (%)	HIV negative, *n* (%)	Total, *n* (%)
CIN I	47 (17.3)	45 (16.4)	92 (16.8)
CIN II	20 (7.4)	0	20 (3.7)
CIN III	11 (4.0)	0	11 (2.0)
Others	194 (71.3)	230 (83.6)	424 (77.5)
Total	272 (100)	275 (100)	547 (100)

$\chi^2=42.83$, df=3, $P=0.000$. CIN: Cervical intraepithelial neoplasias, HIV: Human immunodeficiency virus

high-grade lesion. Three women were diagnosed with carcinoma *in situ* amongst the HIV+ women.

The comparison of sociodemographic factors and sexual variables in relation to the presence or absence of positive smear is shown in Table 3. There was no statistically significant difference between those with positive smears and those with negative smears in terms of parity, marital status, the age at coitarche and educational level. There was, however, a significant difference in the age ranges and having a positive smear ($P = 0.001$). The women with a CD4 count of <300 had a higher number of positive smears (29.3% $n = 39$) than those with a CD4 count of 500 and above (24.7% $n = 19$). All women denied history of smoking.

DISCUSSION

The women in the study were from various tribes; most were from the southern part of Kaduna State (44.6%) and the Hausa/Fulani having 36.7%. Out of a total of 272 HIV positive women, one hundred and fourteen had post secondary education. Majority of these HIV positive women (120) were married. This is not surprising since the most common mode of transmission of the virus in our environment is heterosexual and often within the context of marriage. This is similar to the finding from Jos by Tanko *et al*.[21] There were more divorced and widowed women in the HIV+ group; they also had more sexual partners, and this is similar to the aforementioned Jos study.

The prevalence of SILs in this study was significantly higher in HIV+ than in HIV− women 28.7% and 16.4%, respectively.[22] This is in keeping with reports from both the developed and the developing countries. In a study from Baltimore, the United States of America, 13% of HIV+ women had abnormal cervical cytology compared with 2% of HIV− women.[21] Furthermore, from New York, during a 30-month follow-up of 328 HIV-infected and 325 HIV-non-infected women, 20% of the HIV-infected women and 5% of uninfected women developed SIL, showing that 1 in 5 HIV-infected women without prior evidence of cervical disease developed biopsy-confirmed SILs within 3 years.[16,22] Another study from Thailand by Hluangdansakul and others showed a prevalence of 10.5% in HIV+ women.[23] African researchers have also demonstrated high prevalence in their results. The highest prevalence so far reported was from Zambia with a figure of 76%.[23] Tanko *et al*. from Jos reported a prevalence of 21% in the HIV+ group and 6% in the HIV− group,[21] but it is higher than the report from Lagos with a prevalence of 10.9% in the HIV+ group and 4.3% in the HIV− women.[24] Saidu from Ilorin reported higher prevalence (23.8% compared to 11.3%) in HIV+ women when compared with HIV− women; this is similar to Chama in Maiduguri.[19,24,25] Other factors such as age, parity, marital status, educational level and number of sexual partners were found to be confounding factors

Table 3: Comparison of baseline characteristics of human immunodeficiency virus-positive women based on cytopathologic diagnosis

	Pap smear negative, *n* (%)	Pap smear positive, *n* (%)	Total, *n* (%)	*P*
Age				
15-24	16 (94.1)	1 (5.9)	17 (100)	0.001
25-34	104 (77)	31 (23)	135 (100)	
35-44	53 (68.8)	24 (31.2)	77 (100)	
≥45	21 (48.8)	22 (51.2)	43 (100)	
Marital status				
Married	85 (70.8)	35 (29.2)	120 (100)	0.836
Unmarried	109 (72.7)	41 (27.3)	150 (100)	
Parity				
<5	158 (75.9)	50 (24.0)	208 (100)	0.047
≥5	38 (59.4)	26 (40.6)	64 (100)	
Number of sexual partners				
Single	121 (69.5)	53 (30.5)	174 (100)	0.117
Multiple (including polygamy)	74 (75.5)	24 (24.5)	98 (100)	
Age at coitarche				
<15	26 (65)	14 (35)	40 (100)	0.434
15-30	166 (72.2)	64 (27.8)	230 (100)	
≥30	2 (100)	0	2 (100)	
Educational level				0.211
Less than or equal to primary	47 (65.3)	25 (34.7)	72 (100)	
Greater than primary	147 (73.5)	53 (26.5)	200 (100)	
CD4 count				
<300	94 (70.7)	39 (29.3)	133 (100)	0.568
300-499	42 (67.2)	20 (32.8)	62 (100)	
≥500	58 (75.3)	19 (24.7)	77 (100)	

in the development of SILs in HIV women in different studies.[19,25-28] In this study, only age was found to be statistically significant in Pap smear-positive and Pap smear-negative HIV+ women. This is similar to a report by Audu from Maiduguri[29] although they also noted associations with parity. HIV infection was the strongest association in the development of SILs amongst all the variables in this study. It has been reported that women on highly active ARV agents (HAART) have an added advantage of potential regression of HPV infection and subsequent induction of regression of SILs.[30-32] In this study, despite the fact that the majority of HIV+ women were on HAART, they still had a higher prevalence than the HIV+ women. The regression or progression rate of the cervical changes noticed could be studied further in another prospective study.

CONCLUSION

Several studies have demonstrated the high association between HIV infection in women and squamous intraepithelial changes. The finding from this study is in tandem with other studies carried out in different centres across the country. In view of the ongoing HIV pandemic, especially in Sub-Saharan Africa, more women would be at risk of developing pre-invasive and invasive cancer of the cervix. As progress continues with the management of HIV+ women with ARV, immune-supportive therapy and in preventing and treating opportunistic infections, the lifespan of these women is expected to increase. The clinical significance of more severe infection with HPV may overtime be manifested in higher rates of cervical dysplasia and carcinoma in the population of HIV-infected women. There is, therefore, a need to intensify efforts to prevent HPV infection and pre-cancer and cancer of the cervix.

Recommendations

Based on the findings in this study of the high risk of developing high-grade SIL by HIV+ women, it is recommended that cervical smear should be more frequent with intervals between smears shorter; such as every six months in these women.

Cervical cancer prevention services in HIV-affected women should be integrated with the ARV therapy programmes; this will afford the opportunity to reduce the burden of HIV infection and cervical cancer in resource poor settings where both diseases are prevalent.

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Conflicts of interest

There are no conflicts of interest.

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