Prevalence and Predictors of Cervical Cytological (Pap Smear) Abnormalities Among HIV-infected Women at the HIV Treatment Center of Jos University Teaching Hospital Jos, Nigeria.

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Abstract

Introduction:

Cervical cancer is the most common cancer among women living with HIV with the highest burden in sub-Saharan African countries with the highest prevalence of HIV. Early detection of precursor cervical lesions through routine Pap smear screening is central to cervical cancer prevention. This study was aimed at determining the prevalence and predictors of abnormal Pap smear findings among women with HIV in our cervical cancer screening program.

Methodology:

We carried out a cross sectional study of adult women with HIV who presented for Pap smear test for the first time at the Jos University Teaching Hospital, Jos, North Central Nigeria between November 2018 and January 2020. Prevalence of abnormal cervical finding was reported in percentage and also expressed per 100 population of women. The effects of the characteristics of the women of the abnormal pap smear finding was determined using the logistic regression model where 95% confidence interval and adjusted odds were used as point and interval estimates respectively while a probability value of < 0.05 was considered statistically significant.

Results:

A total of 949 women with HIV participated in the cervical screening program with mean age 43.3 ± 8.1 years. Abnormal smear findings were observed among 183 (19.3%; 19 cases per 100 women) with ASCUS, ASC-H, LSIL, HSIL, HSIL with suspicion of invasion and AGUS accounting for 96 (10.1%), 50(5.3%), 27 (2.9%), 6 (0.6%), 2 (0.2%) and 2(0.2%) respectively. Of the abnormal smear findings, 125 (68.3%) were adjudged to have mild cytological feature while the complementing proportion adjudged to have severe cytological features. Unadjusted odds of abnormal Pap smear result was associated with increasing age, OR 1.15(95% CI 1.127, 1.186; p = 0.001); parity, OR1.08 (95% CI 1.019, 1.141; p = 0.009). In the adjusted model, increasing age remained the only factor predicting abnormal Pap smear finding.

Conclusion: Prevalence of abnormal Pap smear results remains high in HIV- infected women and is associated with increasing age. Advocacy to institutionalize screening at earlier age is therefore key to improving dismal outcomes.

Introduction

Cervical cancer though preventable has continued to pose as a public health threat in sub-Saharan Africa. [1] According to WHO, 19 out of the top 20 countries worldwide with the highest burden of cervical cancer in 2018 were in Africa. [1] Ninety per cent of 311 000 cervical cancer deaths globally per year occur in low- and middle-income countries (LMICs), with the highest burden borne by sub-Sahara African countries that have the highest burden of Human Immunodeficiency Virus (HIV). [2]
HIV-positive women are at increased risk of human papillomavirus (HPV) infection and progression to invasive cervical cancer (ICC). [2] The likelihood that a woman living with HIV will develop invasive cervical cancer is up to five times higher than for a woman who is not living with HIV.[2] Few diseases reflect global inequities as much as cancer of the cervix. In LMICs its incidence is nearly twice as high, and its death rates three times as high, compared with high income countries (HICs). [2, 3] Proven and cost-effective measures for eliminating cervical cancer such as avoidance of risk factors, HPV vaccination, papanicolaou screening (pap smear) and treatment of precancerous lesions exist, but to date have not been widely implemented in regions of the world where the disease burden is highest.[2–6]

In Nigeria as in other sub-Saharan African countries there is no organized screening program, and the few services available are only opportunistic with little or no impact.[7–12] Development of cervical cancer screening policy and institution of organized screening program targeted at covering ≥ 80% of population at risk is fundamental. [13–15]

Though HIV care and treatment in countries worst hit by HIV epidemic has resulted in prolongation of life expectancy, cervical cancer in women living with HIV has not received the attention and resources that is needed to address its prevention and treatment. [16, 19]

We therefore sought to determine the prevalence and predictors of abnormal Pap smear findings among a group of HIV-infected women accessing an opportunistic cervical cancer screening service newly established at the HIV treatment center in Jos, 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 Jos University Teaching Hospital (JUTH), Jos between November 2018 and January 2020.

Study Area

JUTH is a tertiary health institution located at Jos, Plateau state with a catchment area of the four states of the north-central geopolitical region of Nigeria. These are Benue, Nassarawa, Kaduna and Bauchi states. Plateau state is located in Nigeria's middle belt with an area of 26,899 square kilometers and an estimated population of about three million people in 2019. [20]

Study Population

The study population comprised 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.

**Data Collection**

De-identified data of HIV-positive women attending the adult HIV clinic in JUTH for the first time was obtained from the secured electronic records of the clinic. The cervical Pap smear cytology screening outcomes were reported according to the Bethesda 2001 cytology reporting system. [21]

The key dependent variable was the cervical cytology (Pap smear) screening outcomes. Data on sociodemographic and reproductive characteristics as well as clinical information such as nadir viral load and nadir CD4 counts were also obtained. The age, CD4 count and viral load were used as continuous variables while categorical variables were parity (0, 1–4, ≥ 5), age (≤ 43, >43), age at first sexual debut (< 15, 15–18, ≥ 19), number of sexual partners (1, 2–4, ≥ 5) and use of contraception (used, not used). Viral load was further log transformed for analysis in view of the skewed nature of the measurement. Pap smear results was categorized into normal squamous intraepithelial lesion (SIL) and abnormal SIL while the abnormal SIL was further categorized into mild dysplasia and severe dysplasia. Abnormal SIL were ASCUS, ASC-H, LSIL, HSIL, and HSIL with suspicion of invasion and AGUS while mild dysplasia and severe dysplasia were ASCUS, AGUS, LSIL and ASC-H, HSIL, HSIL with suspicion of invasion respectively.

**Data analysis**

The data collected was analyzed with STATA software, version 14 college station (Stata Corporation, TX, USA; 1985). Continuous variables were expressed as means, medians, standard deviations and interquartile range and categorical variables as percentages and proportions. Logistic regression models were developed to explore the association of selected variables with cervical cytological outcomes among the women.

Three level of analysis were done. The first level analysis was a descriptive analysis to determine the overall prevalence and pattern of cervical cytological abnormalities based on various sociodemographic and clinical characteristics of the women. Differences in proportions and means of observable measures between the cervical cytology outcomes were assessed using Chi-square test for proportions and t-test for difference of means.

The second level analysis was bivariate logistic regression analysis performed to assess the association between apriorically selected sociodemographic, clinical (viral load and CD4 count), reproductive characteristics and (1) cervical cytology results (normal and abnormal squamous intraepithelial lesion) (2) mild dysplasia (3) severe dysplasia. The third level analysis was a multivariate logistic regression analysis involving all the factors that were significantly associated with cervical cytology (Pap smear) results at the second level analysis. Box plots graphs of ages of these women by Pap smear results was
plotted. $P < 0.05$ was considered as statistically significant. The results are presented as crude odds ratios (CORs) or adjusted odds ratios (AORs) and their 95% CI.

**Methodology**

We performed a cross-sectional study of adult women with HIV who presented for Pap smear screening test at the Jos University Teaching Hospital, Jos, North Central Nigeria between November 2018 and January 2020. Prevalence of abnormal cervical finding was reported in percentage and also expressed per 100 population of women. Association between characteristics of the women and finding of pap smear screening was determined using logistic regression with 95% confidence interval and crude odd ratio used as interval and point estimates of the effect of the characteristics of the women on the outcome of the screening while a p-value of $< 0.05$ was considered statistical significant.

**Results**

A total of 949 HIV positive women's data was analyzed with mean age 43.3 ± 8.1 years. Abnormal smear findings were observed among 183 (19.3%; 19 cases per 100 women) with ASCUS, ASC-H, LSIL, HSIL, HSIL with suspicion of invasion and AGUS accounting for 96 (10.1%), 50(5.3%), 27 (2.9%), 6 (0.6%), 2 (0.2%) and 2(0.2%) respectively.

Abnormal SIL consisted of mild dysplasia 125(68.3%) and severe dysplasia 58(31.7%). Those with parity $\geq 5$ had the highest frequency 493(51.9%). The age group with highest frequency at first sexual debut was 15–18 years, 449(47.3%). Those who did not use any form of contraceptive accounted for 540(53.9%). [Table 1]

In the bivariate analysis of the relationship between certain sociodemographic and clinical factors and Pap smear results only age and parity were statistically significant. [Table 2]

Results for the bivariate and multivariate logistic regression with unadjusted and adjusted odds ratio of the association of clinical, sociodemographic parameters and total Pap smear results (normal SIL and abnormal SIL): In the unadjusted model age OR 1.15(1.128, 1.186; $p = 0.001$), parity OR 1.08 (1.019, 1.141; $p = 0.009$) and $\geq 5$ number of sexual partners OR 0.49(0.290, 0.818; $p = 0.006$) were statistically significantly associated with Pap smear results. While only age OR 1.16 (1.130, 1.191; $p = 0.001$) remained statistically significant in the adjusted model. [Table 3] Mild dysplasia: In the unadjusted model age OR 1.14(1.111, 1.173; $p = 0.001$) and $\geq 5$ number of sexual partners OR 0.49(0.266, 0.917; $p = 0.026$) were statistically significantly associated with mild dysplasia. While only age OR 1.15(1.114, 1.179; $p = 0.001$) remained statistically significant in the adjusted model. [Table 4] Severe dysplasia: In the unadjusted model age OR 1.09(1.064, 1.135; $p = 0.001$) and nadirCD4 count OR 0.99(0.995, 0.999; $p = 0.006$) were statistically significantly associated with severe dysplasia. While only age OR 1.09(1.064, 1.136; $p = 0.001$) and Nadir CD4 count OR 0.99(0.995, 0.999; $p = 0.007$) remained statistically significant in the adjusted model. [Table 5]
First Box plot shows a higher median age 52 years for women with abnormal squamous intraepithelial lesion than median age 42 years for those negative squamous intraepithelial lesion. [Figure1] Second Box plot shows equal median ages 52 years for women with both mild and severe dysplasia. [Figure2]

Table 1 Baseline socio-demographic characteristics and pap smear results of HIV positive women who were screened at HIV treatment center of Jos University Teaching Hospital (JUTH) at Jos, Nigeria (N = 949)

Discussion

Our results highlights the distribution of sociodemographic and clinical factors associated with morphologic cervical cytological findings from an opportunistic Pap smear screening among adult HIV women managed in our HIV treatment center at Jos, Nigeria. We found that the median age and mean age at onset of screening was 43 years. [Table 1] This is in variance to the 35 years reported from an earlier study done in the same hospital but at a different center that screens for the general population. [22] This might be due to the lower sample size in this study. Other similar studies in other centers in the region also report a lower mean age at first screening. [23–26]

The prevalence of abnormal Pap smear results from this study was 19.3% which is higher than that reported in previous studies from same center but is consistent with reports of studies from other regions [22, 23] This study had a lower sample size than that of the previous studies in the same hospital .[24–27] In this study as in most similar studies ASCUS was the commonest and AGUS the least common subtype of the abnormal SILs.[22–27] Of the abnormal SILs reported, proportion of mild dysplasia was twice that for severe dysplasia which is consistent with similar studies.[22–27]

The average CD4 count in this study was about 260 cells/mm$^3$ which is lower than that reported in a similar study in Southeastern Nigeria (325 cells/ mm$^3$).[28] Cluster differentiation( CD4) count level has been reported in other studies to be related (inversely proportional) to severity of cervical dysplasia in HIV women.[Table 1][28–30]

Higher age of HIV positive women at screening is found to be predictive of abnormal pap smear result in general and both mild and severe dysplasias specifically which is consistent with similar studies. [Tables 2,3,4,5][Figures 1,2],[26–30] Since the mean age in this study was 43 years which is far higher than the age 21 years recommended by WHO and age 35 years previously reported as onset of ICC in the same setting, it implies that many of the women will have developed dysplasia at time of screening which can progress to invasive lesions.[31]

In this study we found a significant negative correlation between Nadir CD4 count and severe dysplasia. [Table 5] This is consistent with most similar studies that show that lower CD4 counts are associated with severity of dysplasia. [22–32]
Weakness of this study could be from the fact that these patients might not be representative of general HIV population since they are accessing care in the treatment center against all odds thus introducing bias. There is also the possibility of misinformation bias regarding some of the sociodemographic variables obtained from the women which they consider private and for fear of stigmatization. However, the strength of this study is the fact that the last study done specifically on HIV women in our center was as far back as eleven years ago (2009). This study therefore provides current reality.

Recommendations

Early age (21 years) at initiation of screening in line with WHO guideline should be encouraged to largely prevent cervical cytological abnormalities and ICC. This should be integrated with protocol for normal care of HIV positive women which will reduce incidence of cervical ICCs in this vulnerable group. Future research with larger sample size to increase the power of the measures and including other variables like cigarette smoking, presence of sexually transmitted infections, educational and economic status should be done. Widespread education of the populace on the burden of cervical cancer and importance of screening at early age using the mass media, counseling at antenatal clinics, and the involvement of men will contribute immensely to reduction in the incidence of ICC. Decentralization of services by incorporation of cervical screening and treatment in primary health care programs will ensure adequate rural-urban coverage.

Conclusion

This study shows that prevalence of abnormal cervical cytology has remained high with increasing age at onset of screening in our setting. Thus, there is need to intensify education on early Pap smear screening including making this screening accessible, affordable and a necessary part of care among our HIV positive women.

Declarations

Ethics Statement

The studies involving use of secondary data were reviewed and approved by Jos University Teaching Hospital’s (JUTH) Ethical committee and AIDS prevention initiative in Nigeria (APIN). Written informed consent from the participants’ legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Consent for publication

Not applicable.

Availability of data and materials
All the relevant data for this analysis have been presented in the body of this manuscript. The original data sources and the dataset used in this analysis is available upon reasonable request to the corresponding author.

**Competing interests**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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**Authors’ contributions**

OAS conceptualized the study. JM, POA, TOA, CA, FHW and LH made technical inputs in the conceptualization and design of the study. OAS, JM, BMM, SAS and LH produced the first draft of the manuscript. SAS, RLM, LH, SRO and ETC contributed in further interpretation of findings and editing of the final draft of the manuscript. All co-authors contributed in revising the manuscript and approved the final version for submission.

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Tables

Table 1: Summary statistics of the socio-demographic and cervical cytology (Pap smear) outcomes of women who received first screening in an opportunistic cervical cancer screening program in Jos Nigeria (N = 949)
| Characteristics          | Frequency | Percentage (n = 949) |
|--------------------------|-----------|----------------------|
| Age Group (years)        |           |                      |
| ≤ 43                     | 521       | 54.9                 |
| > 43                     | 428       | 45.1                 |
| Total                    | 949       | 100.0                |
| Age (years)              | Mean 43.31612 | SD (8.099537)          |
|                          | Median 43.0 | IQR (38 – 49)           |
| Normal CIL               | 766       | 80.7                 |
| Abnormal CIL             | 183       | 19.3                 |
| Total                    | 949       | 100.0                |
| Mild dysplasia           | 125       | 68.3                 |
| Severe dysplasia         | 58        | 31.7                 |
| Total                    | 183       | 100.0                |
| Nadir CD4 count (cells/mm³) | Mean 259.883 | SD (151.0319)          |
|                          | Median 251 | IQR (383- 134)         |
| Log(Nadir viral load) (copies/ml) | Mean 5.377711 | SD(1.451614)         |
|                          | Median 5.713733 | IQR(6.289716 - 5.273) |
| Current CD4 count copies/mm³ | Mean 294.1739 | SD (157.3366 )        |
|                          | Median 290 | IQR (421 – 168)       |
| Log(current viral load)copies/ml | Mean 3.271483 | SD (1.776495 )       |
|                          | Median 3.951244 | IQR (4.430817 - 3.465736) |
| Parity                   |           |                      |
| Nulliparous              | 37        | 3.90                 |
| 1-4                      | 419       | 44.15                |
| 5 and more               | 493       | 51.95                |
| Parity | Mean | SD(2.775) | Median | IQR(3-7) |
|--------|------|-----------|--------|----------|
|        | 4.863014 |          | 5.0    |          |

| Age at first sexual debut (years) |       |       |
|----------------------------------|-------|-------|
| < 15                             | 65    | 6.85  |
| 15-18                            | 449   | 47.31 |
| ≥19                              | 435   | 45.84 |

| Number of sexual partners |       |       |
|----------------------------|-------|-------|
| 1                          | 285   | 30.0  |
| 2-4                        | 478   | 50.4  |
| ≥ 5                        | 186   | 19.6  |
| Total                      | 947   | 100.0 |

| Use of any form of contraceptive |       |       |
|----------------------------------|-------|-------|
| Use                              | 409   | 43.10 |
| Not use                          | 540   | 53.90 |

Log = logarithm; CD4 = cluster differentiation; contraceptive = barrier, non-barrier

Table 2 Bivariate analysis of socio-demographic characteristics by cervical cytological (pap smear) abnormalities (NSIL and ASIL) of HIV positive women who were screened at HIV treatment center of Jos University Teaching Hospital (JUTH) at Jos, Nigeria (N = 949).
| Characteristics                        | NSIL (n=766) | ASIL (183) | P   |
|---------------------------------------|--------------|------------|-----|
| Age (mean ± SD)                       | 766 (41.6±7.3) | 183 (50.1±7.6) | 0.001 |
| Parity (mean± SD)                     | 183 (5.4±2.8)  | 766 (4.8±2.8) | 0.001 |
| Age at first sexual debut (mean± SD)  | 766 (18.8±3.7) | 183 (18.7±3.8) | 0.597 |
| Number of sexual partners             | 766 (3.3±4.7)  | 183 (2.8±2.3) | 0.383 |
| Use of any form of contraceptive      |              |            |     |
| Use                                   | 426          | 114        |     |
| Not use                               | 340          | 69         |     |
| Nadir CD4 count (Cells/mm³)           | 766 (262.3±151.6) | 183 (249.8±148.8) | 0.279 |
| Log Nadir viral load (Copies/ml)      | 766 (5.4±1.4)  | 183 (5.4±1.2) | 0.465 |

NSIL = Normal squamous intraepithelial lesion; ASIL = Abnormal squamous intraepithelial lesion

Table 3: Univariable and multivariable Logistic regression with unadjusted and adjusted odds ratio of the association of HIV-clinical parameters and other sociodemographic variables and cervical cytology results (pap smear test) in Jos, Nigeria (N=949)
| Variable                  | Unadjusted (95% CI)                | p-value | Adjusted HR (95% CI) |
|--------------------------|------------------------------------|---------|----------------------|
| Age                      | 1.16(1.127917,1.186286)            | 0.001   | 1.16(1.128791,1.19015) |
| Parity                   | 1.08(1.019118,1.140563)            | 0.009   | 0.97(0.904746,1.035065) |
| Number of sexual partners|                                    |         |                      |
| 1                        | 1                                  |         | -                    |
| 2-4                      | 0.87(.60724,1.240166)              | 0.436   |                      |
| ≥ 5                      | 0.49(.2903536,.8176697)            | 0.006   |                      |
| Age at first sexual debut|                                    |         |                      |
| ≤ 15                     | 1                                  |         | -                    |
| 15-18                    | 0.89(.4812841,1.662634)            | 0.725   |                      |
| >18                      | 0.67(.3582139,1.261373)            | 0.216   |                      |
| Use of contraception     |                                    |         |                      |
| Not used                 | 1                                  |         | -                    |
| Used                     | 1.32(.9468724,1.836364)            | 0.102   |                      |
| Nadir CD4 count          | 0.99(.9983782,1.000526)            | 0.317   |                      |
| Nadir log (viral load)   | 1.02(.9107995,1.143346)            | 0.727   |                      |

Referent values were contraception (not used), Age at first sexual debut (≤15), number of sexual partners (1), age (<34), Nadir CD4 count (cells/mm$^3$), Nadir viral load (copies/ml)

Table 4: Univariable and multivariable Logistic regression with unadjusted and adjusted odds ratio of the association of HIV-clinical parameters and other sociodemographic variables and mild cervical dysplasia at pap smear test in Jos, Nigeria (N = 125)
| Variable                          | Unadjusted (95% CI)            | p-value | Adjusted HR (95% CI)               |
|----------------------------------|--------------------------------|---------|-----------------------------------|
| **Age**                          | 1.14 (1.111543 1.172786)       | 0.001   | 1.15 (1.114464 1.179861)          |
| **Age (Group)**                  |                                |         |                                   |
| <34 (ref.)                       | 1.0                            |         |                                   |
| ≥ 34                             | 6.77 (4.219456 10.87706)       | 0.001   |                                   |
| **Parity**                       | 1.06 (.9966807 1.13217)        | 0.063   | 0.95 (.8841163 1.027615)          |
| **Number of sexual Partners**    |                                |         |                                   |
| 1                               | 1.0                            |         |                                   |
| 2-4                             | 0.92 (.606069 1.388794)        | 0.684   | 1.22 (.7685212 1.920938)          |
| ≥ 5                             | 0.49 (.265705 .9172436)        | 0.026   | 0.79 (.4048118 1.533719)          |
| **Age at first sexual Debut**    |                                |         |                                   |
| ≤ 15                            | 1                              |         |                                   |
| 15-18                           | 1.20 (.5499461 2.644928)       | 0.640   |                                   |
| >18                             | 0.97 (.4369926 2.141434)       | 0.935   |                                   |
| **Use of contraception**         |                                |         |                                   |
| Not used                         | 1                              |         |                                   |
| Used                             | 1.15 (.7892526 1.69922)        | 0.453   |                                   |
| Nadir CD4 count                  | 1.00 (.9992692 1.001756)       | 0.420   |                                   |
| Nadir log (viral load)           | 1.02 (.8935557 1.166512)       | 0.760   |                                   |

Referent values were contraception (not used), Age at first sexual debut (≤15), number of sexual partners (1), age (<34). Nadir CD4 count (cells/mm³), Nadir viral load (copies/ml)
Table 5: Univariable and multivariable Logistic regression with unadjusted and adjusted odds ratio of the association of HIV-clinical parameters and other sociodemographic variables and severe cervical dysplasia at pap smear test in Jos, Nigeria (N = 58)

| Variable                          | Unadjusted (95% CI) | p-value | Adjusted HR (95% CI)         | p-value |
|-----------------------------------|---------------------|---------|-----------------------------|---------|
| Age                               | 1.09(1.063574 1.134968) | 0.001   | 1.09(1.063579 1.135905)     | 0.001   |
| Age (Group)                       |                     |         |                             |         |
| <34(ref.)                         | 1.0                 |         |                             |         |
| ≥ 34                              | 4.59(2.442268 8.631273) | 0.001   |                             |         |
| Parity                            | 1.08(.9911224 1.172712) | 0.080   |                             |         |
| Number of sexual partners         |                     |         |                             |         |
| 1                                 | 1.0                 |         |                             |         |
| 2-4                               | 0.812(.4537969 1.452818) | 0.483   |                             |         |
| ≥ 5                               | 0.565(.265705 .9172436) | 0.181   |                             |         |
| Age at first sexual debut         |                     |         |                             |         |
| ≤ 15                              | 1                   |         |                             |         |
| 15-18                             | 0.593(.2492119 1.412231) | 0.238   |                             |         |
| >18                               | 0.420(.1711417 1.032148) | 0.059   |                             |         |
| Use of contraception              |                     |         |                             |         |
| Not used                          | 1                   |         |                             |         |
| Used                              | 1.59(.9089841 2.808791) | 0.103   |                             |         |
| Nadir CD4 count                   | 0.99(.9954877 .9992402) | 0.006   | 0.99(.9953228 .9992535)     | 0.007   |
| Nadir log (viral load)            | 1.01(.840942 1.222482) | 0.885   |                             |         |

Referent values were contraception (not used), Age at first sexual debut (≤15), number of sexual partners (1), age (<34). Nadir CD4 count (cells/mm$^3$), Nadir viral load (copies/ml)
Figures

Figure 1

Box plot of age at screening by Pap smear result
Figure 2

Box plot of age at screening by severity of dysplasia.