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Precancer Lesions of the Cervix among Treatment Experienced HIV Positive Women at University College Hospital, Ibadan, Nigeria

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Authors' contributions

This work was carried out in collaboration between both authors. Author OAA conceived the idea of the study, participated in the design of the study, reviewed the protocol, statistical analysis, first draft of the manuscript, vetted the final manuscript and performed the statistical analysis. Author SOO developed the first draft of the data abstraction form, performed the abstraction of the data and reviewed the first draft of the manuscript. Both authors read and approved the final manuscript.

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ABSTRACT

Background: Cervical precancer lesions, caused by persistence of human papilloma virus (HPV) infection, is common among women living with Human immunodeficiency virus (HIV) infection. However, there remains paucity of information on these dysplastic lesions especially in low- and middle-income countries of the world as there are few programmes that have incorporated routine screening as a standard of care.
Aim: To determine the pattern of precancer lesions of the cervix among treatment experienced HIV positive women in a large antiretroviral therapy programme in South West Nigeria.
Study Design: Retrospective review of clinical records.
Place and Duration of Study: HIV Programme in College of Medicine, University of Ibadan/University College Hospital, Ibadan, Nigeria between January 2014 and December 2015.

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Methodology: A review of the Pap smear results of 468 women attending the antiretroviral therapy (ART) clinic at the University College Hospital (UCH) Ibadan over a 2-year period was done. The cytological results were analyzed with biosocial variables. Level of significance was set at 95% confidence level.

Results: The mean age of the participants reviewed was 37.1+/- 8.7 years. The mean duration of ART among the participants was 19.5 (±14.0) months. The prevalence of any form of squamous Intraepithelial lesions (SIL) varied from 10.0% among those on ART for up to 12 months to 1.4% among those with more than 18 months of ART use (p=022) and polygamous relationship is significantly associated with dysplastic cervical lesions among this studied cohort (p=0.043)

Conclusion: While ART appears to have anti-Human Papillomavirus (HPV) activities as observed in the pattern of cervical dysplastic lesions, polygamy, a common family setting in this environment seems to promote development of SIL among these WLHIV. These findings require further studies to corroborate in the light of limitations of difficulty in disaggregating the duration of HIV diagnosis from the onset of treatment as most were already on treatment before the screening and failure of baseline Pap smear test at the entry point to determine the rate of progression.

Keywords: Pre-malignant cervical lesions; HIV positive; durations of treatment.

1. INTRODUCTION

Carcinoma of the uterine cervix is the second leading women cancer both for incidence and mortality worldwide and the leading cause of cancer deaths in women in many low- and middle-income countries (LMIC) [1] These countries account for over 80% of the cervical cancer incidence and mortality of the world [2]. In SSA, it is estimated that 34.8 new cases of cervical cancer are diagnosed per 100,000 women each year. It is estimated in SSA that invasive cervical cancer represented one-quarter of all cancer cases in the continent and constituted the most common cause of cancer death among women of the region, with the highest incidences occurring in East Africa (42.7 per 100,000), West Africa (29.3 per 100,000) and southern Africa (31.5 per 100,000). Mortality from cervical cancer in Africa is very high, primarily due to lack of adequate medical resources; it is estimated that cervical cancer was responsible for 266,000 deaths globally, translating into 22.5 per 100,000 women in SSA [3,4]. However, cervical cancer has been found to be among the few highly preventable and treatable malignancies [5].

Cervical cancer is initiated by persistence of acquired infection with human papillomavirus (HPV) [6-8] which may generally progress in stages from low-grade squamous intraepithelial lesions (LSIL) to high-grade squamous intraepithelial lesions (HSIL). HSIL may then progress to invasive squamous carcinoma. The risk of progression from LSIL to HSIL or invasive cancer is low and usually occur over many years [8,9]. HPV is a ubiquitous, mostly transient and vaccine preventable infection the disease pathogenesis of which depends on a number of factors including immunosuppression. This makes women living with HIV (WHIV) a significant group at higher risk of HPV acquisition, persistence and progression to dysplastic cervical lesions and invasive cervical cancer (ICC).

Human immunodeficiency virus infection (HIV) and cervical cancer constitute major public health concerns in Nigeria and Sub-Saharan Africa at large [1,10-12]. Cervical cancer, according to WHO and CDC, is an AIDS defining illnesses [13,14]. In HIV infected individuals, higher rates of HPV infection with faster and more frequent progression have been well documented [15-19]. There is, also, poor treatment outcomes for ICC associated with HIV co-infection [19-21]. Some evidence, also, suggest that HIV infected women with ICC are more likely to have advanced disease at presentation and a higher recurrence rates than the non-HIV infected counterparts [22]. Most of these evidences were products of research conducted before wide availability of effective antiretroviral treatment for HIV. Today, HIV infections have become a chronic, manageable infective condition due to availability of many effective cocktails of antiviral agents. These are expected to modulate the prevalence and pattern of HPV induced cervical lesions. However, data on the direct effects of the available ARTs on cervical precancer lesions are few especially in our environment, like many LMIC. This has been difficult for a number of logistic and programmatic challenges.

This study, thus, aimed to describe the pattern of squamous intraepithelial lesions of the cervix among a cohort of women who have been on ART for at least one months and clinically stable at our centre.

2. MATERIALS AND METHODS

This was cross sectional review of data of 468 consenting females confirmed HIV positive, receiving treatment at the University College Hospital antiretroviral (ARV) clinic who had cervical precancer screening over a 2-year period of January 2014 and December 2015. The ARV clinic situated in Ibadan, Oyo state of Nigeria, since its inception in 2002, has continued to serve as a referral center on HIV/AIDS for people from many parts of the state and the country as a whole. The HIV program has a robust hybrid paper and electronic database system that capture the sociodemographic, biological and programme-related information of all enrolled patients utilizing a unique identification numbering system. Consent is usually obtained from every patient for programme service provision and archiving of data for future research and evaluation process. In 2008, as part of standard of care for the HIV programme, cervical cancer screening using cytology method was commenced and offered routinely to all eligible female patient in the HIV clinic. This paper is based on data from the electronic database of female patients that were at least on antiretroviral treatment for one month, non-pregnant, 18 years and above, gave consent and have satisfactory Pap smear results. The data were abstracted into a proforma to capture information on the participants' socio-demographic data, reproductive history, duration of HIV diagnosis, antiretroviral history, history of sexually transmitted infections (STI) and results of cervical cancer screening.

The women with abnormal smears were classified into either Atypical squamous cells [Atypical squamous cells of undetermined significance (ASC-US or Atypical squamous cells – cannot exclude HSIL (ASC-H)], Low-grade squamous intraepithelial lesion (LSIL), High grade squamous intraepithelial lesion (HSIL), Squamous cell carcinoma, Atypical Glandular Cells not otherwise specified (AGC-NOS), Atypical Glandular Cells, suspicious for AIS or cancer (AGC-neoplastic), Adenocarcinoma *in situ* (AIS). The participants with features of inflammation, but no cells suggestive of intraepithelial cells or malignancies were, also, reported. Participants with abnormal results suggestive of intraepithelial neoplasia and that were referred for further evaluation at the gynaecologic clinic of the hospital were noted. The usual treatment algorithm for the cytology related services included repeat test for those with inadequate/unsatisfactory Pap Smear, treatment with antibiotics for those with inflammatory cells and repeat of the Pap test 3-6 afterward. The participants with Pap smear report of LSIL were, also, requested to repeat the test 6-12 months later while those with HSIL lesions underwent colposcopy and biopsies with those confirmed with CIN 2+ offered loop electrosurgical excision procedure (LEEP) in the hospital cytology and colposcopy unit (results not included in this review). All the cytology tests, and biopsies as well as LEEP were covered under the funded HIV programme of the institution. Cases with suspected invasive cervical malignancy underwent examination under anaesthesia and biopsy for staging and, subsequently referred for radiotherapy when confirmed with invasive cervical cancer that is amenable to more than what simple hysterectomy can be performed for.

Collected data were collated, cleaned and entered and analyzed using SPSS version 23. The data were presented in tables and charts along with the outcome of their analyses. The associations were tested using chi-square test for categorical variables. The level of significance for all analyses was put at probability value of 0.05.

3. RESULTS

The mean age of the cohort of participants under review was 37.0± 8.6 years with mean age of marriage being 23.3± 4.4 years. Among the patients reviewed, 64.8% had at least a secondary education with 82.5% currently married of which 47.9% are in polygamous family setting. The modal parity was 2 (mean, 3.2± 1.9) (Table 1).

The median duration of HIV diagnosis was 22 months with 71.6% having been on ARTfor 12 or more months (Table 2). A history of previous STI was reported among 23.1% of the participants while very few (6.8%) have had a previous screening service for cervical precancer. On visual inspection, 11.1% had abnormal cervix ranging from contact bleeding to cervical erosion, polyps, hyperaemic lesions, cervical discharge,

or cervical mass (results not shown). A review of ART history of the 468 women who participated in the cervical screening service over the study period showed that 403 (86.1%) were on first line ART of a combination of 2 nucleoside reverse transcriptase inhibitor like zidovudine and lamivudine and 1 non-nucleoside reverse transcriptase inhibitor like nevirapine or efavirenz. Few other participants, (13.9%) were on second line antiretroviral therapy. None of the participants was on third line antiretroviral therapy.

Table 1. Socio-demographic profile of subjects

Characteristics	Mean (SD)
Age (Years)	37.0 (8.6)
Parity	3.2 (1.9)
Age at marriage (Years)	23.3 (4.4)
Characteristics	**Frequency (%)**
Education	
None	50 (10.7)
Primary	115 (24.6)
Secondary	204 (43.6)
Tertiary	99 (21.2)
Marital status	
Single	57 (12.2)
Married	386 (82.5)
Separated	10 (2.1)
Widowed	15 (3.2)
Family setting (n=386)	
Monogamy	201 (52.1)
Polygamy	185 (47.9)
Previous Cervical Precancer Screening	
Yes	32 (6.8)
No	436 (93.2)

The Pap smear results showed that 82.1% had normal results, 7.5% had results reported as inflammation, 0.9% has ASCUS, 5.3% had low grade squamous intraepithelial lesions (LSIL), 3.8% as high grade squamous intraepithelial lesions (HSIL) and 0.4% as invasive carcinoma (Fig. 1). The rate of LSIL and HSIL varied from 10.0% and 6.7% among those on ART for up to 12 months to 1.4% among those with more than 18 months of ART use, respectively which on bivariate analysis showed a significant association (p=0.022). Also, polygamous family stting was significanty associated with risk of cervical precancer lesions (p= 0.043) (Table 3).

4. DISCUSSION

The prevalence of any form of abnormal results in this study group of HIV positive women was 13.3% while the prevalence of cervical precancer lesions was 10.0 % and that of invasive cervical cancer (ICC) was 0.4%. This study also shows that there is a positive relationship between the duration of ART use and the rate of of pre-malignant cervical lesions. It is worth noting that LSIL (5.3%) and HSIL (3.8%) and ASCUS (0.9%) were highest among those with at most primary education compared with those with higher levels of education, even-though it was not statistically significant (p=0.49). However, it is surprising that inflammatory lesions were highest (12.7%) among those with tertiary education than others with either primary, secondary or no education at all.

Prevalence of cervical precancer lesions among HIV positive women in Nigeria differ in different regions, ranging from 6.3% to 32.7% [23-30]. From our study, the prevalence of cervical precancer lesions among women living with HIV (WLHIV) on HAART was 10.0%`which was higher compared with with findings by Agboeze et al 2015, (6.3%), but lower than what was find by Ezechi et al., 2014 (14.3%), Swende et al., 2012 (17.8%), Ogu et al (19.05 %) from different studies in Nigeria [23, 31-33]. This may be due to differences in population characteristics, and sample size. However report of Dim et al., (2011), Ugbuaja et al., (2017) , Chama et al (2005) and Muhammad et al. (2017) who worked on HIV positive women not on HAART were 12.6%, 28.2%, 31.3% and 32.7% respectively [25,26,29,30]. A protective effect of antiretroviral treatment on the risk of squamous intraepithelial lesions have not been satisfactorily established by previous studies [34-36]. In this study there was a reduction from 10.0% to 1.4% and 6.7% to 1.4% for LSIL and HSIL, respectively, among WLHIV with up to 12 months of HAART compared to those with use greater than 18 months. This was statistically significant (p=0.022) showing a strong relationship between duration of HAART use and prevalence of cervical precancer lesions. Mogtomo *et al* reported that while LSIL incidence in women with HIV infection on HAART therapy decreased from 8.6% to 5.7% in the first 10 months of HAART use, it increased to 11.4% after 10 months. In contrast, HSIL cases decreased from 14.3% to 5.7% after 10 months [37]. Kim et al concluded that HAART decreases risk of progression to cervical dysplastic lesions in HIV-

infected women [38] a finding, also, demonstrated in our study. Heard et al showed that HAART had a positive impact on regression of SIL, and this was associated with increasing CD4 cell counts [39] with ARV treatment and the mean log 10 viral load increased from 3.6 among those with infection to 5.55 in the woman with malignancy while the median CD4 count followed a reverse pattern, though the trend was not statistically significant. In our study, the viral loads (p=0.528) and CD4 cell (p=0.114) were statistically not significant among the participants. There was significant positive relationship between the degree of cervical dysplasia and family setting with inflammatory results (9.5%), and HSIL (7.1%) were commoner among those from polygamous setting than their monogamous counterpart (p=0.043). This is consistent with the principle of multiple sexual partnering associated with polygamy and its known risk factor for transmission of HPV which is the causative agent for cervical precancer and cancerous lesions. The strong association between these, possible, infection-related inflammatory process of the cervix and cervical intraepithelial lesions re-emphasized the synergistic effects of genital infections and genital viral induced pathologies including HPV in the pathogenesis of cervical dysplasia and subsequent cancer. While it would have been desirable to recommend use of HPV DNA as primary screening method for precancer lesions in this population, the logistics associated with this method are still less established compared with cytology or VIA methods. Therefore, regular Pap smear screening and appropriate referral for treatment of precancerous lesions, especially in a setting with such infrastructure and personnel remains an effective method for decreasing the incidence of cervical cancer among WHLHIV as demonstrated in this study.

The majority of women in the present study were between 30 years and 49 years with a median age of 35 years. This is about 15 to 25 years before the peak age of invasive cancer (50 to 60 years) in the general population. However, HIV positive women with invasive cervical cancer were about 10 to 15 years younger than HIV negative controls in Kenya and South Africa [23,24], suggesting that HIV shortens the progression from pre-malignant lesions to invasive cervical cancer. The two patients with invasive cervical cancer in this study were 40 years and 48 years which were 2 years and 10 years, respectively, younger than the lowest age of 50 years. Therefore, if it is required that every woman should have at least a Pap smears in their lifetime in a normal situation starting from 40years of age, it is recommended that WLHIV start earlier to prevent missing some of those with early onset lesions as seen in this study in which one of the two cases with ICC was 40 years and 53.2% (25/47) of the patients with dysplastic lesions of the cervix (ASCUS+) were less than 40 years [40,41].

The limitations of this study include the fact that there was no baseline Pap smear screening test for patients at entry point. Secondly, the information on the number of lifetime sexual partners was not included in our questionnaires. It is also possible to have under-estimated the rate of dysplasia in the study because the LSIL and HSIL were determined using cytology without histologic confirmations. The last limitation is the unavailability of the facilities to detect different strains of HPV using the HPV DNA PCR.

Table 2. HIV Characteristics of participants

Characteristics	**Frequency (%)**
ART types	
First line ART	403 (86.1)
Second line ART	65 (13.9)
Characteristics	**Mean (SD)**
Duration of HIV diagnosis (Months)	23.4 (19.4)
Duration of ART (Months)	19.5 (14.0)
Viral Load/cpm	65704.43 (230270.5)
Log _VL	3.3 (2.8)
CD4 cell Count/mm^3	382.2 (230.3)

Table 3. Bivariate analysis of selected characteristics & premalignant cervical lesions

	Pap smear results (%)					
	Normal	**Inflammation**	**Ascus**	**Lsil**	**Hsil**	**p-value**
Age						
20 - 29	90.2	5.4	0.0	3.3	1.1	0.23†
30 – 39	81.7	8.2	1.4	6.2	2.4	
40 – 49	76.6	8.6	0.8	5.5	8.6	
50 – 59	90.6	3.1	0.0	3.1	3.1	
≥60	66.7	16.7	0.0	16.7	0.0	
Education						
None	78.0	8.0	0.0	6.0	8.0	0.49†
Primary	84.1	3.5	0.0	8.0	4.4	
Secondary	82.8	9.3	1.0	4.4	2.5	
Tertiary	81.8	8.1	2.0	4.0	4.0	
Marital status						
Single	87.7	3.5	1.8	3.5	3.5	0.258†
Married	82.0	7.6	0.5	6.0	3.9	
Separated	90.0	10.0	0.0	0.0	0.0	
Widowed	66.7	20.0	6.7	0.0	6.7	
Family setting						
Monogamy	87.1	5.4	0.5	6.0	1.0	0.043†
Polygamy	76.9	9.5	0.5	6.0	7.1	
Duration of ART						
≤ 6 months	91.6	6.4	0.0	2.1	0.0	0.022†
7 – 12 months	79.3	2.0	2.0	10.0	6.7	
13 – 18 months	71.2	13.3	2.2	8.9	4.4	
> 18 months	88.8	7.9	0.5	1.4	1.4	
VL (copies/ml)						
≤1000	81.8	8.9	0.7	5.6	3.0	0.528†
1001 – 10000	84.0	4.0	1.3	2.7	8.0	
10001 – 100000	81.0	6.3	0.0	9.5	3.2	
100001 – 1000000	84.7	6.8	1.7	3.4	3.4	
$CD4^+$ count(cells/mm^3						
≤250	87.5	4.6	0.0	3.9	3.9	0.114†
251 – 499	81.9	7.8	2.1	4.7	3.6	
≥500	76.9	10.7	0.0	8.3	4.1	

†*Fishers exact test*

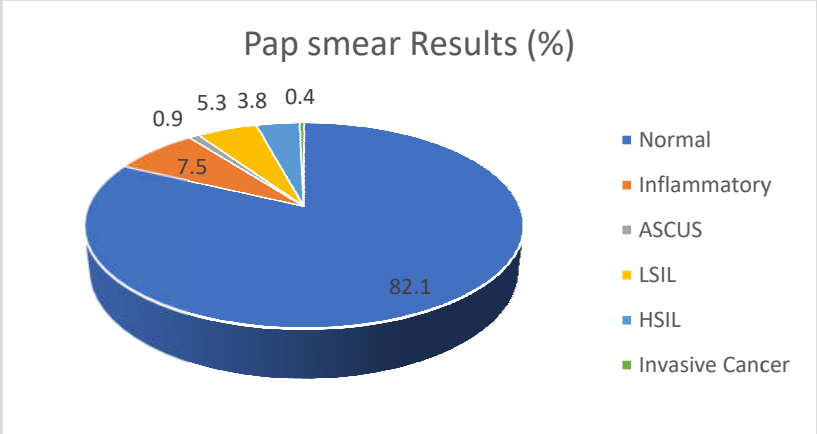

Fig. 1. Pap smear results

5. CONCLUSION

This study showed that antiretroviral therapy appears to have anti-HPV effect as observed in the pattern of cervical lesions and in relation to the duration of HIV treatment. Also, the increased rate of inflammatory and HSIL lesions among the patients in polygamous setting suggest the significant risk associated with multiple sexual partnering, the possibilities of multiple HPV infection and synergistic effects of possible other microbial infections in aethiopathogenesis of cervical precancer lesions by HPV. These need validation with more studies and correlation of Pap smear results with the gold standard, histopathology results.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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