The Influence of HIV Infection on the Prevalence and Pattern of Cervical Cytological Abnormalities in Women in Lagos, Nigeria

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Abstract

Background: *Human immunodeficiency virus (HIV) has become a worldwide pandemic with over sixty percent of those infected in sub Saharan Africa. African women are disproportionately affected compared to their counterpart in other parts of the world. Cervical cancer is one of the leading causes of death in sub Saharan Africa including Nigeria. This study was carried out to determine the prevalence of cervical abnormalities, to determine the frequencies of various types of cervical abnormalities and the relationship between types of abnormal smears and CD4 count in HIV positive women, in Lagos, Nigeria,*

Methods: *This is a cross sectional case control study of HIV positive patients attending the Lagos University Teaching Hospital HIV/AIDS clinic. The control group comprises patients undergoing routine Pap smear in LUTH and St. Kizito's clinic, a missionary hospital in Lekki, Lagos. In all five hundred and ninety two women were included comprising 292 HIV positive women as case and 300 HIV negative women as control. Pap smear test and CD4 count were performed on the case group and HIV confirmation test on the control group.*

Results: *The study found that there is a higher prevalence of squamous intraepithelial lesion among the HIV positive women compared with their HIV negative counterpart (20.2% vs 9.4%); also there is higher rate of human papillomavirus cytopathic effect among the HIV positive women (6.8% vs 3.7%). It was also observed that there is a decrease in abnormal smear pattern with high CD4 count ($p<0.05$).*

Conclusions: *The study showed that there is a higher prevalence of abnormal cervical smears among the HIV positive women (HPW) compared to the HIV negative women (HNW) and there is relationship between the CD4 count and abnormal cervical smear among the HPW. Pap smear should be incorporated into the management of HIV positive.*

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Background

Since the Human immunodeficiency virus (HIV) was discovered in 1983 as the causative agent of Acquired Immunodeficiency Syndrome (AIDS), it has attained an epidemic proportion. HIV is now endemic worldwide and of the total 38.6 million adults and children estimated to be living with HIV/AIDS as of December 2005, 24.5 million (63.5%) are in sub-Saharan Africa.[1.] In Nigeria, there are about 2.9 million Nigerians carrying the virus, and the overall national prevalence was 4.4% as at the end of 2005.[2,3]

Disproportionate numbers of women are infected compared with men in sub Saharan African, Nigeria inclusive. Women make up an estimated 58% of the HIV positive adult population in sub Saharan African compared with 50% worldwide.[1.]

One of the common gynaecological conditions among HIV positive women is squamous intraepithelial lesion – the pre cancerous phase of cervical cancer.[4.] Human papilloma virus (HPV) infection is associated with an increased incidence and severity of squamous intraepithelial lesion and cervical cancer in women with HIV infection.[5.]

Women infected with HIV have greater risk than other women of developing cervical cancer and its precursor lesions. The prevalence of squamous intraepithelial lesion in these women ranges from 15% to 40% depending on the level of immunosupression.[6-8.] People with immunosuppression caused by HIV appear to be more vulnerable to HPV, and the inability of the immune system to clear the infection results in an increased risk of squamous intraepithelial lesions and cancer.[9] The Centres for Disease Control and Prevention in 1993 January designated moderate and severe cervical dysplasia as a category B defining condition, and invasive cervical cancer as a category C defining condition of AIDS.[10, 11.]

The objective of this study was to determine the cervical cytologic pattern in HIV positive women; to determine the frequency of the various types of cervical abnormalities in HIV positive women; to confirm the relationship between types of abnormal smears and CD4 level in HIV positive women and to confirm the relationship between HIV/AIDS infection and cervical dysplasia.

Material and Method

This is a cross sectional study of HIV positive patients attending the Lagos University Teaching Hospital HIV/AIDS clinic in the department of Haematology and Blood Transfusion. The test population included patients in Lagos State and its environs. The study spanned a period of six months from August 2006 to January 2007. A total of 292 HIV positive women (HPW) were included in the study as well as 300 HIV negative women (HNW) who came for routine Pap smear test in LUTH and St. Kizito's Clinic during the period of the study as control group. Included in the test population were all patients visiting the HIV/AIDS clinic as new enrollee and old patients that have never had a Pap smear test during the course of their management. Simple random system was used to select among the old patients. Structured questionnaires were applied to both the test and control groups.

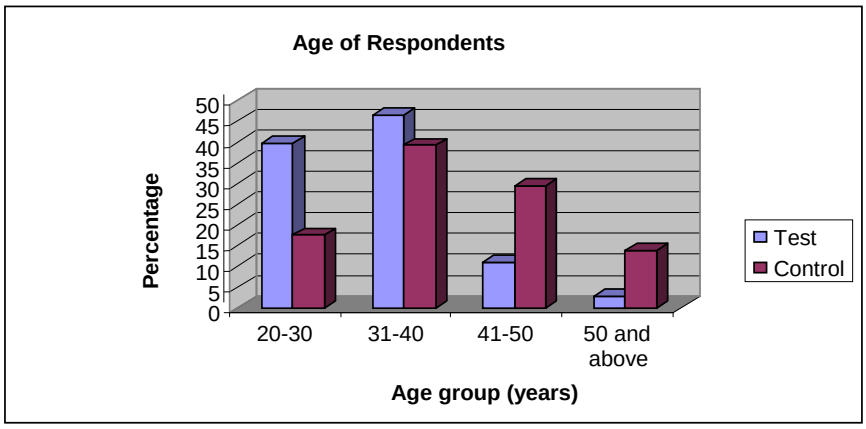
Each subject signed the consent form following explanations about the nature and aim of the study. The questionnaires were in two parts; part I was on respondent's biodata and part II contained specific questions based on the risks of contracting HIV, HPV and also questions about awareness of Pap smear which will be published in another paper. HIV screening was performed on the test and control group after informed consent using the parallel method of screening of Capilux and Determine. The positive results were confirmed by Western Blot. Blood sample was taken from the HIV positive women to ascertain their CD4 count using the Partec Cyflow Counter following standard procedure. Conventional Pap smear was taken from both the patients and the control group using the Ayres spatula, and the smeared frosted end slides were immediately fixed in 95% ethyl alcohol. Thereafter, Papanicolaou stain was carried out, following

standard procedure. The slides were reported by the first author and reviewed by the third and fourth authors who are consultant pathologists using Bethseda Classification 2001. The results were collated and analyzed using SPSS version 16 and presented as frequency tables, graph, pie chart and histogram. Test of relationship was confirmed using chi square testing. Individual results were made known to the respondents and appropriate counseling and referral made where necessary.

Result

A total of 592 women were recruited into the study of which 292 were HPW and the rest were in control group. Majority of the women were in the fourth decade accounting for 46.6% and 39.2% among the HPW and HNW respectively. See Figure 1.

Figure 1



Among the test group, over half (58.6%) of the patients were married, 27.1% were single while 9.6% were widowed and 4.7% gave no response on their marital status. In the control group, 90.4% were married and 9.6% were single.

Most of the patients (55.5%) were diagnosed to have HIV after chronic ill health. Other factors that prompted presentation include antenatal screening, spouses' confirmation of HIV positivity amongst others. See Figure 2.

Majority of the patients in the test group (69.5%) had negative smear designated as

Table 1: CD4 counts of the subjects

Count (cell/mm^3)	Frequency	%
0 -100	24	8.2
101 -200	35	12.0
201 -300	42	14.4
301 -400	47	16.1
401 – 500	39	13.4
Above 500	63	21.6
Not available	42	14.4
Total	292	100

Table 2: Duration of Highly Active Anti-Retroviral Therapy (HAART)

Duration	Frequency	%
Less than 6 months	77	26.4
6 months - 1yr	34	11.6
1-2 years	65	22.3
2 -5 years	55	18.8
Above 5 years	7	2.4
Not Stated	54	18.5
Total	292	100

NILM. The abnormal smears, accounting for 23.6% included ASCUS, 3.4%; ASC-H, 1.0%; LSIL, 16.1%; and HSIL, 3.1%. In the control group, 80.9% had a negative cytology (apparently normal) while 17.1% had abnormal cytology, with ASCUS accounting for 7.7%; LSIL, 5.7%; and HSIL, 3.7%. See Figure 3. Among the LSIL group, those with recognizable HPV cytopathic effects were 6.8% and 3.7% for the test and control groups respectively.

Figure 2: Events prompting diagnosis of HIV in subjects.

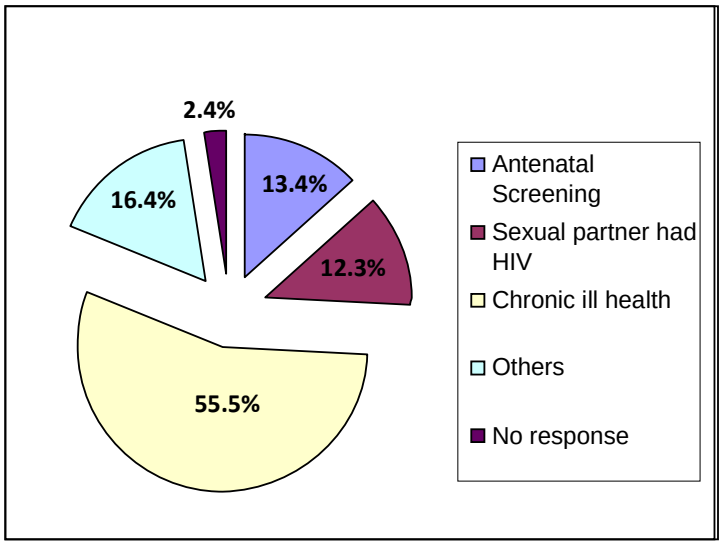
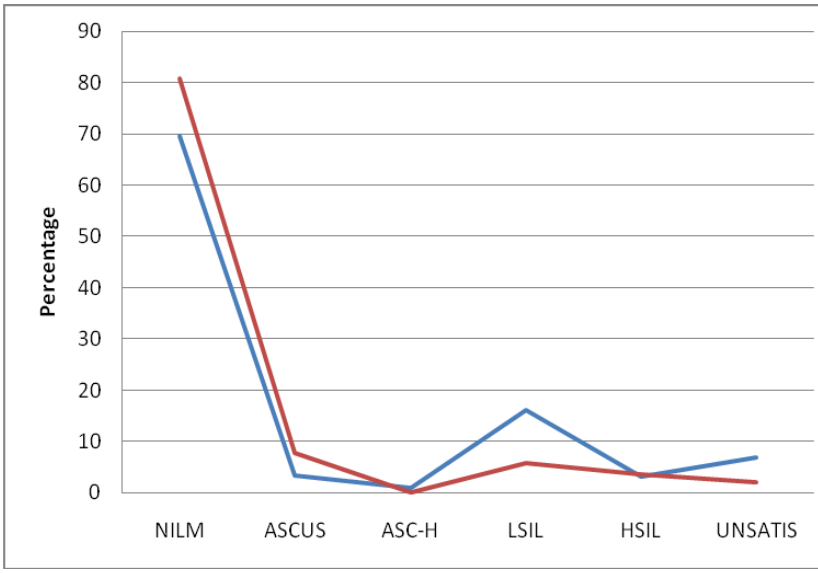


Figure 3: Comparison of the Cytologic pattern among the HIV posi women



CD4 count was available for 250 patients; of this 63 (21.6%) had count greater than 500 cells/mm^3 while 20.2% had less than 200cells/mm^3. See Table 1.

with lower CD4 counts (p = 0.023) and LSIL and HSIL were significantly associated with CD4 cells <200 cells/mm^3 (p=0.0058 and p=0.03 respectively).

Table 3: Comparison of the CD4 count with Cytologic Pattern among the HIV positive women

Cytologic pattern	0 -200 cells/mm^3	Above 200 cells/mm^3	Total
NILM	31 (19.7%)	126 (80.3%)	**157**
ASCUS	3 (42.9%)	4 (57.1%)	**7**
ASC-H	0	2 (100%)	**2**
LSIL	13 (41.9%)	18 (58.1%)	**31**
HSIL	4 (57.1%)	3 (42.9%)	**7**
Unsatisfactory	3	12	**15**
Total	**54**	**165**	**219**

p = 0.023

Table 3 compares the CD4 count of patients with the cytologic pattern. The CD4 count was grouped into those below 200cells/mm^3 and those above 200 cells/mm^3. A fall in CD4 count below 200cells/mm^3 was found to be associated with increase in prevalence of abnormal smears and also in the severity of the abnormality. Only 19.7% had a CD4 count of 0-200 cells/mm^3 among the NILM compared to 58.1% for low grade lesions and 57.1% for high grade lesions. These figures showed that high grades of dysplasia are seen more frequently in patients with lower CD4 counts (p = 0.023) and LSIL and HSIL were significantly associated with CD4 cells <200 cells/mm^3 (p=0.0058 and p=0.03 respectively).

Table 4: Comparison of duration of the use of HAART with the CD4 count

Duration (years)	0-200 cells/mm^3	Above 200 cells/mm^3	Total
0-2 years	43 (27.9%)	111(72.1%)	154
Above 2 years	6 (12.5%)	42(87.5%)	48
Total	49	153	202

p = 0.030

HAART use was common amongst the HPW. A total of 166 HPW had used HAART in the last 2 years with about a quarter of the patients in the last 6 months. See Table 2.

Among those who had taken HAART for up to 2 years, 27.9% had a CD4 count of 0-200 cells/mm^3 and 72.1% had a CD4 count of 200cells/mm^3 and above (Table 4). For those who have used HAART for over two years, 87.5% had a CD4 count of 200cells/mm^3 and above while 12.5% had CD4 count of 0-200

Table 5: Comparison between duration of HAART use with the cytologic pattern

Duration (years)	Normal	Abnormal	Total
0-2 years	101 (69.7%)	44 (30.3%)	145
Above 2 years	45 (84.9%)	8 (15.1%)	53
Total	146	52	198

p = 0.031

cells/mm^3. This finding showed that there is significant increase in CD4 count within the period of use of HAART. p= 0.030.

Table 5 shows a tabulation of HAART use and cytological findings . The cytology in this case was grouped as normal or abnormal smears, while the duration of HAART use was grouped as those below two years and those above two years. Of the 145 patients who were on these drugs in the last 2 years, 69.7% of them showed a normal smear while 30.3% showed abnormal smears. Of those who had taken the drugs for over two years, 84.9% showed normal cervical smear while 15.1% were abnormal. This indicates that there is reduction in the rate of abnormal smears seen with longer duration of HAART use. (p = 0.031.)

Discussion

The test group-HIV positive women (HPW) and the control group-HIV negative women (HNW) have their age and other social risk factors matched. The mean age in the subjects is 33 years (age range 20 – 74 years) while that of the control group is 40 years (age range 24-60 years) with majority of respondents in both groups in the 31-40 years age group. This finding is similar to the finding of Anorlu *et al*; also from Lagos, which showed a mean age of 36.6 ± 11.6 years (range 16-81 years) and that reported by Parham *et al* in Zambia, who recorded a median age of 36 years (range 23-49 years) [12,13].Denny *et al* reported a median age of 39 years (range 35 -65 years) with 16% of the subject being 50 years and above among the unscreened population in Cape Town which is comparable to our control group where 13.7% were 50 years and above[14].

Among the HPW, only 58.6% were married compared to 90.4% for the control group. This high percentage among the control group is also in agreement with an earlier study done among unscreened urban people in Lagos by Anorlu *et al* 2003, where 91.7% were married[12]. However, of the 9.6% who were widowed among the HPW, half (50%) of their spouses died as a result of complications of HIV/AIDS which was what prompted them to seek HIV screening.

The high percentage of the HPW presenting late (for diagnosis) indicates that majority of them present at the stage of profound immunosupression with attendant high rate of opportunistic infections. This is a major setback in the management of these conditions. This was also the view of Taylor *et al* in US who reported that many women infected with HIV are unaware of their status and that prompt identification of these patients and preservation of immune function through early control of HIV infection would reduce the incidence of genital dysplasia and subsequent cancer[15].

The mean CD4 count in the present study is 385.12 ± 240.2 cells/mm^3 (range 0 – 1576). This is higher than 165 cells/mm^3 (range 7 - 942) recorded by Parham *et al,* at Lusaka, Zambia and 289 ± 223 cells/mm^3 reported by Taylor *et al*, in Baltimore, US[13, 15]. However, in the present series, the CD4 count is in agreement with that seen by Taylor *et al* among HPW who are on HAART where there was a higher mean of 368.4 cells/mm^3[3,15].

The cytologic pattern seen in the HPW test group showed 69.5% to be normal smear while 23.6% were abnormal. The abnormal smear included atypical smears, low grade and high grade squamous intraepithelial lesions. The HNW control group showed 80.9% normal and 17.1% abnormal smears. Comparison of the prevalence of abnormal smears between the HPW and HNW (23.6% vs 17.1%) showed that there is significant percentage of abnormal smear in the HPW compared to the HNW ($p < 0.05$). The prevalence of abnormal smear in HNW in this study is in agreement with 16.2% and 17% recorded respectively by Massad *et al* (USA) and Denny *et al* (Cape Town)[14,16]. The prevalence of abnormal smear seen (23.6%) in the HPW in the present series is however lower than that of Massad *et al* (USA) who reported 38.3% abnormal smear among the HPW study group[16].

The frequency of Squamous intraepithelial lesions (SIL) seen were 9.4% and 20.2% in the control and the subject groups respectively. The study by Denny et al showed a comparable frequency of 8.1% with the control HIV negative women[14]; other studies across Nigeria in unscreened patients showed between 4.1% and 21.8% SIL rate[17-19]. The figure of 20.2% SIL rate among the HPW agrees with the findings of Chama *et al* who reported that cervical dysplasia was commoner among HIV infected women than in HIV negative women (31.3% vs 7.8%); although that of this study is lower (31.3% vs 20.2%) than the prevalence for the index study[20]. La Ruche *et al* also showed that the prevalence of SIL in their study as 11.7% while Leroy et al reported a SIL prevalence of 24.3% vs 6.5% for HPW and HNW respectively[21, 22]. However in other studies on HPW, there is variation in SIL prevalence. For example Kapiga *et al* in Tanzania recorded a SIL prevalence of 2.9% while Parham et al in Zambia showed a prevalence of 76%[13,23]. This wide difference could be attributed to the stage of illness in 1999, when many of the infected women may be in the early infection period and immunity may not have been highly compromised. However the high prevalence of SIL in the Zambian study could be related to the general low immunity among the patients examined whose average CD4 counts is 165/microL (range 7-942).

Bagga *et al* in India reported a cervical dysplasia of between 15-40% of HPW in his study; Chirenje *et al* in Zimbabwe recorded a prevalence of 25.6% in HPW and 6.7% in HNW[6, 24]. Chirenje *et al* also reported a 6.4% HPV changes among the HPW and 1.7% HPV changes among the HNW group as against that seen in our study which showed more HPV cytopathic effects among the HPW compared to HNW (6.8% to 3.7%) [24]. The incidence among the HPW group in our study is in agreement while that of the HNW is higher in this study compared with the Harare study.

NILM accounted for 65.% of cases in this study, similar to 66% and 65% respectively reported by Carlucci *et al* and Bagga *et al* among HPW[6,25]. The inflammation rate of 20.1% and 8.6% in the two studies quoted above are higher than 4.1% recorded in our study. However, the abnormal smear of 20.2% recorded in this study contrasts with 15% and 29% reported in the two studies quoted earlier[6,25]. Also this study showed that there is higher frequency of low grade lesion (16.1%) compared with high grade lesion (3.1%), a finding which agrees with that of Kapiga *et al* and La Ruche *et al*[21,23].

Massad *et al* however reported that low grade lesion was more frequent among younger women infected with HIV, whereas ASCUS rates remained elevated and high grade lesion remained low for all age groups. They also found a frequency of 2.5% high grade lesion among the HPW and 1.2% among the HNW[16]. The frequency of high grade lesion in this index study is 3.8% which is in agreement with Chirenje *et al* which showed 3.1%[25] but was substantially higher than that reported by Massad and his group which showed 1.2%[16]. The frequency of the cytopathic effect of HPV among the test and control group was 6.8% and 3.7% respectively. It could therefore be stated that HPV effects and cervical dysplasia are twice as much in HPW than HNW. These findings are in agreement with the study of Chirenje *et al* who reported that HPW had twice the risk of having abnormal cervical smear than HNW and that of Massad *et al* who reported that the rates of SIL were five times greater among HIV infected than uninfected women[16,24]. Folkers, found that HIV infected women were three times more likely to have persistent Human papillomavirus (HPV), and twice as likely to have cervical abnormalities[26].

The present study showed significant relationships between the CD4 count and HAART use; CD4 and cervical dysplasia and between the duration of diagnosis and CD4 counts. Hence the use of HAART improved the CD4 count which in turn improved their immune status. This can also be attributed to

the significant relationship between the duration of diagnosis and CD4 count, since once diagnosed they are bound to start treatment as soon as possible with appropriate therapy.

Although there is no significant relationship between the cytologic pattern and the CD4 count, when the CD4 count was grouped into those below 200 cells/mm^3 and those above 200cells/mm^3, it showed a significant relationship. This shows therefore a positive relationship between AIDS and cytologic pattern and agrees with the findings of Kapiga *et al* in which the risk of SIL was significantly increased among women with CD4 cell count of less than 200 cells/mm^3[1,23] . Similarly, the findings of Schuman and Chirenje also showed that the progression of SIL to high grade lesion was associated with a CD4 cell count below 200 cells/mm^3 and to a lesser extent with a CD4 count between 200 and 500 cells/mm^3[1,9,24].

Chirenje however showed that several case control studies have demonstrated a two to twelve times higher cytologic abnormality rate against control HNW. Also Maiman suggested that the risk of cervical dysplasia appears to increase as the CD4 count decreases[27]. Taylor *et al* reported that a history of greater immunosupression, as measured by the lowest figure of a patient's CD4 count, is the strongest predictor of genital dysplasia in women infected with HIV[15].

Conclusions

This study confirms the existing knowledge that there is a higher prevalence of abnormal cervical smears among HPW compared to HNW and it also documents the relationship between the CD4 count and abnormal cervical smears as well as the role of HAART in reducing cervical abnormalities. It also confirms that there is no significant difference in the prevalence of high grade lesions between HPW and HNW. It is hereby recommended that routine Pap smear screening should be incorporated into the monitoring and follow up of all HPW. The study population is being followed up for progression of disease and determination of the risk factors for those who progressed.

List of Abbreviations

CD – Cluster of Differentiation,
NILM – Negative for Intraepithelial Lesion or Malignancy
BCC – Benign Cellular Change,
LSIL – Low Grade Squamous Intraepithelial Lesion
ASCUS – Atypical Squamous Cells of Undetermined Significance,

ASC-H – Atypical Squamous Cells- High Grade cannot be ruled out,

HSIL – High Grade Squamous Intraepithelial Lesion,

AIDS – Acquired Immune Deficiency Syndrome

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