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The Role of Highly Active Antiretroviral Therapy (HAART) in the Evolution of Cervical Dysplasia in HIV Positive Women in Nigeria

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Abstract
Objective: To ascertain the prevalence of cervical dysplasia and the relationship between the degree of cervical dysplasia and HAART in HIV- positive women. Method: This was a cross-sectional study involving 250 HIV positive women on HAART attending the HIV clinic of the University of Port Harcourt Teaching Hospital (UPTH). Cervical smears were collected from participants, examined and reported using the Bethesda system. Data was analysed using SPSS version 17 software package. Results: The prevalence of cervical dysplasia was 26.4%. CD4 count less than 500 cells/ul and HAART for less than 2 years were significantly associated with cervical dysplasia and high grade lesions. HIV positive women who were on HAART for less than 2 years were 3 and 7 times more likely to have cervical dysplasia and high grade lesions respectively. Conclusion: Abnormal CD4 count and shorter duration of HAART use were significantly associated with cervical dysplasia. The routine administration of HAART to HIV positive women irrespective of CD4 count may be beneficial.

1. Introduction

The uterine cervix is a small part of the female anatomy that is critical to reproduction and by extension, preservation of the human race. It is prone to a compendium of pathologies ranging from infection, dysplastic lesions to malignancy. Cervical dysplasia describes the mild to severe abnormal changes that can occur in the lining of the cervix. It is classified as low-grade squamous intraepithelial lesion (LSIL) when there is nuclear enlargement, irregular nuclear membrane, hyperchromasia, slight chromatin coarseness and cytoplasmic cavities (koilocytes) or high grade squamous intraepithelial lesion (HSIL) were mostly parabasal cells are seen in discrete or syncytium-like groups with nuclear enlargement, marked irregular nuclear membrane, hyperchromasia and coarseness of chromatin. [1] LSIL progresses very slowly and typically resolves on its own while HSIL has a significant propensity to progress to cervical cancer. [1] Cervical cancer is the commonest female genital tract malignancy and a major cause of morbidity and mortality among women in Nigeria. [2]

More women are infected with human immunodeficiency virus and acquired immunodeficiency syndrome (HIV/AIDS) than men in Nigeria as in other countries in

sub-Saharan Africa. Globally, in 2007, an estimated 33.2 million people were HIV infected; 22.5 million of these people live in sub-Saharan Africa with 61% (13.75 million) of these being women. [3]

A common gynaecological disorder in HIV positive women is cervical dysplasia. [4] Genital infection by human papilloma virus (HPV) is one of the most common sexually transmitted infections known to be the cause of cervical cancer and dysplasia. [5] HIV positive women are 4-5 times likely to develop HPV infection, thus HIV-positive women have a greater risk of developing cervical cancer and dysplasia. [4] The prevalence of cervical dysplasia in these women ranges from 15 to 40% depending on their level of immunosuppression. [6-8].

Massad et al in a study on evolution of cervical abnormalities among women with HIV-1, observed that progression of cervical dysplasia was significantly increased among the most immunosuppressed women, and regression of cervical dysplasia was significantly reduced in all HIV seropositive women except those with the best controlled HIV disease. [9] Omar et al studied the progression and regression of premalignant cervical lesions in HIV-infected women from Soweto and observed that a very large proportion of HIV infected women had abnormal cervical smears and that women with CD4 count <500 cells / uL were more likely to have a high grade lesion. [10] Similar finding was reported by Bassey et al [11].

Highly active antiretroviral therapy (HAART) by prolonging the lives of HIV-positive women may increase cumulative exposure to oncogenic HPV, as well as permit longer HPV persistence and the accumulation of somatic mutations and epigenetic changes that contribute to cervical carcinogenesis. [12] The effects of HAART on HPV infection and cervical neoplasia in HIV-positive women have remained uncertain. [13-15] A clearer understanding of the relationship between HAART and HPV-related disease may have been obscured by the failure of prior studies to account for variations in patient adherence with HAART. Adherence was associated with a significant reduction in the prevalent and incident detection of oncogenic HPV, as well as decreased prevalence and more rapid clearance of oncogenic HPV and Squamous intraepithelial Iesion. [12] Amongst women with pre-existing abnormal cervical cytology, HAART was associated with enhanced HPV clearance but not with Pap test regression. [16] Cervical dysplasia was found to be significantly more in HIV positive women before HAART therapy initiation and significantly reduced following HAART use.[17] HAART was also associated with regression of dysplasia in HIV positive woman. [18]

2. Materials and Methods

In a prospective cross-sectional study, 250 HIV-positive women on HAART attending the HIV clinic of the University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria were enrolled. Approval for the study was obtained from the ethical committee of the University of Port Harcourt Teaching Hospital, and all women provided consent for participation.

The sample size was calculated from the formula $n = z^2p(1-p)/d^2$ [19] where n is the sample size; z is the proportion of normal distribution corresponding to the required significance level of 5% (1.96); p is the proportion of HIV positive women with abnormal cytology observed in a similar study (20%) [20] and d is the relative precision or tolerable error of the estimate from the study (5%). Thus $n = (1.96)^2 \times 0.2 \times (1-0.2)/(0.05)^2 = 246$. A minimum of 246 HIV positive women were required for the study.

A structured proforma was used to obtain sociodemographic and other relevant information from participants. Information obtained include name, age, phone number, marital status, educational level, tribe, religion, parity, latest CD4 cell count, risk factors for cervical dysplasia, use of condom, prior knowledge of pap smear, previous pap smear, duration and compliance to HAART therapy. The procedure for the collection of the Pap smear was explained to them in details. Cervical smears were taken from participants using Ayres spatula and cytobrush, smeared on frosted end slides, which were promptly fixed in 95% ethyl alcohol. Samples were collected over a six (6) month period in the HIV clinic from May to November 2012. Papanicolaou staining was done using standard procedure. Slides were reported and an internal quality control was observed by sending the abnormal smears to another consultant for review. The slides for which a consensus was not reached in terms of the cytologic diagnosis were not used as positive slides. The cervical smears were reported using the modified Bethesda system of classification. All data were entered into a spread sheet using SPSS version 17 (IBM, Armonk, NY, USA) which was also used for analysis. The mean, standard deviation and percentages of variables were calculated. Significant difference in categorical variables were determined by Chi-square (x^2) test. Difference was considered significant at p-value of less than 0.05.

3. Exclusion Criteria

Cervical smear was not collected from women who were menstruating, had active genital tract infection and clinically obvious cervical lesion. HIV positive women who were not compliant with HAART were excluded from the study. Also women who had sexual intercourse and vaginal douching in the past 48 hours and without a CD4 count result in the last 3 months were also excluded.

4. Results

Two hundred and fifty Pap smears were collected. Four smears were unsatisfactory due to obscuring haemorrhage and profuse inflammatory cells infiltrate and were excluded. Therefore, two hundred and forty six (246) samples were analyzed.

There were 65 abnormal smears with prevalence rate of 26.42%. The distribution of the abnormal smears are as follows; 18 (7.31%) atypical squamous cells of undetermined significance (ASC-US), 28 (11.38%) low grade squamous intraepithelial lesion (LSIL), 18 (7.31%) high-grade squamous intraepithelial lesion (HSIL) and 1 (0.40%) atypical glandular lesion (AGC).

The mean age of participants was 35.10±8.05 years and ranged from 21–58 years. The highest number of participants were in the age group of 31-40 years. One hundred and seventy six (70.4%) women were less than 40 years while 74 (29.6%) were 40 years and above. Ten women who were 40 years and above had HSIL while eight women who were less than 40 years had HSIL and the difference was statistically significant (x^2 = 6.27, p = 0.012). Table 1 shows the relationship between age and abnormal cervical smear.

One hundred and seventy eight (71.2%) of the participants were married while sixty seven (26.8) were single and five (2.0%) were divorced. Ninety six (38.40%) of the participants had knowledge of Pap smear but seven (2.8%) had had a previous Pap test. One hundred and forty nine (59.60%) participants had sexual debut at less than 20 years of age and twenty one (8.4%) participants used condoms consistently.

One hundred and fifty two (61.79%) had CD4 count less than 500 cells/ul while 94 (38.21%) had CD4 count of ≥ 500 cells/ul. Sixty one women with CD4 count of less than 500cells/ul had dysplastic lesions while 4 women with CD4 count of ≥ 500cells/ul had dysplastic lesions and the difference was statistically significant (x^2 = 38.45, p = 0.0000000, Odds ratio (OR) = 15.08). Sixteen of the 152 women with CD4 count less than 500cells/ul had HSIL while 2 of the 2 of the 94 women with CD4 count of 500cells/ul or more had HSIL and the difference was statistically significant. (x^2 = 6.04 p = 0.0139, OR = 5.41). Table 2 shows the relationship between CD4 count and dysplastic lesions.

One hundred and thirty six (55.3%) of the participants had been on HAART therapy for less than 2 years while 110 (44.7%) had been on HAART therapy for 2 years or more. Twenty four of the 136 women who had been on HAART for less than 2 years had CD4 count of 500 cells/ul or more while 70 of the 110 women who had been on HAART for 2 years or more had a CD4 count of 500cells/ul or more and the difference was statistically significant (x^2 = 54.48, p = 0.0000000, OR = 8.17). Forty nine women who had abnormal smears were on HAART treatment for less than 2 years while 16 women who had dysplastic lesions were on HAART for 2 years or more and the difference was statistically significant (x^2 = 14.44, p = 0.00014, OR = 3.31). In terms of high grade lesion and duration of HAART use, sixteen women who had used HAART for less than 2 years had HGSIL while 2 women who had used HAART for longer period had HGSIL and the difference was statistically significant (x^2 = 8.87 p = 0.0029, OR = 7.20). Table 3 shows the relationship between duration of HAART use and dysplastic lesions.

Table 1. *Distribution of abnormal smears in the various age groups.*

ABNORMAL SMEARS	AGE CATEGORY				TOTAL
	20-30 years	31-40 years	41-50 years	>50 years	
ASCUS	6(33.3%)	6(33.3%)	4(22.2%)	2(11.1%)	18(100%)
LSIL	6(21.4%)	16(57.1)	4(14.3%)	2(7.1%)	28(100%)
HSIL	2(11.1%)	6(33.3%)	6(33.3%)	4(22.2%)	18(100%)
AGC	0(0%)	1(100%)	0(0%)	0(0%)	1(100%)
TOTAL	14(21.5%)	29(44.6%)	14(21.5%)	8(12.3%)	65(100%)

ASCUS = Atypical Squamous Cell of Undetermined Significance
LSIL = Low grade Squamous Intra-epithelial lesion
HSIL = High grade Squamous Intra-epithelial lesion
AGC = Atypical glandular cell

Table 2. *Distribution of abnormal cervical smears and CD4 cell count.*

Dysplastic Lesions	CD4 count less than 200µl(% of total)	CD4 count 200- 499 cells/ µl(% of total)	CD4 count Greater than ≥ 500 µl(% of total)	Total
ASCUS	8(44.4%)	10 (55.6%)	0(0.0%)	18(100.0%)
LSIL	14(50.0%)	12(42.9%)	2(7.1%)	28(100.0%)
HSIL	10(55.6%)	6(33.3%)	2(11.1%)	18(100.0%)
AGC	1(100.0%)	0(.0%)	0(.0%)	1(100.0%)

Table 3. *Duration of HAART and abnormal cervical smear.*

Abnormal smears	Duration of HAART		P – value
	< 2 years	≥2years	
ASCUS	8	10	0.3366
LSIL	24	4	0.00058
HSIL	16	2	0.0029
AGC	1	0	0.5528

5. Discussion

The mean age of participants in this study shows that HIV is predominantly a disease affecting young persons and correlates well with sexual activity as more than 50% of the study population had early coitarche (59.60%). This is in consonance with other epidemiological finding. [21-23] This study demonstrated that women who were more than 40 years of age were significantly more like to develop high grade lesions than younger persons, therefore early detection of the early stages of the disease in younger HIV positive women with the institution of early treatment will positively reduce the occurrence of high grade lesions which has a higher propensity of developing into cervical cancer. It is therefore imperative that HIV positive women will require increased surveillance for early detection of cervical dysplasia and prompt treatment. The poor knowledge and poor utilization of pap smear amongst the study population is definitely a huge limitation to prompt diagnosis and treatment of cervical dysplasia among HIV positive women. The gross disparity between knowledge (38.6%) and utilization (1.6%) of Pap test observed in this study may be due to the current high cost of Pap smear of four thousand naira at the study centre, thus subsidizing for the cost of Pap test will bridge the gap and encourage the utilization of Pap test amongst HIV positive women. It is also recommended that Pap test should be part of the routine test conducted for HIV positive women as this will enhance the uptake of Pap smear. It was observed that only 8.4% of the study population used condoms consistently, thus encouraging the use of condoms will help curtail the spread of this deadly disease.

The prevalence rate of cervical dysplasia of 26.4% noted in this study was higher than that observed in other studies [8, 21, 23-25] but lower than what other researchers reported. [10, 11, 20, 26] The variation in prevalence in the above studies may be due to the level of immunosuppression, the peculiarity of the study population and the stage or duration of HIV infectivity at the time smears were collected.

Women with CD4 count less than 500 cells/ul were significantly higher in this study and had more abnormal smears. This was worse in those with CD4 count <200 cells/ul, of which most were high-grade lesions. HIV positive women with CD4 count less than 500 cells/ul were about 5 times more likely to harbour high grade lesions than those with higher CD4 count. This is in keeping with several works previously done linking the development and severity of cervical dysplasia to the degree of immunosuppression as assessed by the CD4 count. [23, 25, 26, 27]

This study showed a significant relationship between the duration of HAART therapy and cervical dysplasia as women on HAART for less than 2 years had more abnormal and high grades lesions. HIV positive women who were on HAART for less than 2 years were more likely to have dysplastic lesions and to suffer from severe form of the disease. Thus prolonged use of HAART may have a beneficial role and this is in consonance with previous studies. [12, 17] HIV positive women who were on HAART for more than 2 years significantly had fewer abnormal smears and higher CD4 count thus implying improvement in the immune status. Few studies [13, 14] did not demonstrate the beneficial effect of HAART on cervical dysplasia. However, the duration and adherence to HAART were not assessed in the above studies which might have influenced their findings. Current literature have shown that effective HAART use typically results in CD4 count increases of 50 cells/ul within weeks after viral suppression and increases of 50-100cells/ul per year. [27]

6. Conclusion

There is a high prevalence of cervical dysplasia amongst HIV positive. Knowledge and use of Pap smear amongst the study population was very low. Abnormal CD4 count and short duration (less than 2 years) of HAART were significantly associated with cervical dysplasia and high grade lesions. The prolong use of HAART was associated with reduction in prevalence of cervical dysplasia. The routine administration of HAART to HIV positive women irrespective of CD4 count may be beneficial.

References

[1] Kumar V, Abbas A, Fausto N. Robbins and Cotran Pathologic Basis of Disease 7th "ed" WB Saunder and Elsevier; 2006. 1073-1078.

[2] Emembolu JO and Ekeme CG. Cancer of the cervix uteri in Zaria – Aetiological factors. Int J Gynecol Obstet. 1988; 26: 265-269.

[3] UNAIDS. Global report: UNAIDS report on global AIDS epidemic 2010. www.unaids.org/documents/20101123. Global Report em.pdf. Published 2010.

[4] Pereira DB, Antoni MH, Danielson A, Simon T, Efantis-Potter J, O'Sullivan MJ. Inhibited interpersonal coping style predicts poorer adherence to scheduled clinic visits in HIV infected women at risk for cervical cancer. Ann Behav Med. 2004; 28(3): 195-202.

[5] Hawes SE, Critchlow CW, Sow PS, et al. Incident High grade squamous Intraepithelial lesion in Senegalese women with and without HIV type 1(HIV-1) and HIV-2. J Natl Cancer Inst. 2006 Jan 18; 98(2): 100-9.

[6] Bagga R, Wanchi A, Rajwanshi A et al. Pap smear abnormalities in HIV infected in North India. Asia- Pac J Clin Oncol; 2005. 2-3: 77-80.

[7] Gorna R. One hope, One world, One gender**.** J Int Assoc Physicians AIDS Care. 1996; 2(10): 28-30, 32-4.

[8] Kreitchmann R, Bajotto H, daSilva DA, Fuchs SC. Squamous Intraepithelial lesions in HIV-infected women: prevalence, incidence, progression and regression. Arch Gynecol Obstet 2013; 288(5): 107-13.

[9] Massad LS, Ahdieh L, Benning L, Minkoff H, Greenblatt RM, Watts H, et al. Evolution of cervical abnormalities among Women with HIV-1: evidence from surveillance cytology in women in the interagency HIV study. Journal of AIDS; 2001. 15; 27; (5): 432-42. Or AIDS; 2001. 15; 27; (5): 432-42.

[10] Omar T, Schwartz S, Hanrahan C et al. Progression and regression of premalignant cervical lesion in HIV infected women from Soweto: a perceptive cohort. AIDS. 2011; 25 (1): 87-94.

[11] Bassey G, Jeremiah I, Ikimalo JI, Fiebai PO, Athanasius BP. Abnormal cervical cytology among HIV-positive women in Nigeria. Int J Gynaecol Obstet 2014; 125(2): 103-6.

[12] Howard M, Ye Z, Robert D, Joel M, Xiaonan X, Heather W et al. Influence of adherent and effective antiretroviral therapy use on HPV infection and squamous intraepithelial lesion in HIV positive women**.** J infect dis; 2010(5): 681-690.

[13] Minkoff H, Massad LS, Anastos K, et al. The effect of highly active antiretroviral therapy on cervical cytology changes associated with oncogenic HPV among HIV-infected women**.** AIDS; 2001. 15: 2157–2164.

[14] Heard UM, Schmitz V, Costagliola D, Orth G, Kazatchkline MD. Early Regression of Cervical Lesion in HIV-seropositive Women receiving highly active antiretroviral therapy. AIDS.1998; 12 (12): 1459–64.

[15] Denslow SA, Rositch AF, Firnhaber C, Ting J, Smith JS. Incidence and progression of cervical lesions in women with HIV: a systematic global review. Int J STD AIDS 2014; 25(3): 163-77.

[16] Sirera G, Videla S, Lopez-Blazquez R, et al. Evolution of cervical cytologic changes among HIV infected women with normal cytologic in the HAART era. AIDS Res Hum Retroviruses. 2007; 23(8): 965-71.

[17] Del Mistro A, Bertorelle R, Franzetti M, Marzia F, Annamaria C, Angela T et al. Antiretroviral therapy and the clinical evolution of HPV –associated genital lesions in HIV –positive women. Clin Infect Dis. 2004; 38(5): 737-42.

[18] Rabiu K, Akinbami A, Adewunmi A, Akinola O, Wright O The Need to Incorporate Routine Cervical Cancer Counseling and Screening in the Management of HIV Positive Women in Nigeria. Asian Pac J Cancer Prev. 2011; 12(5): 1211-4.

[19] Araoye MO. Subject selection. In: Araoye MO (editor). Research Methodology with Statistics for Health and Social Sciences, Ilorin. Nathadex; 2003, 115-29.

[20] Agada PA, Thacher TD, Ekwempu CC, Idoko JA. Cervical dysplasia in Nigerian women infected with HIV. Int J Gynecol Obstet 2009; 107(2): 99-102.

[21] Adefuye PO. Knowledge and practice of cervical screening among professional health workers in a suburban district in Nigeria. Nigerian Medical Practitioner 2006; 50: 19-22.

[22] Banura C, Franceschi S, Vandoom L, Arslan A, Wabwire MF, Mbidde E. Infection with HPV and HIV in young women in Kampala, Uganda. J infect dis. 2008; 197: 555-556.

[23] Anorlu RI, Igwilo CI, Akanmu AS, Banjo AA, Odunukwe NN, Okany CC et al. Prevalence of abnormal cervical smear among patients with HIV in Lagos, Nigeria. West Afr J Med 2007; 26 (2): 143-7.

[24] La Ruche G, Ramon R, Mensah-Ado I, Bergeron C, Diomande M, Sylla-Koko F et al. Squamous intraepithelial lesions of the cervix, invasive cervical carcinoma, and Immunosuppression induced by human immunodeficiency virus in Africa. Cancer. 1998; 15.82(12):2401.

[25] Mbizvo EM, Msaya SE, Stray-Pedersen B, Chirenje MZ, Hussain A. Cervical dyskaryosis among women with or without HIV: prevalence and risk factors. Int J STD AIDS 2005; 16(2): 789-93.

[26] Chama CM, Ngada H, Gashau W. Cervical dysplasia in HIV infected women in Maiduguri. Niger J Obstet Gynecol.2005; 25(3): 286-8.

[27] Faduyile FA. The prevalence of cervical abnormalities in HIV positive women**.** National Postgraduate Medical College Dissertation in pathology 2005.