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Original Article

Obstetrics and Gynaecology Section

Effect of Low CD4 Cell Count on Cervical Squamous Intraepithelial Lesions among HIV-Positive Women in Enugu, Southeastern Nigeria

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ABSTRACT

Introduction: HIV-positive women are more likely to develop cervical neoplasm. HIV-positive women with low CD4 T-lymphocyte cell count may be more predisposed to cervical squamous intraepithelial lesions (SILs). This study aimed to determine the association between low cellular immunity of HIV positive women, and the prevalence and grade of cervical squamous intraepithelial lesions.

Materials and Methods: Pap smear was carried out on two cohorts of Highly Active Anti Retroviral Therapy (HAART) experienced HIV-positive women (178 per group) at the AIDS Prevention Initiative in Nigeria-Centre for Disease Control Adult Anti-Retroviral clinic of the University of Nigeria Teaching Hospital, Enugu, Nigeria from June to November, 2012. The study group had CD4 cell count of < 200 cells/μl while the control group had CD4 cell count of ≥200 cells/μl.

Results: The mean CD4 cell counts of participants in the study (low CD4) group was 127.9 ± 47.49 cells/ml while that of the control (high CD4) group was 489.2 ± 186.36 cells/ml ($p < 0.001$). The prevalence of SIL was 10.2% (18/176) for the low CD4 group, and 5.7% (10/176) for the high CD4 group [OR = 1.9 (95% CI: 0.85, 4.22)]. The commonest category of SILs identified was Low-grade Squamous Intraepithelial Lesion (LSIL), thus 11 (6.3%) in the study versus 7 (4.0%) in the control group ($p = 0.703$).

Conclusion: Prevalence of cervical SILs among HIV positive women on HAART in Enugu, Nigeria is low and has no significant relationship with their CD4 cell count.

Keywords: Cellular immunity, Cervical pre-malignant lesions, HIV sero-positivity

INTRODUCTION

Cervical cancer is a preventable malignant lesion of the uterine cervix caused by persistent oncogenic Human papillomavirus (HPV) infection [1]. It is the fourth most common cancer affecting women globally; and a leading cause of cancer deaths in Sub-Saharan Africa including Nigeria [2,3] which reflects the state of cervical cancer control programmes in the sub-region. On the other hand, Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) is a global epidemic especially in the Sub-Saharan Africa where about 68% of people living with HIV reside [4]. In Nigeria, over three million people are living with HIV/AIDS; however, based on sentinel surveys of pregnant women, the country's HIV prevalence appeared to have stabilized between 2005 and 2010 – the median prevalence was 5% in 2003, 4.4% in 2005, 4.6% in 2008 and 4.1% in 2010 [5]. Likewise, the HIV prevalence in Enugu state, Nigeria declined from 6.5% in 2005 to 5.8% in 2008 and 5.1% in 2010 [5]. Nevertheless, a recent population based survey, showed a national HIV prevalence of 3.4% (3.3% for male, 3.5% females) while that of Enugu state was 1.4% (1.0% male, 1.6% females) [6].

It has been shown that women living with HIV/AIDS are more likely to develop cervical Squamous Intra-Epithelial Lesions (SILs) [7-9]. Also, HIV-positive women have high progression rate from low grade to high grade SILs or cancer and are more likely to experience recurrence after treatment [10]. It therefore follows that this high risk group of women should be offered more frequent cervical cytology screening [11,12]. The association between cervical cancer and HIV/AIDS is so strong that the former is an AIDS defining criterion [13]. Since reduced immunity appears to be the predisposing factor to increased cervical neoplasm, it may therefore follow that HIV positive women with lower immunity may be more predisposed to cervical premalignant lesions. In addition, CD4 immunosuppression is associated with persistence of high-risk HPV types [14], and appears to play an important role in controlling the growth of neoplastic cells as well as the disease progression. It is therefore likely that HIV-positive women with lower CD4 T-lymphocyte cell (CD4) count may be more predisposed to cervical premalignant lesions. This assumption has been supported by a few studies that showed increased detection of cervical lesions in women with low immune status as measured by low CD4 counts [15-17]. Nevertheless, few reports have shown no correlation between CD4 cell immunity and cervical pre-malignant lesions [18,19]. A critical review of the above studies revealed some disagreement on the actual relationship between the level of immunity and degree of cervical SILs which calls for more studies. On the other hand, a related study from the same region [7], had also recommended further studies on the association of CD4 cell count and SILs. Therefore, the aim of this study was to determine the association, between the degree of immunosuppression of HIV positive women as measured by CD4 cell counts, and the prevalence and grade of cervical SILs.

MATERIALS AND METHODS

Study center

This was a study of HIV-positive women receiving care at the AIDS Prevention Initiative in Nigeria-Centre for Disease Control Adult Anti-Retroviral (APIN-CDC ARV) clinic of the University of Nigeria Teaching Hospital (UNTH), Enugu, Enugu state, South-eastern Nigeria. The study period was June to November, 2012. The hospital is one of the major centers providing free Anti-Retroviral Treatment (ART) in the south eastern Nigeria. The provision of anti-retroviral drugs started in this center in 2002 under the subsidized Federal Ministry of Health's anti-retroviral programme. At the time of this study, the

ART clinic was funded by the Presidential Emergency Plan for AIDS Relief (PEPFAR) programme run by the Harvard School of Public Health in collaboration with AIDS Prevention Initiative in Nigeria (APIN) [20]; a total of 6849 patients (2406 males and 4443 females), were receiving care in this center; and it was the only ART site in the state that has facilities for viral load and CD4 cell count analyses. The center coordinates all ART services to children, pregnant women and adults in the hospital and referrals are from various clinics within UNTH Enugu, and other hospitals in Enugu state and its surrounding. The ART clinics are being held every weekday and also offer services for HIV counseling and testing.

Study design

The study design was cross-sectional analytical. All HIV- positive adult women receiving care at the adult APIN-CDC ART clinic of the hospital were eligible for the study. Exclusion criteria included HAART-naive patients, pregnancy, very ill patients where collection of pap smear was difficult, presence of obvious or suspicious genital lesion(s), newly registered cases, co-infection with tuberculosis. The study group (Low CD4) consisted of 178 HIV-positive women with CD4 cell count of less than 200 cells/μl while the control (High CD4) group consisted of equal number of women with CD4 cell count of 200 cells/μl and above. The sample size per group was based on a SILs prevalence of 12.6% among HIV-positive women in Enugu [7], confidence limit of 95%, sampling error of 5%, and non-response rate of 5%. The last CD4 cell counts prior to the study were used to stratify eligible women into the two categories thus CD4 cell count < 200 and ≥ 200 cells/μl. The former category served as sample frame for the study group while the later served as sample frame for control group. Each frame contained details of patient's age, parity, duration of HAART and marital status. The sample population of 178 for each group (study versus control) was selected from each frame by computer generated simple random sampling method.

DATA COLLECTION AND ANALYSIS

Informed consent was obtained from each woman recruited for the study after individual counseling by a trained female medical intern. Afterwards, she was transferred to a private room at the study site where the Pap smear was collected by one of the investigators, assisted by a female chaperone. In dorsal position, a sterile Cusco's speculum lubricated with water was introduced into the vagina to expose the cervix. The latter was carefully inspected. Ayre's spatula and cyto brush were used to collect cervical smears from the ectocervix and endocervix respectively; each was smeared on a clean slide labeled with participant's study code and smear type. Each smeared slide was immediately immersed into a container of 95% methyl alcohol. The smears were processed at the Histopathology Department of the hospital, and reported by two independent histopathologists using the Bethesda system. The histopathologists were 'blinded' on the immune status (CD4 cell counts) of the participants.

Data analysis was done with SPSS version 15.0 (SPSS INC: Chicago Illinois), values were set at 95% confidence level; a p-value of < 0.05 was considered significant. Chi-square test and logistic regression were used to compare proportions while Student's t-test was used to compare means. Data is presented using simple percentages, tables, odds ratio, etc, as appropriate. To enhance the power for further data analysis, participant's age and marital status were dichotomized into "less than 35 years" versus "greater than 35 years", and "single" versus "ever married" respectively. Participants received their Pap smear report within 4 weeks at the Adult HIV clinic. They were counseled on the findings of the report. Those with abnormal findings were referred to the colposcopy unit of the hospital for further management. The primary outcome measure was the prevalence of SILs in patients with low CD4 cell count i.e. CD4 <200 cells/μl and high CD4 cell count. The secondary outcome measure was the relationship between low CD4 cell count and pattern of cervical SILs.

Approvals for the study were obtained from the Institutional Review Board of the hospital, as well as the PEPFAR office in the USA.

RESULTS

A total of 356 participants were selected for this study, but results of 352 (98.9%) participants (176 per group) were used for final analyses. Two participants were lost from both the study (Low CD4) and control (High CD4) groups. Reasons for their loss were refusal to carry out Pap smear after selection by 2 women, breakage of slides of one participant and inability to collect Pap smear from one participant. The socio-demographic characteristics of participants were comparable between the two groups except for their ages and marital status [Table/Fig-1]. The mean age of the participants in the study group was 36.6 ± 8.71 (range = 21-60) years while that of the control group was 40.6 ± 9.12 (range = 24 -65) years (t = -4.17, p < 0.001). As shown in [Table/Fig-1], 31-40 years was the modal age group of participants in both the study group (46.6%, 82/176) and control group (36.4%, 64/176). Likewise the commonest educational status for both the study and control groups was the secondary level of education (49.4%, 87/176 versus 52.8%, 93/176). The mean parity of the participants in the study and control groups were 2.5 ± 2.53 (range = 0 - 10) and 2.7 ± 2.50 (range = 0 - 10) respectively (t = -0.76, p = 0.45).

The duration of HAART for the study group was significantly lower than that of the control group (27.5±22.98 versus 51.0±32.55) weeks, t = -7.82, p < 0.001. HIV viral load differed between the two groups for instance, the viral load was undetectable (< 400 copies/ml) in 14.8% (26/176) of study group and 69.9% (123/176) of control group (p < 0.001). Also, for participants with detectable viral loads, the mean viral loads differed significantly between the groups (p < 0.001). The mean CD4 cell counts of participants in the study group was 127.9 ± 47.49 (range = 20-199) cells/ml while that of the control group was 489.2 ± 186.36 (range = 203 - 997) cells/ml (t = -24.93, p < 0.001). Details of the HIV disease related characteristics of study participants are shown in [Table/Fig-2].

Variable	Sub-groups	Low CD4 group		High CD4 group		p-value
		Freq.	%	Freq	%	
Age (years)	21-30	50	28.4	28	15.9	< 0.001
	31-40	82	46.6	64	36.4	
	41-50	30	17.0	58	33.0	
	≥51	14	8.0	26	14.8	
Age (years)	≤ 35	84	47.7	53	30.1	0.001
Dichotomized	> 35	92	52.3	123	69.9	
Marital status	Single	50	28.4	30	17.0	< 0.001
	Married	99	56.3	58	33.0	
	Widowed	18	10.2	77	43.8	
	Divorced	9	5.1	11	6.3	
Marital status	Single	50	28.4	30	17.0	0.011
dichotomized	Ever married	126	71.6	146	83.0	
Educational level	None	5	2.8	1	0.6	0.183
	Primary	56	31.8	46	26.1	
	Secondary	87	49.4	93	52.8	
	Tertiary	28	15.9	36	20.5	
Religion	Christian	176	100.0	170	96.6	-
	Moslem	0	0	6	3.4	
Tribe	Igbo	174	98.9	172	97.7	0.135
	Others	2	1.1	4	2.3	
Parity groups	Para 0	46	26.1	56	31.8	0.128
	Para 1-4	93	52.9	74	42.1	
	Para ≥5	37	21.0	46	26.1	

[Table/Fig-1]: Socio-demographic characteristics of participants

HIV characteristic	Sub-group	Low CD4 group	High CD4 group	p-value	t	OR(95% CI)
CD4 cell count	Mean ±SD	127.9 ± 47.49	489.2±186.36	< 0.001	24.93	-
Viral load n=176	Undetected {n (%)}	26 (14.8)	123 (69.9)	< 0.001	-	0.8(0.04, 0.13)
	Detected (Mean ±SD)	196122.8 ± 372562.44	51583.6 ± 92790.11	< 0.001	4.38	-
HAART duration (months)	Mean ±SD	27.5±22.98	51.0±32.55	< 0.001	-7.82	
	≤2 years {n (%)}	100 (56.8)	37 (21.0)	< 0.001	-	4.94(3.09,7.91)
	> 2 years {n (%)}	76 (43.2)	139 (79.0)	-	-	-

[Table/Fig-2]: HIV disease related characteristics of participants

Cytology result	Cytology category	Low CD4 n = 176	High CD4 n = 176	p - value	OR (95% CI)	*Adj OR (95%CI)
		Freq (%)	Freq (%)			
SIL	18 (10.2)	18 (10.2)	10 (5.7)	0.115	1.9 (0.85 - 4.22)	1.5 (0.67, 3.49)
Negative	158 (89.8)	158 (89.8)	166 (94.3)	-	-	-
SIL	HSIL	4 (2.3)	1 (0.6)	0.626	2.6 (0.25- 26.85)	-
	LSIL	11 (6.3)	7 (4.0)	0.703	0.7 (0.13 – 3.51)	-
	ASC-H	0 (0.0)	0 (0.0)	-	-	-
	ASCUS	3 (1.7)	2 (1.1)	1.0	0.8 (0.11 – 5.82)	-

[Table/Fig-3]: Prevalence and pattern of SIL versus participants groups
* Adjusted for effect of participants' age

Variable	Sub-groups	SIL		p-value
		Yes	No	
		Freq (%)	Freq (%)	
Age (years)	≤ 35	19 (13.9)	118 (86.1)	0.001
	> 35	9 (4.2)	206 (95.8)	
Marital status	Single	7 (8.8)	73 (91.3)	0.765
	Ever married	21 (7.7)	251 (92.3)	
HAART Duration (years)	≤ 2	15 (10.9)	122 (89.1)	0.097
	> 2	13 (6.0)	202 (94.0)	

[Table/Fig-4]: Maternal characteristics that varied between Low CD4 and High CD4 groups versus Prevalence of SILs

In all, 28 participants had squamous intraepithelial lesions (SILs) of varying degrees which gave a prevalence of 8.0%. Within the low CD4 group, the prevalence of SILs was 10.2% (18/176) while that of the high CD4 group was 5.7% (10/176). The observed difference was not statistically significant {p = 0.115, OR = 1.9 (95% CI: 0.85, 4.22)}, and this did not change when adjusted for the effects of difference in age between the two groups [Table/Fig-3]. Univariate analysis for each of the maternal variables that varied between the Low CD4 and High CD4 groups versus the prevalence of SILs, showed that only participants age group had significant association with the prevalence of SILs [Table/Fig-4].

Furthermore, the commonest category of SILs identified was LSIL, thus 11 (6.3%) in the study versus 7 (4.0%) in the control group (p = 0.703). Details of the differences in SILs pattern between the participants' groups are shown in [Table/Fig-4].

DISCUSSION

Cervical cancer is one of the commonest cancer affecting women especially in Nigeria [2], and immunosuppression enhances persistence of the causative agent - ongogenic HPVs, therefore, more frequent cervical cancer screening is recommended for HIV-positive women [11,12]. In this study, two cohorts of HIV-positive women that differed in their immune cellular status as measured by CD4 cell counts were studied to determine whether the prevalence of cervical SIL differed between them. Participants modal age group was 31-40 years, which is consistent with the reports of a recent survey in Nigeria [6], as well as the findings of related studies in South-eastern [7], and South-western Nigeria [9]. Outside the difference in age, participants in the two groups were essentially similar in their basic socio-demographics including educational status, religion, and tribe which suggests a homogenous population that is expected to have similar sexual behaviors. This consideration is necessary since the aetiologic agents of cervical cancer and its pre-malignant lesions are high risk HPVs which are sexually transmitted [1], It is not surprising that HIV infection related characteristics such as viral load, varied significantly between the study and control groups [Table/Fig-2] because of their differential cellular immunity. Also, the use of effective anti-retroviral drugs should lead to increased CD4 cell counts which may explain why women in the high CD4 group had significant longer duration of HAART use when compared to those in the low CD4 group.

The overall prevalence of SILs in this study was 8.0%. This prevalence is lower than those of related studies in Nigeria where rates of 12.6%, 10.9%, and 29% were recorded in Enugu [7], Lagos [9], and Jos [21] respectively. All participants in the current study were on HAART which might be related to the observed reduced SIL prevalence when compared to these previous reports, especially the study from the same study area [7]. It is however lower than the SIL prevalence of 17.8% reported among HAART experienced HIV positive women in Makurdi, Nigeria [22] - a setting with high HIV prevalence [5]. Furthermore, the SIL prevalence in the study is very low when compared to the 90% obtained among HIV women in Lusaka, Zambia [23], and 26.7% in Kenya [24]. Interestingly, severe malnutrition and immunosupression were blamed for the very high rate recorded in Lusaka, Zambia [23].

HIV infection is a cell mediated immune dysfunction and it is therefore expected that the odds of developing SIL should worsen as the CD4 cell count reduces [7]. This expectation is partially supported by this study which showed that an SIL positive Pap smear result was about two times more likely to belong to a woman with low CD4 cell count when compared to those with high CD4 count. Nevertheless, the observed difference in the prevalence of cervical SILs between the low CD4 cell counts and high CD4 cell counts groups was not significant [Table/Fig-4]. The SIL prevalence of 9% in the study group is same as that obtained from a study in the USA [25]. Outside the possible effect of sampling error, the observed lack of significant association between low CD4 cell count and prevalence of SIL might have been influenced by use of HAART by all study participants which could have increased their cellular immunity and ability to fight HPV related cervical SILs. This explanation is supported by the reports that showed increased regression [26], and protection against progression [27,28] of cervical SILs in HIV positive women on HAART. The odds of developing SIL among HIV infected women with low CD4 cell count in this study, is same as that reported from Kenya [29], and similar to reports of other related studies [19,30]; it is however lower than 3.6 reported from Makurdi, Nigeria [22]. Though, other categories of SILs did not

vary between the low CD4 count and high CD4 count groups, it may be important to note that the odds of developing HSIL was about 3 times higher in the low CD4 group which may reflect the lower cellular immune status of this group and their reduced ability to clear HPV infections. It is noteworthy that the study in Makurdi, Nigeria equally showed high odds of developing HSIL in the women with low CD4 cell count compared with those with high CD4 cell count [22].

LIMITATION

A larger sample size would have improved precision of the study's estimates especially within the sub-group analysis. Also, the effect of HAART on the participants might have masked the true association between low CD4 cell count and the prevalence of SIL. Therefore, future studies in this subject should target newly registered women before commencement of HAART – a longitudinal study of this cohort will help to evaluate the possible effect of anti-retrovirals on the progression and regression of SIL in our environment.

CONCLUSION

It is concluded that the prevalence of cervical SILs among HIV-positive women on HAART in Enugu, Nigeria is low and has no significant relationship with their CD4 cell count. A larger sample study of HAART naive HIV-positive women at registration will remove its possible effect in the study population

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