Open Access

SCHOLARENA

Journal of Gynecology and Women Healthcare

RESEARCH ARTICLE

ISSN: 2639-7285

Impact of Highly Active Antiretroviral Therapy on Cervical Cytology in Hiv Positive Women in Alex Ekwueme Federal University Teaching Hospital Abakaliki: A Comparative Study

Chinwe Wendy Oliobi, Ayodele Adegbite Olaleye*, Eziaha Eric S Ede, Ifeoma Cecilia Uche-Omovoh, Malachy Chizoba Onyema, John C Irechukwu, Amuchechukwu Veronica Nwafor and Charles Edene

Department of Obstetrics and Gynaecology, Alex Ekwueme Federal University Teaching Hospital, Abakaliki, Nigeria

***Corresponding Author:** Ayodele Adegbite Olaleye, Department of Obstetrics and Gynaecology, Alex Ekwueme Federal University Teaching Hospital, Abakaliki. PMB 102; Ababkaliki; Ebonyi State, Nigeria, Tel: +2347032779183, E-mail: ayodele_olaleye@yahoo.com

Citation: Chinwe Wendy Oliobi, Ayodele Adegbite Olaleye, Eziaha Eric S Ede, Ifeoma Cecilia Uche-Omovoh, Malachy Chizoba Onyema, et al. (2025) Impact of Highly Active Antiretroviral Therapy on Cervical Cytology in Hiv Positive Women in Alex Ekwueme Federal University Teaching Hospital Abakaliki: A Comparative Study. J Gynecology Women Health care 6: 102

Abstract

Background: Cervical cancer is a public health problem and the commonest gynaecological cancer in west Africa, hence there is need for cervical cancer screening for women in the reproductive age group .It is the second most common cause of cancer mortality in women worldwide, and the leading cause of cancer mortality in African women, where access to screening programs is limited. HIV and HPV are sexually transmitted thus women who are HIV positive need to have cervical cancer screening according to SOGON guidelines but this screening is not incorporated in the HIV clinics. Cervical cancer screening reduces deaths from cervical cancer by 80%. This study was conceived based on the need to know the effect of HAART on the cervical cytology findings in HIV positive women receiving care.

Objective: This study was designed to determine the effect of HAART use on the cervical cytology of HIV positive women at Alex-Ekwueme Federal University Teaching Hospital, Abakaliki.

Methods: This was a cross sectional study conducted among HIV positive women and HIV negative women who access care at Alex-Ekwueme Federal University Teaching Hospital Abakaliki, to compare the impact of HAART on the cervical cytology of HIV positive .The HIV positive women were subdivided into 2 groups: those taking HAART and those not on HAART. PAP smear was done for 100 HIV positive women on HAART, 100 HIV positive women not on HAART and 100 HIV negative women who consented to the study .Blood sample were taken for viral load estimation for the HIV positive women. The data obtained were analyzed using statistical Package for Social Science (IBM SPSS) software (version 25, Chicago II, USA). A difference with a P- value of ≤ 0.05 was taken to be statistically significant.

Results: The mean age of the participants were 39.1(±8.7) years in the HIV positive women on HAART, 37.7(±9.1) years in those not on HAART and 39.3(9) years in the HIV negative women. The prevalence of SIL was 11.1% (n=21) in the HIV positive group and 4.3% (n=4) in the HIV negative group, and this was not statistically significant. TThe prevalence of SIL was 5% in the HIV positive women on HAART, 17% in HIV positive women not on HAART and 4.3% in the HIV negative women. ASCUS was the commonest cervical cell abnormality in the HIV positive and negative group. The mean duration of HAART use for all the HIV positive women was 3.51 years. There is a statistically significant difference in the duration of HAART use of (1.25 years ± 1.16) and the development of LSIL (P-value 0.002) when the two groups were compared. There is a statistically significant difference between the mean viral load of the HIV positive participants on HAART and those not on HAART (P-value <0.001).

C**onclusion:** HAART use reduces the prevalence and pattern of cervical smear in HIV positive women and this effect is dependent on its duration of use.

Recommendation: I recommend that the cervical cancer screening be incorporated into the care for HIV positive women at the various HIV clinics.

Keywords: HAART; Screening; HPV; Oncogenic; Cervical; Cytology; Positive; Cancer

Introduction

Cervical cancer is a public health problem in Nigeria and there is need for screening of women in the reproductive age group [1]. Cervical cancer is an AIDS related cancer and the commonest gynaecological cancer in Nigeria. [2, 5]. Cervical cancer is the second most common cause of cancer mortality in women worldwide, and the leading cause of cancer mortality in African women, where access to screening programmes is limited [4, 8]. In Nigeria, it is the second leading cause of death in women with about 10403 deaths annually [9]. The prevalence of cervical squamous intraepithelial lesion in HIV seropositive women in Abakaliki is 6.3%.2 Cervical cancer screening reduces deaths from cervical cancer by 80% [10].

The most important aetiological risk factor for cervical cancer is chronic persistent HPV infection [4] Other risk factors are smoking, early coitarche, immunosuppression, high parity and oral contraceptive use [11]. High risk HPV types 16 and 18 cause about 70% of cervical lesion [4, 10]. Cervical cancer is preventable. Primary prevention of cervical cancer involves health education, vaccination of young girls and use of condom [13] Secondary prevention involves cervical cancer screening by HPV DNA testing, PAP Smear, visual inspection under acetic acid or Lugol's iodine for women who are unvaccinated [4, 13]. Papanicolaou test is a screening tool for the early detection of cervical cancer and has been shown to reduce mortality from cervical cancer [13]. Although there are various methods for screening precancerous cervical lesions, the Pap smear test is still the most commonly used method particularly in developing countries [14]. Cervical cancer has a recognizable premalignant stage which takes up to 10 years or more to develop into a malignancy [2]. Detection of the disease in this premalignant stage has been recognized as an effective means of reducing the morbidity and mortality from cancer of the cervix [15]. The specificity and sensitivity of Pap smear is 65% and 53% respectively [16, 17] HIV is thought to be a co-factor in the association between human papilloma virus and CIN [18].

The guideline for cervical screening of HIV positive women is twice in the first year of diagnosis and yearly thereafter [19]. Screening for these HIV positive women should commence within 1 year of the onset of sexual activity regardless of mode of HIV transmission (e.g sexual activity, perinatal exposure) but not later than age 21 years [19]. If the initial Pap test is negative it should be repeated yearly till there are 3 consecutive normal PAP tests that are normal then follow-up PAP tests should be every 3 years [9,20].

There are about 3.2 million women living with HIV in Nigeria [21, 22]. HIV positive women are at increased risk of developing cervical dysplasia [2, 17]. The prevalence of cervical epithelial lesion in Nigerian is about 7.6–16% in HIV positive and 4.6% in HIV negative [3, 23, 24]. Around 33.4 million individuals are infected by the human immunodeficiency virus (HIV) worldwide [25].Women living with HIV are at higher risk of HPV acquisition which varies immensely with the CD4 Cell count [26], HIV infection affects the CD4 lymphocyte count that is used to assess the immune status. HIV seropositive women are at higher risk of persistent HPV infection. Hence more prone to cervical dysplasia and cancer [1, 7] The characteristic changes in cervical cells throughout its progression can be detected at the pre-clinical stage, allowing for treatment of precursor lesions long before invasive cervical cancer occurs [27]. There is an association between CIN and HIV which varies inversely with the immune status [13, 17]. HIV- infected women are at an increased risk of the incidence, persistence and recurrence of HPV-induced anogenital and cervical neoplastic disease [28]. The prevalence of HPV and HIV in a population tends to correlate with the sexual behavior since both are sexually transmitted [13].

HAART is commenced for all HIV positive persons regardless of CD4 cell count [10]. The use of HAART in seropositive women has improved immunological status leading to decreased incidence of HPV infection, better HPV clearance and prolonged life [4, 15, 26, 29]. The use of HAART probably prevents acquisition of High risk HPV. With HAART therapy, the major cause of death in the later stage of acquired immune deficiency syndrome (AIDS) is malignancy rather than infection [29]. HAART has decreased the incidence of Non hodgkin lymphoma and kaposi sarcoma which are AIDS induced cancer but there is no significant decrease in cervical cancer incidence [2-4, 18]. Some studies have shown that the positive impact of HAART on cervical cytology is only felt in women with CD4 count <350cells/min [4].

Despite the available information on the impact of HAART on all forms of malignancy attributable to HIV/AIDS, evidence from mainly retrospective studies suggest that HAART does not have a significant effect on the incidence of cervical cancer and premalignant lesions of the cervix .This study was designed to correct some of the flaws noted in previous studies which had two arms which may not clearly elucidate if an increase in the incidence of cervical lesion in a patient is dependent on the HIV status and whether or not patient is on HAART. The viral load of the HIV positive patients were not ascertained by most literatures reviewed so as to correlate the level of the virus with the presence of cervical lesions. This study will also determine if the use of HAART will have any impact on the premalignant lesions of the cervix compared to HIV positive women who are not on HAART and to what extent the duration of HAART use and other factors play in this.

Cervical cancer cases are of high public health significance because they are preventable and there is a good knowledge of the theoretical origin of the disease in relation with HPV. Also, in developing countries like ours, HIV cases are on the rise, due to both impact of poor socio-economic factor and ignorance. The knowledge of impact of Highly Active Antiretroviral Therapy on Cervical Cytology in HIV Positive Women in our environment is still deficient. This serves as a means by which huge knowledge gap in this top would be filled, especially in Nigeria. A multicenter studies on the knowledge of the impact of Highly Active Antiretroviral on cervical cytology in Nigeria will help to develop a systemic review, which will help to develop an appropriate guideline in management of cases of HIV positive women with high risk of developing cervical cancer in Nigeria.

Justification

Invasive cervical cancer is an AIDS defining illness with high prevalence in Sub-saharan Africa. There has been a marked reduction in morbidity and mortality with the introduction of HAART. In Nigeria, many HIV infected women are receiving HAART but the cervical cytology pattern are not known because there is no free screening for cervical cancer for these at risk patients in the HIV care centres. HIV positive women on HAART have reduced opportunistic infections. Hence, a decrease in incidence and prevalence of cervical lesions. This study will determine cervical cytological changes seen in women on Highly Active Antiretroviral Therapy in comparison with HIV seronegative women. There is paucity of report about the cytoprotec-

tive effect of HAART on cervix in south eastern Nigeria. This finding may provide strategies for preventing cervical cancer among HIV seropositive women.

Research Question

Does the use of HAART affect the prevalence and pattern of cervical cytology in HIV positive women?

Null Hypothesis

The use of HAART in HIV seropositive women has no effect on cervical cytology pattern and prevalence in AE-FUTHA

Alternate Hypothesis

The use of HAART in HIV seropositive women has a positive effect on the cervical cytology pattern and prevalence in AE--FUTHA.

AIM: To determine the effect of HAART on the cervical cytology of HIV positive women.

Objectives

- To compare the pattern of cervical smear in HIV seropositive women and HIV seronegative women at AE-FUTHA
- To compare the prevalence of cervical squamous intraepithelial lesions among HIV seropositive women and HIV seronegative women at AE-FUTHA
- To correlate the cervical cytology results with the duration of HAART use in HIV seropositive women at AE-FUTHA
- To determine the correlation between viral load and cervical smear result in HIV seropositive women at AE-FUTHA

Methodology

Study Design

A comparative cross sectional study comparing the impact of HAART on cervical cytology in HIV positive women in the communicable disease control centre and well women centre of Alex Ekwueme Federal University Teaching Hospital Abakaliki (AE-FUTHA), Ebonyi State.

Study Site

The study was conducted in the Communicable disease control centre and well women centre of AE-FUTHA.

Study Population

HIV seropositive women who were receiving care in Communicable disease control centre and seronegative women in well women centre in Alex Ekwueme Federal University Teaching hospital, Abakaliki, Ebonyi state.

Study Duration

This study lasted for 6 months

Research Assistants

The research assistants consisted of 8 residents (4 assistants from obstetrics and gynaecology department, 2 assistants each from community medicine and internal medicine department). The assistants were trained on the research methodology. They were trained to understand the aims and objectives of the study, inclusion and exclusion criteria, data collection, study procedure and need for appropriate documentation. This training commenced as soon as ethical approval was obtained. Weekly meetings were held where appraisal of the recruitment and research methodology, including constraints were made and solutions provided. Recruitment of patients was in the Communicable disease control centre and well women centre of AE--FUTHA

Inclusion Criteria

- Confirmed HIV positive women between 21-64 years on HAART
- Confirmed HIV positive women between 21-64 years not on HAART
- Confirmed HIV negative women between 21-64 years

Exclusion Criteria

- Women who had total hysterectomy
- Critically ill patients
- Women with cervical cancer
- Women who have been treated for premalignant cervical lesion
- Women with vaginal atresia
- Vaginal douching or coitus within the past 48hours
- Pregnant women
- Women with diabetes mellitus and on immunosuppressants
- Virgins

Calculation of Sample Size

The Sample size was calculated using the statistical formula N=Z2p q/e2

Where n= minimum required sample size Z= standard variant (1.96)

p=prevalence of squamous intraepithelial lesion in HIV women in Abakaliki =6.3% (Agboeze et al).

p= (1-p) =0.937

e2= acceptable error at 0.05 n=z2pq/e2

=1.962 ×0.063×0.937/0.052

=3.8416×0.063×0.937/0.0025

=0.2267734896/0.0025

= 90.71

n=91 (nearest whole number)

The minimum sample size increased by a 10% attrition rate 91×10/100=9.1

Sample size =91+9=100

Each group had a sample size of 100

Sampling Technique

The recruitment was done by a systematic random sampling method among consenting HIV positive women and HIV negative women until a sample size of 100 was obtained in each of the 3 groups. The first participant for each group was selected using a random method, then for every participant seated on that row to the first participant's right the 3rd was selected and was continued in like matter till the number of eligible participants for the day was recruited. The same procedure was carried out on subsequent days until desired sample size was reached.

Recruitment and Data Collection

Participants were recruited based on eligibility criteria. They were counselled on the study and written consent obtained. The help of a professional nurse with translating skills was sought for the participants who do not speak English. The principal investigator and research assistant who had been trained administered the questionnaire to participants. The study participants' data relative to their socio-demographic characteristics: age, race, marital status, Family type, employment status, educational levels and reproductive characteristics age at first sexual intercourse, age at first pregnancy, number of sexual partners, contraceptive method used and history of sexually transmitted infections, medical history, knowledge of PAP smear cervical cancer were provided by the participants and captured by the researcher. Questionnaires were coded with affixed serial numbers of the clients thus blinding the cytopathologist to the identity of the study participants.

All participants had their HIV status confirmed. Blood sample (5ml) was collected from the HIV positive study participants for measurement of their viral load after collection of cytology smear. Further data (WHO HIV clinical staging, HAART uptake, period on HAART, and HAART adherence) were collected from the patients' folder and cross checked with laboratory result to avoid error. Women whose HIV viral load was greater than 1000 copies/ml despite treatment were referred for adherence counselling as per the standard of care within the clinic.

Study Procedure

Pap Smear

The patients were subjected to both speculum and pelvic examinations to detect any gross abnormal lesion that will be excluded and any abnormal vaginal discharge. General physical and abdominal examination were also done. The women were counselled properly on the procedure to be carried out, we ascertained if they had coitus or vaginal douching at least 48 hours

prior to the procedure. The participants were placed in the lithotomy position, and a sterile disposable plastic bivalve speculum lubricated with sterile water was inserted into the vagina to expose the cervix under good light source. The cervix was visualized to identify the squamo-columnar junction. Excess mucus was cleaned using a cotton swab. Women with cervical lesions were excluded from further participation in the Study and sent to the gynaecological clinic for further evaluation and treatment. Ayre's spatula was inserted through the external cervical os to scrape cells from the squamo-columnar junction of the transformation zone of the cervix by rotating it through 360˚. The cells were smeared on two labelled glass slides and immediately fixed in 95% ethanol. Pathology request forms were filled appropriately. The patient's serial and telephone numbers were clearly written on the request forms to facilitate follow-up. The sample containers along with the request forms were taken to the pathology laboratory for slide preparation. The smears were stained using the Papanicolaou staining technique. This technique involved staining the fixed slide with Harris Haematoxylin, then decolourizing with acid alcohol and rinsing in Scott's tap water. The slides were stained with Eosin Azure 50. The slides were further rinsed in 95% alcohol, cleared in xylene and mounted in a neutral synthetic resin medium. The researcher and cytopathologist prepared the slides and the cytopathologist was blinded to the HAART/HIV

Status of the patient, the slides were read under the microscope and pre-invasive cervical lesions were reported using Bethesda 2001 system of classification. Women with abnormal smear were referred to the gynaeoncologist for further examination, management and follow up.

Outcome Measures

A cytological diagnosis of ASCUS, Low grade intraepithelial lesions, high grade intraepithelial lesions was considered as positive.

Quality Control

Specimen collection was carried out by the principal investigator and research assistants who have been trained in the collection of PAP smear. The smears were stained in line with cytology laboratory standard operating procedure used for staining gynaecologic specimen and approved by the pathologist in-charge .The stains and reagents were prepared using standard operating procedures and filtered before each use to ensure good quality staining .Deteriorated stains were discarded and new stains prepared. The principal investigator examined all the smears followed by the pathologist's review. All abnormal smear and 10% of normal smear were reviewed by two histopathologists. In the cases of conflicting results a 3rd histopathologist acted as a tie breaker.

Study Instruments

Questionnaires, Ayres Spatula, Syringes, Reagents

Statistical Analysis

The data obtained was analysed using statistical package for social sciences (IBM SPSS) software (version 25, Chicago11, USA). Continous variables were presented as mean and standard deviation .Categorical variables were compared with CHI-square.

Ethical Considerations

Ethical clearance was sought and obtained from the Health Research and Ethics committee of Alex Ekwueme Federal University Teaching Hospital Abakaliki. In designing this study, the following ethical issues were put into consideration:

Informed consent: A signed consent was obtained from each participant before recruitment into the study. The study objec-

tives, procedure and full implications of participation was discussed with the participants before their consent was obtained. The participants were made to understand that declining to participate in the study or withdrawal from the study at any stage would have no consequences in obtaining care.

Confidentiality of data: All information including history, physical examination findings and results obtained from the participants were kept strictly confidential. The participants were assured that their identity would be kept in confidence by the investigator.

Beneficence to participants: All the patients were managed according to standard protocol and benefitted from the researcher who bore the cost of the procedure and investigation.

Non-maleficence to the participants: This study caused not more than minimal harm to the participants.

Justice: Method of patient selection will be scientifically objective and ensured fairness.

Cost: The researchers bore the cost of materials and consumables used.

Dissemination of Results from Study

The results from this study was submitted to the Human Research and Ethics Committee (HREC) - AE-FUTHA. A dissertation made out from the findings of this study submitted to the Faculty of Obstetrics & Gynaecology, West African College of Surgeons. It will also be presented at the departmental clinical conference as well as at the Society of Obstetricians and Gynaecologists of Nigeria (SOGON) conference. The results will also be published in a reputable journal such as the Tropical Journal of Obstetrics and Gynaecology.

Limitations of Study

The CD4 cell count of HIV positive women was not done and PAP smear was done once. The study was a single centre study.

Results

A total of 300 women were recruited between March 20th 2021 and September 27th 2021. A total of 282 were analyzed, 18 were excluded for unsatisfactory smear and carcinoma.

Table 1: Socio-demographic characteristics of participants

Socio-demographic characteristics	HIV Positive on HAART (n=100)	HIV Positive not on HAART (n=100)	HIV Negative (n=100)	$\chi 2$	P-value
Age					
21-30	17(17.0%)	24(24.0%)	19(19.0%)	3.453	0.75
31-40	39(39.0%)	35(35.0%)	33(33.0%)		
41-50	35(35.0%)	36(36.0%)	39(39.0%)		
51-60	9 (9.0%)	5 (5.0%)	9 (9.0%)		
Mean (±SD)	39.1 (±8.7)	37.7 (±9.1)	39.3 (±9.0)		
Marital Status					

Married	45(45.0%)	46(46.0%)	61(61.0%)	7.333	0.292
Single	34(34.0%)	37(37.0%)	25(25.0%)		
Divorced/Separated	6 (6.0%)	6 (6.0%)	5 (5.0%)		
Widowed	15(15.0%)	11(11.0%)	9 (9.0%)		
Occupation					
Civil Servant	23(23.0%)	25(25.0%)	34(34.0%)	6.948	0.542
Trader	34(34.0%)	37(37.0%)	30(30.0%)		
Farmer	18(18.0%)	12(12.0%)	15(15.0%)		
Artisan	15(15.0%)	11(11.0%)	12(12.0%)		
Others	10(10.0%)	15(15.0%)	9 (9.0%)		
Education					
None	9 (9.0%)	11(11.0%)	8 (8.0%)	1.344	0.97
Primary	21(21.0%)	18(18.0%)	17(17.0%)		
Secondary	33(33.0%)	36(36.0%)	37(37.0%)		
Tertiary	37(37.0%)	35(35.0%)	38(38.0%)		
Parity					
0	27(27.0%)	25(25.0%)	22(22.0%)	5.472	0.858
1	8 (8.0%)	13(13.0%)	11(11.0%)		
2	14(14.0%)	9 (9.0%)	11(11.0%)		
3	17(17.0%)	13(13.0%)	12(12.0%)		
4	13(13.0%)	17(17.0%)	16(16.0%)		
≥5	21(21.0%)	23(23.0%)	28(28.0%)		

Table 1 above shows the socio-demographic characteristics of participants. This showed no statistically significant difference in the socio-demographic variables of the three groups. Thus the participants in this study had similar characteristics. The mean age of the participants were 39.1(8.7) years in the HIV positive women on HAART, 37.7(9.1) years in those not on HAART and 39.3(9) years in the HIV negative women. Majority of the respondents were married. Nulliparity was more in the HIV positive group than in the HIV negative group who were mainly multiparas. Secondary level of education was the commonest educational qualification of the HIV positive participants, the HIV negative participants had higher educational status.

Table 2: Pattern of cervical smear in HIV positive women and HIV negative women in AE-FUTHA.

Cytology Results	HIV Positive on HAART	HIV Positive Not on HAART	HIV Negative (n=93)	$\chi 2$	P-value
	(n=100)	(n=89)			
Normal	85(85.0%)	60(47.4%)	85(91.4%)	18.611	<0.001
ASCUS	10(10.0%)	13(14.6%)	4 (4.3%)	5.642*	0.06
LSIL	4 (4.0%)	12(13.5%)	4 (4.3%)	8.069*	0.018

HSIL	1 (1.0%)	4 (4.5%)	0 (0.0%)	5.984*	0.044

* Fisher's exact test used

The table 2 shows the pattern of cervical smear seen in the study group. Participants in the HIV negative group had more normal cervical smear than those in the HIV positive group and this was statistically significant (p-value <0.001). Less than 50% of HIV positive women not on HAART had a normal smear. ASCUS was the commonest cervical cell abnormality in the HIV positive and negative group. LSIL was seen in both group of participants .HSIL was seen in the HIV positive group but none in the HIV negative group.

Table 3: Prevalence of squamous intraepithelial lesion in HIV positive women and HIV negative women in AE-FUTHA.

Cytology Results	HIV Positive on HAART	HIV Positive not on HAART	HIV	χ2	P-value
	(n=5)	(n=16)	Negative (n=4)		
LSIL	4(80.0%)	12(75.0%)	4(100%)	1.248*	0.535
HSIL	1(20.0%)	4(25.0%)	0 (0.0%)		
Relative Risk	0.50 (0.25– 1.00)	0.75 (0.57–1.00)			

* Fisher's exact test used

The table 3 above shows the prevalence of squamous intraepithelial lesion in the three arms of participants. The prevalence of SIL was 5% in the HIV positive women on HAART, 17% in HIV positive women not on HAART and 4.3% in the HIV negative women. There was no statistically significant difference between the prevalence of SIL in the HIV positive and negative women (P-value 0.535). HSIL in the HIV Positive women not on HAART was 4 times that of the positive women on HAART while none was seen n the HIV negative women.

Table 4: Relationship between duration of HAART use and cervical cytology in HIV positive women in AE-FUTHA.

Cytology	Duration of HAART Use (years)				Mean	χ2	P-value
Results	<1	1–2	3–4	≥5	(±SD)		
Normal (n=85)	6 (7.1%)	20(23.5%)	17(20.0%)	42(49.4%)	3.81(±1.86)	19.511*	<0.001
ASCUS (n=10)	3(30.0%)	4 (40.0%)	1 (10.0%)	2 (20.0%)	2.20(±1.85)	5.583*	0.134
LSIL (n=4)	3(60.0%)	0 (0.0%)	1 (20.0%)	0 (0.0%)	1.25(±1.16)	15.229*	0.002
HSIL (n=1)	1 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.50(±0.00)	6.757*	0.08

* Fisher's exact test used

The table 4 shows the relationship between the duration of HAART use in the HIV positive women with the cervical cytological findings. The mean duration of HAART use for women with normal cervical cytology was 3.81 years ±1.86, ASCUS 2.20 years ±1.85, LSIL 1.25years

±1.16 and HSIL 0.50 years ±0.00. There was a statistically significant difference in the duration of HAART use of (1.25 years ± 1.16) and the development of LSIL(P-value 0.002).There was a difference in the mean duration of HAART use for those with normal cervical cytology (3.81 years ± 1.86) and abnormal cytological finding. HSIL was highest in women who had used HAART for less 1 year(0.5 years).The mean duration of HAART use for all the HIV positive women was 3.51 years

There was an inverse relationship between the cervical cytology findings in HIV positive women on HAART and the duration of HAART use.

Table 5: Relationship between cervical cytology result and viral load in HIV positive women in AE-FUTHA.

Cytology Results			Viral load of HAART Users						Viral load of Non HAART Users				
	N	<1000	1000-10000	Mean (±SD)	χ2	P-value	n	<1000	1000-10000	>10000	Mean (±SD)	χ2	P-value
Normal	85	82(96.5%)	3 (3.5%)	659(±830)	20.71*	<0.001	60	8(13.3%)	47(78.3%)	5 (8.3%)	5233(±5759)	14.23	0.001
ASCUS	10	8 (80.0%)	2 (20.0%)	1400(±1800)	1.64*	0.2	13	4(30.8%)	6 (46.2%)	3(23.1%)	5923(±5334)	3.34*	0.188
LSIL	4	1 (25.0%)	3 (75.0%)	3875(±1949)	22.16*	<0.001	12	1 (8.3%)	5 (41.7%)	6(50.0%)	9625(±5504)	9.66*	0.008
HSIL	1	0 (0.0%)	1 (100%)	5000(±0)	10.21*	0.001	4	1(25.0%)	1 (25.0%)	2(50.0%)	8875(±6328)	3.69*	0.157

* Fisher's exact test used

The table 5 compared the relationship between the viral load and cervical cytology result in the HIV positive participants. There is a statistically significant difference between the mean viral load of the HIV positive participants on HAART and those not on HAART (P-value <0.001). The mean viral load of HIV positive women not on HAART (6090) was higher than that of those on HAART (905) for all category of abnormal cervical cytology. There was a statistically significant difference in the viral load of women on HAART and those not on HAART who had normal cervical cytology (P-value 0.001) but no significant difference in those with abnormal cervical cytology. The highest frequency of abnormal cytology was seen in those with viral load >10000copies/ml.

Discussion

HIV Infection is associated with reduced immunity and increased risk of HPV infection leading to cervical changes in women. However, use of HAART improves the immune status [18] Cervical cancer is a public health issue. Hence, the need for screening to detect premalignant lesion and treat them to reduce progression to cervical cancer [30,31]. This study looked at the effect of HAART use on the cervical cytology of HIV positive women on HAART and compared it with HIV positive women not on HAART and HIV negative women.

In this study there was no significant difference in the socio-demographic characteristics of the participants. The respondents were aged between 18-60 years, majority were in the reproductive age group. The mean age of the HIV positive women was 38.4 years (±8.7) while that of the HIV negative women was 39.3years (±9).There was no statistically significant difference in their ages. The finding is comparable to that seen in some studies done in Nigeria [1, 2, 30-33].The major occupation of the HIV positive participants was trading while the HIV negative participants were civil servants. The highest educational qualification of the HIV negative participants was tertiary education compared to the positive group who had more secondary education. Low educational level and trading in majority of the HIV positive women can predispose them to risky sexual behavior which could lead to sexually transmitted diseases like HIV and HPV infection. All the respondents were Christians probably because Christianity it is the commonest religion in this part of Nigeria. Majority of the participants in all the study arms were nulliparas and married. In this part of Nigeria early marriage and polygamy which is common could increase their risk for cervical cancer. The widows and divorced were more in the HIV positive women in this study which is similar to findings in a study

done in Zaria, Nigeria [18].

The predominant abnormal cervical smear was ASCUS in the HIV positive (12.1%) and negative (4.3%) women, this could be due to the sexual practices, reduced cervical immunity which causes persistence of cervical infections despite therapy.15 This finding is in keeping with results from other similar studies [11,14,34,35]. The similarity may be explained by the fact that the prevailing factors noted in this study which modify sexual-behaviors are similar to the ones noted in the reviewed studies. The HIV positive women not on HAART had more abnormal cervical cytology than those on HAART as also seen in other studies [7]. The finding of LSIL as the commonest SIL n the HIV positive group is in keeping with findings in a study done by Katumba in South Africa [7].

The women in the HIV positive group not on HAART (14.6% n=13) had more ASCUS than those on HAART (10% n=10) while the HIV negative women had the least ASCUS finding (4.3% n=4). Majority of the participants had a normal cytological smear in the HIV positive (85% n=85) and HIV negative (91.4% n=85) but there was a statistically significant difference (P-value <0.001) which may be accounted for by none use of HAART in some of the HIV positive women. HSIL was higher in the HIV positive women not on HAART than those on HAART but was not seen in the HIV negative group, this could be due to the sample size, the educational status, reduced risk for cervical dysplasia and immune status of the HIV negative women. This was similar to findings by Nyengidiki in Port harcourt, Nigeria [32]. LSIL was the commonest squamous intraepithelial lesion seen in the HIV negative women similar to other studies [32].

HSIL was the least abnormality seen in both the HIV positive and negative group, owing to the length of time required for progression to premalignant lesions. The HIV positive women not on HAART had more HSIL than those on HAART as expected, possibly due to reduced clearance of HPV infection which occurs in immune-competent women. The finding of ASCUS as the commonest cervical cell abnormality in the HIV negative women was at variance with LSIL found in a study done by Nyengidiki et al in southern Nigeria.32

The prevalence of SIL was 11.1% (n=21) in the HIV positive group and 4.3% (n=4) in the HIV negative group, and this was not statistically significant. The prevalence of SIL in the HIV positive women was 5% for those on HAART, 17% for those not on HAART and 4.3% in the HIV negative women. The difference in prevalence of SIL in the HIV positive and negative women in this study is possibly due to the reduced clearance of HPV infection, decreased regression of cervical premalignant lesions from the reduced immunity in HIV positive women [34]. This finding is consistent with findings from studies done in Africa and developed countiries [1, 2, 25-28].

The prevalence of cervical SIL in the HIV positive women in this study is comparable to that reported in other studies ranging 9.2-12.6% [1, 3, 14, 23, 25, 33]. It is lower than the prevalence of SIL of 14.3% seen in a study by Ezechi in eastern Nigeria and 28.7% by Sulaiman in northern Nigeria which could be as a result of early initiation of HAART, adherence to HAART and non-inclusion of ASCUS [18,24,38]. Other studies have shown higher prevalence of SIL in HIV positive than seen in this study ranging from 14.6-29% which could be due to inclusion of pregnant women, sample size, sexual behavior, poor knowledge of cervical cancer, inclusion of ASCUS and the screening method used [13, 33, 35, 37].

The prevalence of 4.3% in the HIV negative group is similar to findings in research done within and outside Africa ranging from 3.3-5.9% [24, 25, 33]. This was lower than that seen in some studies ranging from 6.7-16.4% [14, 23, 57, 37]. This higher prevalence in the HIV negative could be due to high risk sexual behavior and smoking. Other contributory factors may include the screening method used in those studies, the sample size and sampling method. A lower prevalence of 0.7% in the HIV negative women was seen in a study done by sulaiman in Zaria. This probably was as a result of the sample size, the educational level, possible HPV vaccination, previous screening for cervical cancer, the histopathology method used in analysis of PAP smear

and inclusion of only CIN 2 and 3 as noted in the reviewed study [18].

There was no case of HSIL seen in the HIV negative group which could be due to the immune status of the women, reduced possibility of indulgence in high risk sexual behavior, as majority were married and in a monogamous relationship. There was a statistically significant difference between the duration of HAART use and the cervical cytological finding. Women who had received HAART for 5years or more had the highest number of normal cytological findings and there was no case of SIL detected which could be due to regression of previous cervical lesion as a result of improved immune status from prolonged use of HAART. The use of HAART in HIV positive persons tends to restore the immunity. Hence, the reduced risk of development of cervical premalignant lesions and cervical cancer. However, the prolongation of life from use of HAART may lead to exposure to more oncogenic factors with advancing age leading to cervical cancer.6 Previous studies have established a protective effect of antiretroviral therapy on the risk of SIL, this study noted same but the higher the duration of therapy the less the risk of SIL [33]. The duration of HAART use is inversely related to the risk of SIL

Women who used HAART for less than 1 year had the least number of normal cytological findings and the highest number of HSIL. Women who had used HAART between 1-2 years had the highest number of ASCUS, this could be as a result of risky sexual behavior. Firhabner noted a 0.63 times increase in incidence of cervical dysplasia in women receiving HAART when compared to those not on HAART.36 There is a statistically significant difference between the viral load of the HIV positive participants on HAART and those not on HAART. The mean viral load of HIV positive women not on HAART was higher than that of those on HAART for all category of abnormal cervical cytology.

The finding of a statistically significant difference in the mean viral load of women on HAART(905) and those not on HAART(6090) who had normal cervical cytology (P-value 0.001) in this study is similar to findings from a study done in South Africa [7]. Viral load is a good surrogate indicator for antiretroviral therapy [7]. The finding of more cervical abnormalities in women with high viral load >10000cells/ml in this study is in keeping with studies done by onwuka et al in uyo, Nigeria and Swende et al in Markurdi [15.39] This difference could be as result of participants having detectable viral load. However it contrasts with finding from other studies [7,35]. The use of HAART leads to reconstitution of the immune status leading to a decrease in viral load. Incidence of HPV infection and cervical dysplasia [15]. LUI et al found that the risk of HPV infection was higher among HIV positive women with viral load >10,000copies/ml [26]. The finding of a significantly higher viral load in women with SIL compared to those without SIL in this study is similar to finding in other similar studies done in Africa [39].

Conclusion

This study showed that prevalence of SIL is higher in HIV positive women than HIV negative women. The use of HAART is associated with a reduced incidence of SIL in HIV positive women.

Appendix Information

https://www.scholarena.com/article/Appendix-Information.pdf

Recommendation

We recommend that cervical cancer screening should be implemented in the HIV clinics as this study has demonstrated that doing so will detect these lesions before they become cancerous, In the same vein, HAART should be commenced as soon as a woman is confirmed HIV positive. There should be multi centre studies.

Strength

The inclusion of HIV positive women on HAART and those not on HAART.

Limitation

This was a one centre study which could limit the type of cervical abnormalities detected. The adherence to HAART was not ascertained. PAP smear was done once, this did not help to determine if there was regression or progression of the cervical lesions.CD4 cell count was not done. Aslo, this is a centre based study with possibilities of Centre bias. The readiness to have a CD4 count available and lack of longitudinal follow up are also part of limitations encountered in the course of this study.

Conflict of Interest

There was no conflict of interest.

References

1. Lawal I, Agida TE, Offiong RA, Oluwole PO (2017) Cervical Cytology among HIV Positive and HIV Negative Women in a Tertiary Hospital in North Central Nigeria: A Comparative Study. Ann Med Health Sci Res, 7: 308-11

2. Agboeze J, Umeora O, Ozumba B, Onoh R, Ezeonu P et al. (2015) Prevalence and pattern of abnormal cervical smear among women infected with HIV in Abakaliki, Nigeria. Afr J Med Health Sci, 14: 92-5

3. Anorlu RI, Igwilo CI, Akanmu AS, Banjo AA, Odunukwe NN, et al. (2007) Prevalence of abnormal cervical smears among patients with HIV in Lagos,Nigeria.West Afr J med, 26: 143-7

4. Menon S, Rossi R, Zdraveska N, Kariisa M, Archarya KD (2017) Associations between highly active antiretroviral therapy and the presence of HPV, premalignant and malignant cervical lesions in sub-Saharan Africa, a systematic review: current evidence and directions for future research. BMJ Open, 7: e015123.

5. Ekwedigwe KC, Ezeonu PO, Edegbe F, Esike C, Agbata AT, et al. (2018) Prevalence and Pattern of Abnormal Pap Smear among Pregnant Women Attending Ante-natal Clinic in a Missionary Hospital in Abakaliki, Southeast Nigeria. OJOG, 8: 728-40.

6. Bekolo CE, O'Bryan G, Tchago FE, Nangue C, Bekoule PS (2016) Integrating Cervical Cancer Screening with HIV Care in Cameroon: Comparative Risk Analysis of Cervical Disease in HIV-Infected Women Receiving Antiretroviral Therapy to Women in the General Population. PLoS ONE, 11: e0149152.

7. Katumbaa AC, Rejib E, Gitauc T , Firnhaber C (2016) World Health Organisation staging, adherence to HAART and abnormal cervical smears amongst HIV-infected women attending a government hospital in Johannesburg, South Africa. SA J Infect Dis, 31: 112-8.

8. Viviano M, DeBeaudrap P, Tebeu P , Jovanny T, Fouogue JT (2017) Review of screening strategies for cervical cancer in human immunodefciency virus-positive women in sub-Saharan Africa. IJWH, 9: 69-79

9. Human Papillomavirus Disease: Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents. https://aidsinfo.nih.gov/guidelines.Accessed 17th April, 2020

10. World health organization (2013) WHO guideline for screening and treatment of precancerous lesions for cervical cancer prevention. World health organization.

11. Ugboaja JO, Ubajaka CF, Oranu EO, Oguejiofor CB, Anyaoku CS, et al. (2017) Determinants of cervical cytological abnormalities among HIV-positive women receiving care in a tertiary health facility in Southeast Nigeria. Niger J Gen Pract, 17: 31-6.

12. Akinola OI, Aimakhu CO, Ezechi OC, Fasubaa OB (2018) Society of obstetrics and gynecology of Nigeria – Clinical practice guidelines: Guidelines for the prevention of cervical cancer. Trop J Obstet Gynaecol, 35: 371-6.

13. Bawa US, Kolawole AO, Madugu NH, Shehu SM (2017) Cervical cytology pattern and human immunodeficiency virus serostatus of women seen in Ahmadu Bello University Teaching Hospital, Zaria, Nigeria. Port Harcourt Med J, 11: 90-95.

14. Ogu CO, Achukwu PU, Nkwo PO (2019) Prevalence and risk factors of cervical dysplasia among Human Immunodefciency Virus Sero-Positive females on highlyactiveantiretroviral therapy in Enugu, Southeastern, Nigeria. Asian Pac J Cancer Prev, 20:

2987-94.

15. Onwuka CO, Ojeh SO, Okorie C, Adekunbiola FB (2018) Abnormal Cervical Epithelial Cytology in HIV-Seropositive Women and Correlation with CD4 Counts and Viral Load in Uyo, Akwa Ibom State, Nigeria. JMSCR 6: 160-169.

16. Karmacharya K, Batra RB, Kandasamy S (2017) A case control study of HPV and abnormal cervical cytology among HIV infected and non-infected females. Med J Shree Birendra Hosp, 17: 3-9.

17. Anderson J, Lu E, Sanghvi H, Kibwana S , Lu A (2020) Cervical Cancer Screening and Prevention for HIV-Infected Women in the Developing World, Cancer Prevention - From Mechanisms to Translational Benefits, Dr. Alexandros G. Georgakilas (Ed.) 2012, ISBN: 978-953-51-0547-3, InTech, Available from: http://www.intechopen.com/books/cancer-prevention-from-mechanisms-to- translational-benefits/preventing-cervical-cancer-in-women-living-with-hiv. Accessed 22nd february ,2020

18. Sulaiman BU, Omolara KA, Sunday SO, Mohammed SS (2014) Cervical Cytopathology pattern among HIV seropositive and HIV seronegative women In Zaria. The Internet Journal of Gynecology and Obstetrics, 18: 1-7.

19. Boardman C (2020) What are the ACOG guidelines for cervical cancer screening in women with HIV infection.

20. Avert: HIV & AIDS in Nigeria. (2020)Available from: https://www.avert. org/professionals/hiv- around-world/sub-saharan-africa/Nigeria.Assessed 12th March 2020

21. UNAIDS .3.4 million Nigerians contracted HIV/ AIDS in 2014. Available at http://www.informationng.com/2015/09/3-4m-nigerianscontracte-hivaids-in-2014.Accessed 11th April, 2020.

22. Ajah LO, Ezeonu PO, Ozonu NC, Iyoke C A, Nkwo PO (2015) A Five year review of cervical cytology in Abakaliki, Nigeria. AJCP, 3: 23-6.

23. Ezechi OC, Pettersson KO, Okolo CA, Ujah AO, Ostergren PO (2014) The Association between HIV Infection, Antiretroviral Therapy and Cervical Squamous Intraepithelial Lesions in South Western Nigerian Women. PLoS ONE, 9: e97150.

24. de Lemos PAP, Garc´ıa-Zapata MTA, do NascimentoTavares SB (2012) Cervical Cytopathology in a Population of HIV--Positive and HIV-Negative Women. J trop Med, 1-4.

25. Liu G, Sharma M, Tan N, Barnabas R (2018) HIV-positive women have higher risk of HPV infection, precancerous lesions, and cervical cancer: A systematic review and meta- analysis. AIDS, 32: 795-808.

26. Bratcher L F, Sahasrabuddhe VV (2010) The impact of antiretroviral therapy on HPV and cervical intraepithelial neoplasia: current evidence and directions for future research. Infectious Agents and Cancer, 5: 1-13 .

27. Nweke IG, Nwadike VU, Kalu IE, Ojide KC (2014) Human papilloma virus and cervical neoplasm in HIV positive women: A non-systematic review. AJMR. 8: 1-10.

28. Lang TU, Khalbuss WE, Monaco SE, Michelow P, Pantanowitz L (2011) Review of HIV related cytopathology. SAGE-Hindawi Access to Research Pathology Research International Volume. Article ID, 256083: 1- 12.

29. Tisler A, Ojavee SE, Veerus P, Soodla P, Uuskula A (2021) Cervical cancer screening patterns among HIV-positive women in Estonia: a population-based retrospective cohort study. BMC Cancer, 350: 1-9.

30. Ntuli ST, Maimela E, Skaal L, Mogale M, Lekota P (2020) Abnormal cervical cytology amongst women infected with human immunodeficiency virus in Limpopo province, South Africa. Afr J Prm Health Care Fam Med, 12: 1-4.

31. Nyengidiki TK, Oranu EO (2018) Pattern of cervical cytology and high risk human papillomavirus strains in non HIV positive women presenting for cervical cancer screening in Port Harcourt, Nigeria. J Biosci Med, 6: 68-76.

32. Dim CC, Ezegwui HU, Ikeme AC,Nwagha UI, Onyedum CC (2011) Prevalence of cervical squamous intraepithelial lesions among HIV-positive women in Enugu,south-eastern,Nigeria. J Obstet Gynaecol, 31: 759-62

33. Mula MO, Mathenge SG, Njoroge WG, Karuga TK, Mutinda KC (2021) Prevalence and patterns of cervical cytological lesions among HIV-positive women in Machakos county hospital Kenya. Int J Res J Oncol, 4: 28-35.

34. Jaya C, Ankita C, Minaxi T, Abhishek KS, Shyam S (2016) Prevalence of human pappillomavirus and cervical abnormalities in HIV-positive women in eastern India. Indian J Med Res, 143: 79-86

35. Firnhaber C, Westreich D, Schulze D, Williams S, Siminya M (2012) Highly active antiretroviral therapy and cervical dysplasia in HIV-positive women in South Africa. JAIDS, 15: 17382.

36. Jolly PE, Mthethwa-Hleta S, Padilla LA, Pettis J, Winston S (2017) Screening, prevalence, and risk factors for cervical lesions among HIV positive and HIV negative women in Swaziland. BMC public health, 17: 1-8.

37. Eze JN, Umeora OU, Obuna VE, Ejikeme BN (2012) Cervical cancer awareness and cervical screening uptake at the Mater Misericordiae hospital,Afikpo,south-east Nigeria.Ann Afr Med J, 11: 238-43.

38. Swende TZ, Ngwan SO, Swende LT (2012) Prevalence and risk factors for cervical squamous intraepithelial lesions among women infected with HIV-1 in Makurdi, Nigeria. Int J Women`s Health, 4: 55-60.