Scientific Research Publishing

Open Journal of Obstetrics and Gynecology, 2022, 12, 124-139
https://www.scirp.org/journal/ojog
ISSN Online: 2160-8806
ISSN Print: 2160-8792

Gynaecological Cancers in HIV Positive and Negative Women—A Single-Center Retrospective Study (2008-2017)

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How to cite this paper: Ezeome, I.V., Nwankwo, T.O., Umeh, U.A. and Ajah, L.O. (2022) Gynaecological Cancers in HIV Positive and Negative Women—A Single-Center Retrospective Study (2008-2017). *Open Journal of Obstetrics and Gynecology*, **12**, 124-139.
https://doi.org/10.4236/ojog.2022.122013

Received: December 27, 2021
Accepted: February 14, 2022
Published: February 17, 2022

Abstract

Background/Objective: The association between Human Immunodeficiency Virus (HIV) and invasive cervical carcinoma is fully recognized. However, the effect of HIV and antiretroviral therapy on the morbidity and mortality of other gynaecological cancers have not been conclusively determined. Our study objective was to examine the effects of HIV on patient age at presentation, prevalence, and severity of the illness of various gynaecological cancers diagnosed in University of Nigeria Teaching Hospital (UNTH), Enugu over the period 2008-2017. **Methods**: This was a retrospective cross-sectional study of 224 patients who were managed in UNTH for different gynaecological malignancies. Ethical clearance was obtained from the Research Ethics Committee of the UNTH, Enugu. Data analysis was done with SPSS software with results expressed in descriptive statistics of simple frequency and percentage, and p-value set at <0.05. **Results**: A total of 224 patients were studied. Twenty-five percent of HIV positive patients were aged 31 - 40 years at presentation compared to 12% of HIV negative patients. The commonest gynaecological cancer was cervical cancer with a higher proportion among the HIV-positive patients. While 32% of HIV negative patients presented at FIGO stages 1 - 2 Versus 8.3% of HIV positive patients, 58.3% and 33.3% of HIV positive patients presented at stages 3 and 4 respectively. Only 8.3% of HIV positive patients presented with ovarian cancer compared with 31% of HIV negative patients. A higher proportion of HIV positive patients presented with vulvar cancer (16.7%), but no endometrial or choriocarcinoma/GTD, compared with HIV negative patients. **Conclusion**: HIV positive clients present at an earlier age with more advanced disease, mostly cervical cancer of the squamous cell variety, with minimal non-AIDS defining cancers over the study

period in UNTH, Enugu.

Keywords

Invasive Cervical Cancer, Non-AIDS Defining Cancers, Severity of Illness, Combination Anti-Retroviral Therapy

1. Introduction

Gynaecological malignancies are a major public health problem. Approximately, 1 out of 6 and 1 in 4 cancer cases among women worldwide and in developing countries are a gynaecological cancer respectively [1]. It accounted for 25% of all new cancers diagnosed in women aged up to 65 years compared with 16% in the developed world according to a global report shown by the International Agency for Research on Cancer [2]. While endometrial cancer is commonest in developed countries, cervical cancer is commonest in developing countries including Nigeria, where it is the leading cause of death among women aged 35 to 45 years [3].

The increased incidence and mortality from cervical cancer in developing nations have been attributed to ignorance, poverty and the absence of an organised screening program as obtainable in most developed nations [4] [5]. Epidemiologically, HIV, human papillomavirus (HPV), and cervical cancer are associated, and invasive cervical carcinoma is one of the Autoimmune Deficiency Syndrome (AIDS)-defining malignancies [6]. Women living with HIV present a 5.4-fold higher risk of developing cervical cancer than HIV-negative women [7]. Though there is significant body of literature on cervical cancer in HIV positive women, little is known about other gynecologic cancers in this population [8].

The HAART regimen for the treatment of HIV has led to a marked reduction in disease progression among people living with HIV and AIDS (PLWHA), thereby markedly improving survival [9]. This has exposed HIV positive persons to age related diseases including NADCs with a concomitant decline in the incidence of AIDS defining malignancies such as Kaposi Sarcoma, non-Hodgkin Lymphoma and invasive cervical cancer. However, it is known that HAART does not fully restore health and infected patients remain at increased risk of a number of non-AIDS complications, including cardiovascular disease, liver disease, kidney disease, bone disease, and neurocognitive decline [10]. It is important to note that the incidence of NADMs amongst PLWHA does not appear to be due to age alone, as PLWHA have an increased risk of malignancy compared to age-matched cohorts in the general population, even after controlling for behavioural differences [11]. The HIV positive populations have also been found to be at greater risk of viral co-infection (such as HPV, HBV and EBV) and tumours associated with these viral oncogenic viruses, as well as those with no viral aetiology [12]. Studies of lung, liver, anal and colorectal cancers have shown that there is not only an overall increased risk of NADC diagnosis among HIV

infected individuals, but also an earlier age at cancer presentation [13].

Sub-Saharan Africa carries a disproportionate burden of HIV, accounting for more than 70% of the global burden of infection [14]. Nigeria is estimated to have the second highest burden of HIV/AIDS worldwide with its >160 million population (2011 World bank estimate) and HIV prevalence rate of 3.4% among ages 15 - 49 in 2011, giving an estimated 3.2 million people living with HIV in 2011 [15].

HIV prevalence varies among different geographic regions with different socio-cultural practices, being low in Muslim communities with strict practices, as well as variation across different states in Nigeria [16]. The high prevalence of HIV may be related to poverty, early marriage, early age at sexual debut, living in an urban area, and multiparity.

Worldwide, women account for more than half the number of people living with HIV [8]. According to the National Agency for the Control of AIDS [17], with the Nigeria national HIV prevalence rate (2019) at 1.4% among adults aged 15 - 49, women are twice as likely to be living with HIV. It is therefore important to study the effects of HIV infection on the incidence and prognosis of gynaecological cancers, the outcome of which may guide the implementation of a comprehensive organised program of care for WLWHA (Women Living with HIV and AIDS) in Nigeria.

While several studies [2] [18] [19] [20] [21] have been carried out to determine the pattern of presentation, age distribution and disease severity of gynaecological cancers in the general population, there is a dearth of data among HIV positive patients in this environment.

2. Aims

The study objectives were therefore to examine the effects of HIV prevalence on patient age at presentation, prevalence, and severity of illness of various gynaecological cancers, as well as the prevalence of NADC among the HIV positive population, compared to the HIV negative population in University of Nigeria Teaching Hospital Enugu over the period 2008 to 2017.

3. Methods

We conducted a retrospective study of all adult female patients 18 years and above diagnosed with gynaecological cancers from January 2008 to December 2017 at University of Nigeria Teaching Hospital, Enugu Nigeria.

After Human Research Ethics Committee (HREC) approval was obtained from the hospital, with the aid of a study proforma, data was collected from patient gynae-oncology case notes, HIV clinic records for those that were retroviral positive, theatre and gynaecological ward records for those that had operative interventions or were admitted into the wards. Data extraction was between June 2018 and February 2019.

Extracted data include age at presentation, retroviral status, type of cancer (s)

diagnosed, risk factors, stage of illness at presentation, treatment given, histologic diagnosis, and status of patient during the study. Data on viral load and CD4 count were poorly recorded or unavailable, hence not part of data collected.

Data analysis was done using the Statistical Package for Social Sciences Software (SPSS) version 20 (Chicago, IL, USA) with results expressed in descriptive statistics of simple frequency and percentage. The Pearson Chi-square test was used to compare age range at presentation, age at first coitus, clinical diagnosis, stage of illness and status at study period between HIV positive and negative patients, with level of significance set at $P < 0.05$.

4. Results

Out of 250 case notes available over the study period, 224 had adequate data for inclusion into the study giving an 89.6% data retrieval rate.

4.1. Demographic Characteristics

As shown in Table 1, the commonest age at presentation among the 224 studied women was 51 - 60 years (32.1%). Majority were married (71.4%), multiparous (66%), Christians (98.2%), self-employed (59.8%) and had at least secondary education (59.8%). Twenty-four (10.7%) were HIV positive.

4.2. Factors Associated with Gynaecological Cancers

As depicted in Table 2, among the 224 studied women, 22 (9.8%) and 108 women (48.2%) had coitarche at less than 10 years and 10 - 13 years respectively giving a total of 58%. Only 10.7% had their sexual debut at 18 - 21 years of age. One hundred and eight-eight women (83.9%) had no knowledge of Pap smear, and only twelve (5.4%) had a pap smear done within 3 years prior to their presentation. Most of the patients (73.2%) gave history of no multiple sexual partners.

4.3. Presenting Symptoms#

The most common symptoms at presentation were intermenstrual bleeding (57.1%), Abdominal swelling (50.9%), postmenopausal bleeding (25%), and Postcoital bleeding (18.4%). Other symptoms include abdominal pain (13.4%), vaginal discharge (8%), Weight loss (4.5%), vulval swelling (4.5%) and leg swelling (4.5%). Less common symptoms include vulval mass, vulvar pain, incomplete urinary emptying, and generalized body pains. There was no significant difference in symptomatology between the HIV positive and HIV negative patients.

Patients presented with multiple symptoms.

4.4. Clinical Diagnosis and International Federation Gynaecology and Obstetrics (FIGO) Staging of Illness at Presentation

As depicted in Table 3, most patients presented at stage 4 (40.2%) followed by

stage 3 (30.3%). The least number of patients presented at stage 1 (11.6%). The more common clinical diagnoses of the patients were Cervical cancer (50%) and Ovarian cancer (28.5%). Only 10.7%, 6.3% and 4.5% of the studied patients had a diagnosis of uterine, vulva and Choriocarcinoma/GTD.

Table 1. Demographic characteristics.

Variable	Frequency (224)	Percentage (100%)
Age (in years)		
21 - 30	16	7.1
31 - 40	30	13.4
41 - 50	50	22.3
51 - 60	72	32.1
61 - 70	46	20.5
>70	10	4.5
Marital Status		
Single	30	13.4
Married	160	71.4
Separated	8	3.6
Divorced	8	3.6
Widowed	18	8.0
Parity		
0	38	17.0
1 - 4	148	66.0
or >5	38	17.0
Religion		
Christianity	220	98.2
Islam	2	0.9
Traditional	2	0.9
Educational status		
Non-formal	28	12.5
Primary	62	27.7
Secondary	82	36.6
Tertiary	52	23.2
Employment status		
Unemployed	46	20.5
Self-employed	134	59.8
Private/Govt employ	44	19.7
HIV status		
HIV positive	24	10.7
HIV negative	200	89.3

Table 2. Factors associated with gynaecological cancers.

Variable	Frequency (224)	Percentage (100%)
Age at first intercourse (years)		
<10	22	9.8
10 - 13	108	48.2
14 - 17	64	28.6
18 - 21	24	10.7
>22	4	1.8
Not indicated	2	0.9
Multiple sexual partners		
Yes	60	26.8
No	164	73.2
Knowledge of Pap smear		
Yes	36	16.1
No	188	83.9
Had Pap smear within 3 years prior to presentation		
Yes	12	5.4
No	212	94.6

Table 3. Diagnosis and FIGO stage of Illness.

Variable	Frequency (224)	Percentage (100%)
FIGO Stage of illness		
1	26	11.6
2	40	17.9
3	68	30.3
4	90	40.2
Clinical Diagnosis		
Cervical cancer	112	50.0
Ovarian cancer	64	28.5
Uterine cancer	24	10.7
Vulva cancer	14	6.3
Choriocarcinoma/GTD	10	4.5

4.5. Treatment and Outcome of Illness

As depicted in **Figure 1**, ten patients (4.5%) were discharged against medical advice (AMA) due to lack of funds and ignorance of the disease, while twelve patients (5.4%) had examination under anaesthesia (EUA), staging and biopsy after which they were lost to follow-up. Sixty-nine patients (30.4%) had sequential chemoradiation (chemotherapeutic agents-paclitaxel and carboplatin), sixty-two patients (27.7%) had debulking surgery and chemotherapy, and thirty-six

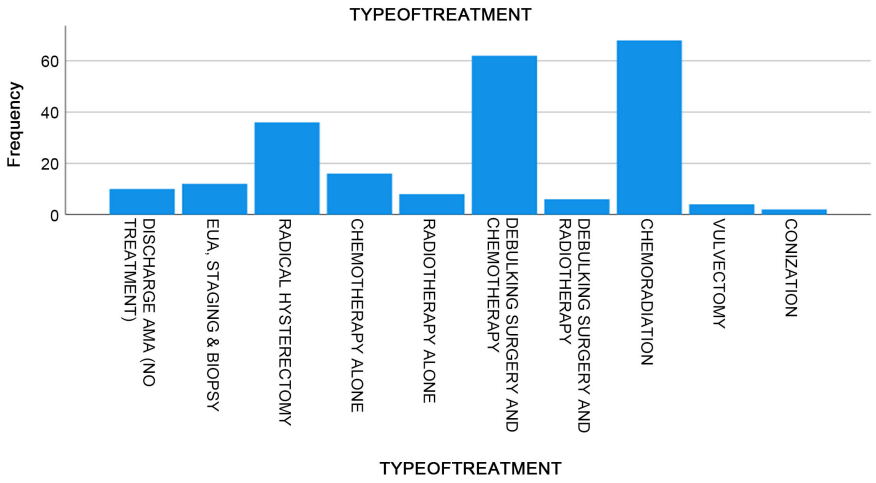

Figure 1. Treatment.

(16.1%) had radical hysterectomy. Other forms of treatment included debulking surgery and radiotherapy for 6 patients (2.7%), chemotherapy alone for 16 patients (7.1%), radiotherapy alone for 8 patients (3.6%), vulvectomy for 4 patients (1.8%) and conization for 2 patients (0.9%). Cervical cancer was treated with radical hysterectomy and lymphadenectomy for stages 1-2A. Stages 2B and above had adjuvant chemotherapy (3 to 4 courses of carboplatin & paclitaxel) and for those downgraded to 2A was further treated with radical hysterectomy, and/or followed by radiotherapy. Ovarian cancer, uterine cancer, gestational trophoblastic disease/choriocarcinoma and vulval cancers were treated according to National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. However, completion of the courses of treatment was dependent on patients' financial status and understanding of the course of the illness.

All the HIV positive patients were on HAART (Tenofovir, lamivudine and dolutegravir) for varied periods ranging from 1 to 6 years. The CD4 counts and viral load were not found in the case records, hence not part of the data analysis.

4.6. Comparison between Age Range at Presentation, Age at First Intercourse, Clinical Diagnosis, Stage of Illness and Status at Time of Study between HIV Positive and HIV Negative Women

As depicted in Table 4, twenty-five percent and 41.7% of the HIV positive clients presented at 31 - 40 and 41 - 50 years of age compared to 12% and 20% of HIV negative women respectively. The proportion of HIV positive and negative patients aged 51 - 60 years were similar, but there was no HIV positive patient presenting in the second, sixth and seventh decades of life.

There is also a significantly higher frequency of early coitarche among HIV positive patients with, six (25%) and fourteen (58.3%) at ages less than 10 years, and 10 - 13 years compared to sixteen (8%) and ninety-four (47%) for the same age groups in HIV negative women.

Table 4. Comparison between Age range at presentation, Age at first intercourse, Clinical diagnosis, Histological diagnosis, Stage of illness, and status at time of study between HIV positive and HIV negative women.

Variable	HIV +ve women (24)	HIV –ve women (200)	Pearson chi-square test
Age range			
21 - 30	0	16 (8%)	
31 - 40	6 (25%)	24 (12%)	
41 - 50	10 (41.7%)	40 (20%)	*0.007
51 - 60	8 (33.3%)	64 (32%)	
61 - 70	0	46 (23%)	
>70	0	10 (5%)	
Age at 1st coitus			
<10	6 (25%)	16 (8%)	
10 - 13	14 (58.3%)	94 (47%)	
14 - 17	4 (16.7%)	60 (30%)	*0.037
18 - 21	0	24 (12%)	
≥22	0	4 (2%)	
Unindicated	0	2 (1%)	
Clinical Diagnosis			
Cervical cancer	18 (75%)	94 (47%)	
Ovarian cancer	2 (8.3%)	62 (31%)	*0.003
Uterine Cancer	0	24 (12%)	
Choriocarcinoma/GTD	0	10 (5%)	
Vulva cancer	4 (16.7%)	10 (5%)	
Histopathology of specimen			
Cervix			
No histology (Discharged AMA—No treatment)	0	10 (5%)	
Adenocarcinoma	0	12 (6%)	
Adeno-squamous Ca	0	4 (2%)	
Well diff. invasive SCC	18 (75%)	66 (33%)	
Undifferentiated SCC	0	2 (1%)	
Ovary			
Serous cyst-adenoCa	2 (8.3%)	34 (17%)	
Mucinous cystadenoCa	0	8 (4%)	
Endometriod Ca	0	3 (1.5%)	
Granulosa cell Tumour	0	8 (4%)	
Dysgerminoma	0	2 (1%)	
Mixed Mullerian Tumour	0	2 (1%)	
Sertoli-Leydig cell Tumou	0	2 (1%)	
Immature teratoma	0	2 (1%)	
Serous Papillary Ca	0	1(0.5%)	
Uterus			
Endometriod adenocarcinoma	0	22 (11%)	
Uterine rhabdomyosarcoma	0	2 (1%)	
Chorio-Carcinoma/GTD	0	10 (5%)	
Vulva			
Invasive Sq. cell Ca	2 (8.3%)	10 (5%)	
Verrucous carcinoma	2 (8.3%)	0	

Continued

FIGO Stage of Illness			
1	0	26 (13%)	*0.008
2	2 (8.3%)	38 (19%)	
3	14 (58.3%)	54 (27%)	
4	8 (33.3%)	82 (41%)	
Status at study period (06/18-02/19)			
Alive	4 (16.7%)	52 (26%)	*0.011
Alive with recurrence	0	10 (5%)	
Terminally ill	0	14 (7%)	
Lost to follow-up	18 (75%)	76 (38%)	
Dead	2 (8.3%)	48 (24%)	

*Significant $p < 0.05$.

The HIV positive patients more frequently had a clinical diagnosis of cervical cancer (75%) compared to HIV negative patients (47%). Only 8.3% of HIV positive patients had ovarian cancer compared to 31% of HIV negative patients. There was also no uterine cancer or choriocarcinoma among HIV positive patients compared to 12% and 5% respectively among HIV negative patients in this series. A higher proportion (16.7%) of HIV positive patients were noted to have vulva cancer compared to HIV negative women (5%).

The HIV positive patients tended to present more commonly in stage 3 (58.3%) compared to 27% for HIV negative patients. Stage 4 disease comprised of 33.3% of HIV positive as against 41% of HIV negative patients. Only 8.3% of HIV positive patients presented with stage 2 disease as against 19% of HIV negative patients, with no HIV positive patient presenting in stage 1 compared with 13% of HIV negative patients.

The commonest histology among HIV positive patients was invasive squamous cell cancer (ISCC) of cervix (75%). Others were ISCC of vulva (8.3%), verrucous cancer of vulva (8.3%), and serous cystadenocarcinoma of the ovary (8.3%).

A much lower proportion of HIV positive patients (16.7%) compared with 26% of HIV negative patients were alive during the study period. Though only two (8.3%) HIV positive patients compared with fifty-two (26%) HIV negative patients were confirmed dead over the period of the study, a higher proportion of the HIV positive patients (75%) were lost to follow-up compared with HIV negative patients (38%).

5. Discussion

The prevalence of HIV was 10.7% in the studied patients, which is approximately 7.5 times higher than in the general population [17], 5 times higher than a study among surgical oncology patients in Guinea [22], but agrees with the 10.3% obtained in a similar study in Zaria, Nigeria [23]. However, it is much lower than the 21.8% obtained in a South African study [24].

The modal age-range at presentation of the gynaecological cancer patients during the study period was 51 - 60 years, which is much higher than the 41 - 50 years obtained in Zaria [23] and Orlu [19], but similar to that obtained in Abakaliki [20] and the same institution [18] a decade ago. It however remains lower than what obtains in developed countries where the commonest age at presentation is between the 6th and 7th decades of life [25]. This may be related to higher socioeconomic status, with availability and accessibility of organised screening programs for gynaecological cancers. More than two thirds of the HIV positive patients were however aged 30 - 50 years compared to one-third of the HIV negative population. This agrees with the findings by Moodley *et al.* in a South African study [26] where the mean age of HIV-positive patients was 15 years younger than that of the HIV-negative patients. Patients with HIV and AIDS defining Cancers tend to be younger, probably due to a younger HIV population [27].

Majority of the patients had early coitarche with a higher frequency among HIV positive patients, but history of multiple sexual partners was low. In Nigeria as occurs in most African countries, early marriage with associated polygamous unions is common and this increases the risk of infection-related cancers especially among HIV positive persons [28].

Most of our patients presented with cervical cancer, which is the second most common female cancer after breast cancer in Nigeria, with an age standardized rate of 34.5 cases per 100,000 women in 2010 [29]. Our finding is in agreement with previous studies in Enugu [18], Abakaliki [20], and Ghana [30]. However, there was a higher proportion of cervical cancer among the HIV positive patients, which is in agreement with the findings of Adewuyi *et al.* [23] in Nigeria and other regions of the world [31]. Cervical cancer is the third leading cause of death among women in low-income countries [32], which are often regions with the greatest burden of HIV [33].

Ovarian cancer was the second commonest cancer in our series, similar to the findings in previous studies in Enugu [18] and Zaria [23]. However, only 8.3% of HIV positive patients had serous cystadenocarcinoma of the ovary and no endometrial cancer compared to 31% and 11% respectively in the HIV negative patients. This is no surprise as the first documented report of ovarian cancer in a HIV positive patient was in 1992 [34], but differs from the systematic review by Smith *et al.* [8] where the incidence of ovarian and vulvovaginal cancers was higher than the general population, while incidence of endometrial cancer was similar.

Our finding of 16.7% of vulvar cancers among the HIV positive patients confirms that in population with a high prevalence of HIV, there is a high incidence of vulvar cancer [23] [35]. This could be due to the fact that vulva cancer is mostly associated with Human papillomavirus, which is also implicated in cervical cancer. Vulvar cancer in young human immunodeficiency virus-seropositive women may be associated with other human papillomavirus-related diseases and immunosuppression, as evidenced by low CD4 counts and the presence of antecedent acquired immune deficiency syndrome-defining illnesses [36]. Due to poor records, we had no data on CD4 counts.

The commonest histologic diagnosis was well differentiated invasive squamous cell carcinoma of the cervix, similar to findings in other studies [21] [23] [37]. There was no uterine cancer among the HIV positive patients, probably partly due to the fact that majority of our HIV positive patients presented at an age range of 31 - 50 years which is much lower than the 60-year average age at presentation of uterine cancer in our population [38].

Majority of our patients did not have any knowledge of cervical screening with only 5.4% of them having Papanicolaou test within 3 years of the diagnosis of gynaecologic cancer. This result confirms previous reports of low screening coverage among HIV-infected women, ranging from 9% in Tanzania [39], 10% in Nigeria [40], to 13% in South Africa [41]. As in most low-income countries, there are no national screening or prevention programmes for cervical cancer in Nigeria, and awareness of cervical cancer among women remain limited. The lack of regular organized cervical screening in our environment [42], especially among HIV positive patients who are at heightened risk of cervical cancer may be one of the reasons for the increased prevalence of cervical cancer among our HIV-infected patients.

As the primary prevention of cervical cancer by HPV vaccination is not effective in women already infected by HPV, secondary prevention through early detection and treatment of precancerous lesions of the cervix is crucial. It has been suggested that rapid point of care HPV test in self-obtained vaginal samples permitting both first-line screening, as well as triaging of HPV positive women with either visual inspection of the cervix after acetic acid application (VIA), visual inspection after application of Lugol's iodine (VILI), or cytology, followed by treatment may best serve women in low resource settings [43].

Most of the gynaecological cancer patients presented at an advanced stage of the disease. This is consistent with other studies [44] [45] where late presentation, with advanced and metastatic disease is the norm. This is related to poverty, ignorance, and African sociocultural norms of secrecy associated with gynaecological issues [46]. The HIV positive patients presented with more severe disease compared with HIV negative patients. This agrees with the findings by Maiman *et al.* [47], but differs from findings by Levinson *et al.* [31] where greater than half of the patients presented with early-stage disease.

Though all the HIV positive patients had HAART between 1 - 6 years prior to presentation with gynaecological cancer, start of treatment most likely was during the chronic phase of the infection which may have affected their response to the antiretroviral drugs in combating disease progression and incidence of AIDS-defining cancers. Early combination antiretroviral therapy (cART) has been shown to reduce cancer mortality in HIV-infected patients with Kaposi Sarcoma (KS) and Non-Hodgkin Lymphoma [11]. Response to cART have been found to be most beneficial during the acute phase of the infection and within 10 months of infection compared to the chronic phase of the infection [48]. Due to the retrospective nature of our study, we could not determine the time interval between HIV infection and presentation of our patients, but judging from our en-

vironment where there is no organized screening, most of our clients are diagnosed when they report with symptoms of immunodeficiency during which the window of opportunity for maximal response to the cART is already lost. The increased mortality among our HIV positive population may be related to disease stage, and late start off of HAART.

Majority of the patients had standard cancer treatment relevant to the type and stage of cancer, bearing the mind the performance status of the patients. This is the opinion of four-fifth of US gynaecologists [49] and guidelines by the National Comprehensive Cancer Network (NCCN) [50].

Though a higher proportion of the HIV negative patients were confirmed dead in our series, a higher proportion of the HIV positive patients were lost to follow-up. With a higher proportion of them presenting with more advanced disease, it is probable that they were dead. The HIV infected cancer patients were more likely to die than HIV negative ones [51].

6. Conclusion

HIV positive patients present at an earlier age with more advanced disease mostly invasive cervical cancer of the squamous variety. Even though overall survival of HIV-infected patients has improved with HAART worldwide, early onset of treatment is essential to maintain adequate levels of immune competence among patients treated in University of Nigeria Teaching Hospital. This will reduce the onset and progression of the AIDS Defining Malignancies (ADM), including reduction in HIV specific morbidity and mortality. There should also be a concerted program of routine regular cervical screening as part of routine management for all HIV positive women.

Limitations

The following limitations to the study are acknowledged. This is a retrospective study hence some of the case records were unavailable. It is possible some women were not identified for inclusion. Data on CD4 count, viral load, interval between HIV diagnosis and HAART intake, as well as co-morbidities were unavailable.

Authorship Statement

All authors contributed sufficiently to be listed as authors and take responsibility for the work

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1) Drafting the article: Ezeome Ijeoma;

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C.

1) Final approval of the version to be published: Ezeome Ijeoma, Nwankwo Theophilus, Umeh Uchenna, Ajah Leonard.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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