International Journal of HIV/AIDS Prevention, Education and Behavioural Science
2015; 1(2): 14-20
Published online November 12, 2015 (http://www.sciencepublishinggroup.com/j/ijhpebs)
doi: 10.11648/j.ijhpebs.20150102.11

From HIV/AIDS to HIV Cancer: An Analysis of Transition from HIV Infection to Cancer Amongst Patients in Cameroon

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To cite this article:

Enow Orock G., Agyingi L., Nnap L., Ewane T. P., Ngai J., Fewou A., Ndom P., Doh A., Nyambi P. From Hiv/Aids to Hiv Cancer: An Analysis of Transition from Hiv Infection to Cancer amongst Patients in Cameroon. *International Journal of HIV/AIDS Prevention, Education and Behavioural Science.* Vol. 1, No. 2, 2015, pp. 14-20. doi: 10.11648/j.ijhpebs.20150102.11

Abstract: A total of 288 cases of HIV cancers were retained among 3785 HIV infected patients in this retrospective multi-centre pilot study that lasted 18 months between 1st January 2013 and June 30 2014 in Cameroon. This gave a cancer prevalence among HIV infected patients of 7.6%.The study was aimed at looking at the transition time between HIV infection to development of cancer amongst patients. Data on cancer and HIV infection of patients with both diseases in the randomly selected pilot centres were retrieved, assembled and analyzed.The mean age of patients was 44.1years with 30% of them aged between 30-39 years. HIV malignancies occurred predominantly in females (71%). 45.5% of the patients had AIDS-Defining Cancers against 47.6% Non-AIDS-Defining Cancers. Kaposi sarcoma was the commonest cancer, accounting for 50.4% of all AIDS-defining cancers; while breast cancer was the most prevalent non-AIDS-defining cancer, contributing to 32.8% of all cancers in this group. Diagnosis of cancers in these patients (100%) was all made after the diagnosis of HIV at a mean time interval of 3.6 years. Most cancers (16.7%) were diagnosed within 1 year of HIV infection, at CD4 counts between 300-399cells/µL in females, which was significantly different from CD4 counts <100cells/µL in males. HIV serotyping showed a predominance of HIV I (67.7%). There was no sex predilection for any HIV serotype, similarly, there was no association between a particular HIV serotype and cancer type. HIV malignancies are not rare in Cameroon. Though the prevalence of the infection in the entire nation has tipped off in recent years, it is likely that more malignancies would be detected in future amongst HIV/AIDS patients due to prolonged survival as a consequence of increased availability of Highly Active Anti-Retroviral Therapy (HAART). Knowledge of the transition time between HIV infection and the apparition of cancer is a vital tool for comprehensive management of these patients that could improve on the outcome of both diseases. Further in-depth studies to document incidence and trends of HIV malignancies in our community are recommended.

Keywords: HIV/AIDS, Transition, HIV Cancer, Cameroon

1. Introduction

The burden of disease in developing countries is being overwhelmed by known and emerging infections. It has also been shown by various studies that non communicable diseases are becoming a public health problem in these communities. Almost 4 decades after the apparition of the HIV/AIDS pandemic, new challenges to this disease are being faced by patients and the global health systems. Patients are living longer with HIV infection due to the

increase availability of HAART. This increase in survival increases the risk of cancer amongst the patients.

Numerous viral infections have for long been associated with various types of cancers. These include Human herpesvirus 8 (HHV-8), also known as Kaposi sarcoma-associated herpesvirus (KSHV), which is the cause of Kaposi sarcoma, Epstein Barr virus which causes some subtypes of non-Hodgkin and Hodgkin lymphoma, Human papillomavirus (HPV) associated with cervical cancer and some types of anal, penile, vaginal, vulval, and head and neck cancer and Hepatitis B virus (HBV) and hepatitis C virus (HCV) both which can cause liver cancer [1-3]. People infected with Human Immunodeficiency Virus (HIV) have a higher risk of some types of cancer than uninfected people. This is due to a weakened immune system caused by infection with HIV, infection with other viruses, and traditional risk factors such as smoking, alongside prolonged survival amongst people living with HIV AIDS (PLWHA) which all contribute to this higher cancer risk [4, 5].

In resource-stressed communities like ours, numerous difficulties are faced in the management of HIV/AIDS and cancer respectively and the situation is worse in patients who have both diseases. The advent of HIV/AIDS has caused a significant change in the epidemiology of cancer in Cameroon, reducing the average incidence age for the disease in the population by 8 years [6]. The national HIV infection rate has decreased from 12% in 1995 to a rate of 4.5% in 2014, yet there have been an upsurge of both AIDS-defining and other cancers in patients with the infection [7].

The interaction between HIV and host antigens and eventual occurrence of related cancers has not been fully understood. The role of underlying genetics, co-infections, and lifestyle exposure to unknown antigens can never be underestimated, and therefore scientists should continue to investigate the interaction of HIV and its proteins with host machinery in the etiology of oncogenesis from a molecular to epidemiologic level. This explains why we decided to carry out this study on investigating the transition time from HIV infection to development of cancer amongst patients in our community.

2. Materials and Methods

In order to foster research on HIV malignancies in Cameroon, the NCI- USA had sponsored a project on collection of data on patients with both HIV infection and an associated malignancy in multiple centres in the country. For this study, data on patients with both HIV infection and cancer from 5 pilot centres of this NCI-sponsored HIV malignancies project were assembled and analysed during an 18 months period between 1st January 2013 and June 30 2014. The centres had been randomly selected and data on patient vital statistics, HIV infection and associated cancer were abstracted. The important variables obtained from this study were: age, gender, cancer groups (AIDS-defining or non-AIDS defining), types of cancers, transition time between HIV infection and HIV cancer, CD4 count, and HIV serotype. The transition time from HIV infection to cancer was calculated from date of diagnosis of HIV infection to date of diagnosis of associated cancer.

Frequencies were determined for all of the above variables. Chi-square (χ^2) test was used to determine the p value and infer statistical significance between proportions; and the Mann-Whitney U-test was used to compare the medians obtained from certain variables. Ethical clearance for the study had been obtained from the Ministry of Public Health Ethical Review Board and the local ethical review boards of the various institutions involved in the study. The data was analyzed using EPI info, Excel, and presented in the form of tables, graphs and charts.

3. Results

288 cases of HIV cancers were retained among 3785 HIV infected patients giving an HIV cancer prevalence of 7.6% among HIV infected patients.

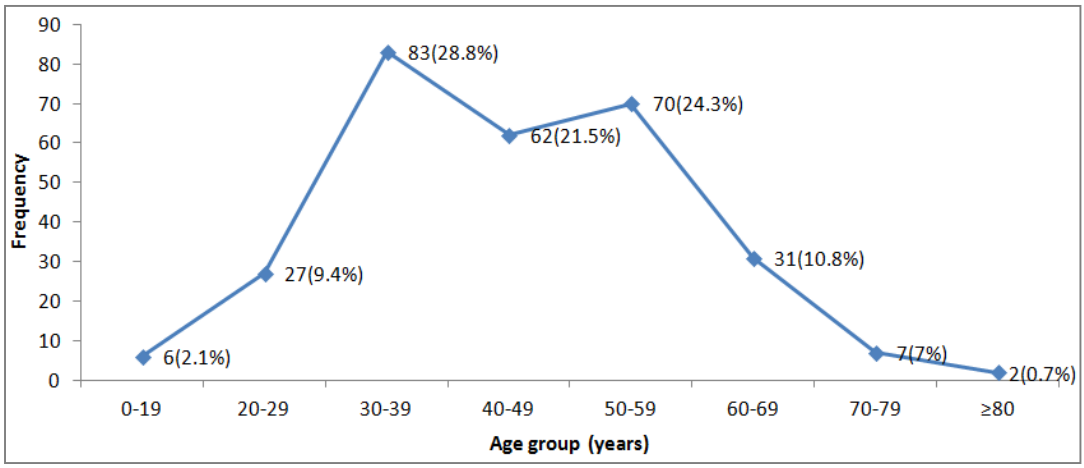

Figure 1. *Age of HIV cancer patients.*

The predominant age of the patients was between 20-69 years with peaks in the 30-39 years age group (28.8%) and 50-59 years (24.3%).there were few patients above below 20 and above 69 years.

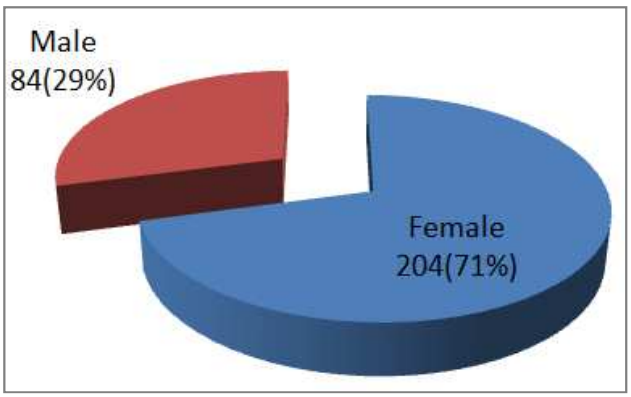

Figure 2. *Sex distribution of HIV malignancies.*

Patients were predominantly females (M:F ratio of 1:2.4).

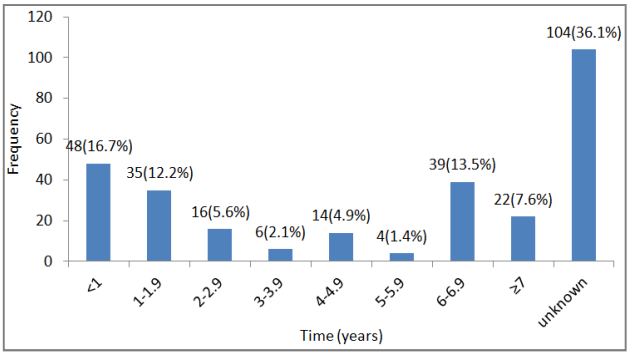

Figure 3. *Transition time interval between diagnosis of HIV and cancer.*

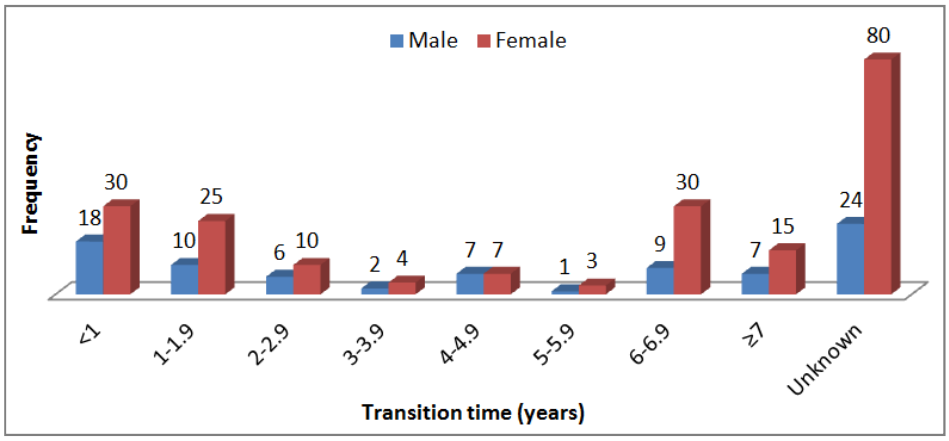

Figure 4. *Transition time by sex.*

Many patients develop cancer within the first year of HIV infection (16.7%). The rate falls to the 4th year after which it begins to rise to a second peak by the 6th year of infection. This pattern is common to both males and females. It would be interesting to find out the transition time for particular cancers. This way a map of "early-onset" and "late- onset" HIV-associated cancers can be elaborated. Also as a subject for further studies, it would be necessary to understand the rate of transition of the particular cancers with respect to the sex of patients. Due to paucity of data for a significant number of patients (36.1%), the transition time from infection to cancer could not be determined.

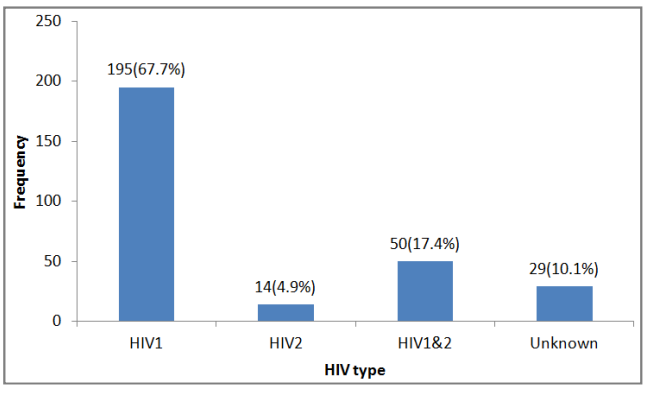

Figure 5. *HIV serotypes infecting HIV cancer patients.*

Our patients were mostly infected by the HIV type 1 (67.7%) compared to type 2 (4.9%). The number of patients who had a co-infection by both serotypes was 17.4%. in about 1 out 10 patients, the serotype of the infecting HIV virus was not indicated. It would be interesting to elaborate a future study that indicates the viral serotype by sex.

Kaposi sarcoma, non- Hodgkin's lymphoma and cervical cancer were the main AIDS-defining cancers, while the breast, other skin cancers (except Kaposi sarcoma), soft tissue cancers and non-Hodgkin's lymphoma in descending order were commonest non AIDS defining cancers. Generally, the most prevalent HIVCAs were Kaposi sarcoma (50.4%), uterine cervical cancer (38.9%), breast (32.8%), other skin (16.8%), soft tissue cancers (12.4%) and non-Hodgkin's lymphoma (10.7%). The cancers which are important in this group of patients compared to the prevalence in the general population in this community are cancers of the bone (5.8%), GIT (5.8%) and endometrium (4.4%). However, it has been recently reported that GIT cancers were on the rise [6] in this community .There is a significantly lower median CD4 count at diagnosis of ADCs than NADCs (281vs. 326, p=0.047at 95% CI).

A CD4 count in HIV infection indicates the capacity of the immune system to 'fight off' the infection. Amongst the patients whose counts were known in this study, a large proportion had counts of and above 200. Only few had

counts below 100 (9.7%). Most patients (20.2%) had counts between 200 and 400. It is to be remarked that in spite of these high CD4 counts, our cases still developed various cancers. Using a CD4 count of 200 as cut off point, we found no significant difference between patients with high (above 200) CD4 and low (below 200) counts. It is most likely that oncogenesis in HIV infected patients occurs irrespective of CD4 count of the patient.

Table I. *HIV malignancies by cancer group and by gender.*

	Male	Female	Total
AIDS-Defining malignancies			
Kaposi sarcoma	32	34	66(50.4%)
NonHodgkin lymphoma	6	8	14(10.7%)
Cervical cancer	/	51	51(38.9%)
Total			131
Non-AIDS-Defining malignancies			
Hodgkin lymphoma	6	3	9(6.6%)
Other Skin cancer	10	13	23(16.8%)
Breast cancer	1	44	45(32.8%)
Oral cancer	0	2	2(1.5%)
oesophagus and stomach	2	2	4(2.9%)
Ano-Colorectal	1	7	8(5.8%)
Ovarian cancer	/	2	2(1.5%)
Endometrial cancer	/	6	6(4.4%)
Vulvar cancer	/	2	2(1.5%)
Bone cancer	2	6	8(5.8%)
Soft tissue cancers	7	10	17(12.4%)
Hepatocellular carcinoma	1	1	2(1.5%)
Prostate cancer	1	/	1(0.7%)
Testicular cancer	2	/	2(1.5%)
lung Cancers	4	0	4(2.9%)
Cancer of the thyroid	1	0	1(0.7%)
Multiple myeloma	1	0	1(0.7%)
Total			137
Unclassified cancers			
Unspecified cancers	7	13	20

Table II. *CD4 counts at diagnosis of cancers in HIV/AIDS patients by sex.*

CD4 count	Male	Female	Percentage (%)
<100	11	17	28(9.7%)
100-199	4	9	13(4.5%)
200-299	8	19	27(9.4%)
300-399	9	22	31(10.8%)
400-499	6	16	22(7.6%)
500-599	1	7	8(2.8%)
600-699	1	3	4(1.4%)
≥700	0	4	4(1.4%)
unknown	44	107	151(52.4%)
Total	84	204	288 (100%)

4. Discussion

Different rates of HIV malignancies have been reported from various studies in Africa. This is attributed to the geographical variability of the prevalence of HIV/AIDS in the continent [8]. Other factors that contribute to this variability include individual genetic susceptibility to developing cancers, variations in the prevalence of oncogenic viruses associated with HIV infections; and variations of prevalence of HIV types between countries in Africa [8].

The prevalence of cancer amongst HIV/AIDS patients in our study was 7.6%, a finding similar to a multicentre study in Italy, where the prevalence was reported to be 7.1% [8]. Our finding is however lower than 10% reported by Crum-Cianflone in the USA [10], and higher than 3.5% found in Uganda by Mbulaiteye [11].

HIV infection is more prevalent in females than males in Sub- Saharan Africa [12] and in our study, a significant dominance of this sex was observed in the prevalence of HIV malignancies ($p<0.01$ at 95% CI) (figure 2), similar to what other studies had found [13]. This is expected because female-specific cancers (particularly the breast and cervix) are more frequent in sub-Saharan Africa. In a previous study on the same population, a similar sex ratio for cancer in both immune competent and immune depressed patients was reported [6]. Our finding is, however, in contrast to that of Park in the USA, where HIV malignancies occurred in 91-95% of males [14 , 15] in a study whose bias population of HIV-infected veterans and military beneficiaries was male-dominated.

The mean age of patients was 44.1years (SD=13.3), and median of 42 years (IQR=35-54). 30% of the patients were between 30-39 years age group. The median age at diagnosis of cancers was 44.0 years in males and 42.0 years in females. There was no significant difference in the median ages at diagnoses of cancers between these two groups ($p=0.54$). (figure 1). This is similar to several studies where the median age was found to be 45-46 years [16, 17].In 2006, Sackoff and associates performed a linkage of the New York City HIV/AIDS registry and death certificates from 1999 to 2004. This study was perhaps the most comprehensive description of non-HIV-related causes of death among people with AIDS in the United States. There were nearly 70% male patients and the median age was 46 years [16, 18].Our finding is much higher than that reported in some other studies [19, 20] with median ages as low as 30-35 years. Amongst our patients 2.1% of the cases involved children aged 0-19 years (figure 1).

The most prevalent Aids Defining Cancer (ADC) we found was Kaposi sarcoma (50.4% of ADCs and 22.9% of all HIVCA), while breast cancer was most prevalent Non Aids Defining Cancer (NADC) (32.8%) (Table I). This finding is similar to that of a study conducted by Akarolo-Anthony, where Kaposi sarcoma was the most frequent ADC and breast cancer, the most frequent NADC [16]. Unlike our study, others have shown significantly greater proportion of NADCs over ADCs [10, 21], while others detected either the predominance of ADCs or no disparity in their prevalence [13, 17, 22]. Another study conducted to compare the incidences of ADCs and NADCs in the developed and developing worlds yielded similar results to ours [23]. Our study found no significant difference in the proportion of ADCs and NADCs (45.5% vs. 47.6%, $p=0.804$) amongst the patients (table I), unlike others that found a prevalence of

ADCs in 41% of cases and NADCs in 59% [16]. Burgi and colleagues found predictors of NADC to include age over 40, a longer duration of HIV infection, and a history of opportunistic infection [24]. This aspect was not included in our study.

Although the introduction of highly active antiretroviral therapy (HAART) in the mid-1990s greatly reduced the incidence of Kaposi sarcoma and non-Hodgkin lymphoma among people infected with HIV [4], we found a predominance of these tumours amongst our patients (table I). It is possible that immune reconstitution in the post-HAART era leads to chronic cytokine activation and possible damage to DNA via oxidative stress [25]. It has even been suggested that HIV medications themselves may have a direct role in oncogenesis [25].

There were a total of 20 different HIV malignancies in this study, commonest amongst which were Kaposi sarcoma, 66 (22.9%), cervical cancer 51 (17.7%), breast cancer 45 (15.6%), other skin cancers, 23 (8%) and Lymphomas 23 (8%) (table I). Previous studies had showed that people infected with HIV are several thousand times more likely than uninfected people to be diagnosed with Kaposi sarcoma, more likely to be diagnosed with non-Hodgkin lymphoma, and, among women, at least 5 times more likely to be diagnosed with cervical cancer [26]. We found a high proportion of breast cancer and GIT cancers amongst our patients. This was different from studies conducted in Ibadan where Ocheni found NHL (20%), breast cancer (19%), cervical cancer (11%), Chronic lymphocytic leukaemia (10%) and multiple myeloma (5%) amongst the commonest cancers in HIV cancer (HIVCA) patients [16], and similar to other previous reports [11,27].

The incidence of breast cancer in HIV infected patients has been shown by some to be significantly increased both in African [28] and developed countries [29] as we found in this study. Only recently have there been studies addressing the rate of colon cancer screening in the HIV/AIDS population and there have also been reports suggesting an elevated risk and earlier age of onset of colonic neoplasia in the HIV/AIDS population [30]. Adenocarcinoma of the digestive tract has been reported by earlier studies to be common in HIV infected patients [31-34]. We found a surprisingly important frequency of cancers of the thyroid, eye and vulva among the HIV/AIDS patients that we studied in this series (table I).

The diagnosis of all cancers (100%) in these patients was made after the diagnosis of HIV. The median conversion time from HIV to HIVCA in our study was estimated to be 4.0 years (IQR=1.1-6.25) (figure 3, figure 4), a value lower than 5.8 years found in a study in the USA [15]. Conversely, this finding is much higher than that of a similar study conducted in India, where the median transition time was calculated to be 1.5years (IQR=0.2-5.6) [22]. The median time interval between diagnoses was 4.0 years (IQR=1.1-6.25) and mean of 3.6 years (SD=3.7). About 16.7% of cancers were diagnosed within 1 year of diagnosis of HIV. The median duration of diagnosis of cancers from HIV diagnosis in females is 2.2 years, which is statistically insignificant from the 2.25 years in males (p=0.661) (figure 4).

HIV positive females have a bimodal time interval between diagnoses of HIV and cancers. The first is at less than 1 year, and the second at 6-6.9years (10.4% in both cases). In males, most cases of malignancies are diagnosed within 1 year of diagnosis of HIV (Figure 4).

The average incidence age for cancer amongst HIV+ patients was similar between the two sexes, except for lymphomas which occur significantly earlier in females (29 years) than males (44.5 years); while GIT cancers (except stomach) occur relatively earlier in males (38 years) than females (45.5 years) . Engels and colleagues from the National Cancer Institute in Maryland used 11 US regions from 1980 to 2002 to identify nearly 376,000 patients with cancer and AIDS, the results of which were published in 2006. Interestingly, other than Hodgkin lymphoma, the authors did not observe a change in risk for NADC over time [35].

The stage of cancer at diagnosis in our patients could not be evaluated due to unavailability of the data, though Enow-Orock [36] had reported that cancers were diagnosed at earlier stages amongst HIV-infected patients than in immune competent patients in this community due to more health surveillance of HIV infected patients.

Mbulaiteye and coworkers performed one of the largest studies using CD4 counts to assess the relationship between immune status and cancer risk [37]. Although CD4+ T cells are important in coordinating with CD8+ T cells and other cell types in tumor surveillance, some studies found no relationship between CD4 count and the risk of NADC [12]. The median CD4 count at diagnosis of cancers in HIV+ patients in our study was 300cells/μL (IQR=134.5-410) (table II), which was higher than that of a similar study in India (median 164cells/μL) [22]. ADCs have been shown to occur more in patients with declining CD4 counts than NADCs [4]. This is reported in our study where there is a significantly lower median CD4 count at diagnosis of ADCs than NADCs (281vs. 326, p=0.047 at 95% CI).There was no significant difference between patients with 'high' (above 200) and 'low' (below 200) CD4 count (p>0.5) at 95 % confidence interval with respect to association of the infection with cancer. The only significant finding was that HIV infected females with cancer had higher CD4 counts than male counterparts. While it is most likely that oncogenesis in HIV infected patients occurs irrespective of CD4 count of the patient, sexual factors seem to influence the level of CD4 at which cancers occur (at high counts in females compared to males). Noteworthy is also the fact that ADC unlike NADC occur at lower CD4 levels as stated above.

The HIV-1 virus is more common and more aggressive than the HIV-2, and hence implicated in a majority of cancers as opposed to the later [38-40]. We found infection by HIV-1 virus alone in about two-thirds of patients with HIV-related malignancies (195, 67.7%) (figure5). The HIV-2 virus was found in 14 (4.9%) of the patients; and co-infection

by the two serotypes was found amongst 50 (17.4%) patients. There was no sex predilection for any HIV serotype, similarly, there was no association between any particular HIV serotype and cancer type.

5. Study Limitations

This study is not without limitations. The small sample size of 288 patients and the short duration of 18 months may impact our findings. The significant proportion of 'unknown' values among the parameters that we studied limits the accuracy of our findings.

6. Conclusion

HIV malignancies are an emerging health problem in our setting. About 4 in 50 (8%) HIV-positive patients are likely to develop one form of cancer or another. The infection always precedes cancer which occurs at variable time intervals depending on the HIV serotype, immune status, and sex of the patient. Averagely HIV cancer conversion occurs within 5 years following infection by the virus. Presently, there is a disconnection in the management of patients suffering from the 2 diseases in our environment, with need for integration and/or stronger linkages between cancer and HIV care. It is vital to understand the epidemiology of HIV and its associated cancers. More importantly, knowledge of the transition time between HIV infection and the apparition of cancer is a vital tool for comprehensive management of the patients. It is hoped that this knowledge would improve on the outcome of both diseases. This would greatly reduce the care-seeking burden of patients, while further studies should be carried out to determine the incidence, trends and transition from HIV infection to HIV cancer in our community.

Acknowledgement

The authors wish to express their sincere gratitude to the technical staff of the 5 pilot centres who collected data, Mr Tawe for data analysis, and Miss Efeti for secretarial duties. We also thank colleagues, residents and specialists in the departments that deal with management of both HIV/AIDS and cancer, for their collaboration. Finally, we wish to acknowledge the financial sponsorship of the NCI, through New York University School of Medicine, NYUSoM, USA.

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