Kaposi's Sarcoma Trends in the Era of Highly Active Antiretroviral Therapy in Zambia

Lubinda Mukololo[1], Lorenda Temwani Phiri[2], Memory Chisha[2], Florence Mwaba[3], Rabecca Tembo[3*], Mildred Zulu[3]

[1]The University of Zambia, School of Medicine, Department of Physiological Sciences, P.O. BOX 50110, Lusaka, Zambia.

[2] The University of Zambia, School of Medicine, P.O BOX 50110, Lusaka, Zambia.

[3] The University of Zambia, School of Medicine, Department of Pathology and Microbiology, P.O BOX 50110, Lusaka, Zambia.

[*]Corresponding author: rabeccaktembo@gmail.com

Mobile: +260978363271

10.53974/unza.jabs.6.3.978

ABSTRACT

AIDS-related Kaposi's Sarcoma (KS) is a multi-centric angiogenic neoplastic proliferation predominantly seen in individuals with Human Immune Virus (HIV-1) infection and men who have sex with men. Although the incidences of aggressive KS have reduced following the introduction of Highly Active Antiretroviral Therapy (HAART) in the treatment of HIV infection, the effect of HAART rollout in relation to population KS incidence in Zambia remains unclear as cases of the malignancy have continued to be reported. This study, investigated the trends of KS in the era of HAART in Zambia. The researchers conducted a retrospective cross-sectional study. Three hundred and twenty cases of HIV-infected individuals on HAART that developed KS between 2008 and 2017 were reviewed. Data was retrieved from the Zambia National Cancer Registry (ZNCR). Of the records reviewed, the researchers observed a sharp increase in KS cases from 5.6 per cent in 2008 to 21.2 per cent in 2014; from 2015 to 2017, there was a general decline in KS cases countrywide in both sexes from 13.1 per cent to 9.4 per cent. KS was more prevalent in Lusaka Province, while Western Province had the least number of cases. For each province, there were more males affected by KS than females. The researchers further observed that 19.1 per cent of the cases reviewed developed KS while on HAART, while 80.9 per cent developed KS before the commencement of HAART. The age group with the highest number of KS cases was 21-40 years, while the age group ≥ 80 had the least number of cases. Our data has shown that although there has been a general decline in KS cases across the ten provinces of Zambia in recent years, more efforts are still required to mitigate AIDS-related KS incidence and improve KS prognosis. There is a need to encourage efforts aimed at HIV infection prevention, wide coverage of HAART across the country, and KS awareness and screening.

Keywords: AIDS, Highly Active Antiretroviral Therapy, Antiretroviral Therapy, Kaposi's Sarcoma-Associated Herpesvirus, Human Herpes Virus 8, Zambia National Cancer Registry.

INTRODUCTION

Kaposi's Sarcoma (KS) is a multi-centric angiogenic neoplastic proliferation that originates from the endothelial cells of lymph and blood vessels that are infected with Kaposi Sarcoma HerpesVirus (KSHV), also known as Human HerpesVirus 8 (HHV8) (1). KS lesions are predominantly present at mucocutaneous sites, but may also involve lymph nodes and visceral organs. The lesions evolve from early macules (patch stage) into plaques (plaque stage) that grow into large nodules (tumour stage) (2).

Kaposi's Sarcoma is considered an Acquired Immune Deficiency Syndrome (AIDS)-defining cancer in individuals with HIV-1 infection (3). It occurs in the context of immunosuppression; immunocompromised individuals, such as those taking immunosuppressive drugs and those who are HIV/AIDS-positive, are at a higher risk of developing KS (4).

Kaposi's Sarcoma is the most common malignancy associated with HIV infection worldwide (5). Despite an overall reduction in incidences of KS, following the introduction of antiretroviral therapy (ART), cases of malignancy have continued to be reported in HIV-infected individuals (6). According to the American Cancer Society, four variants of KS have been typified on the basis of the predisposing factors: Classic KS, Endemic/African KS, AIDS-associated/Epidemic KS, and Transplantation-associated KS (7).

Classic KS presents with lesions that grow slowly and mainly occur in older adults of Eastern Europe, Mediterranean and Middle-Eastern descent, affecting more men than women (8). KS lesions are confined to the skin of the lower limbs and do not affect deeper tissues (9). Another type of KS, which resembles Classic KS and has a good prognosis, has been reported in HIV-negative homosexuals and occurs at a younger age and is limited to the skin (10). African KS occurs in people living in Equatorial Africa (11). KSHV infection is more prevalent in Africa, thereby increasing the risk of developing African KS (12). Other factors that weaken the immune system, such as chronic diseases and malnutrition, also contribute to the development of KS. African KS tends to occur in younger people under the age of forty years, and an aggressive form, which affects the lymph nodes and other organs, is rarely seen in children before puberty (13). Transplant (Iatrogenic) KS develops in people with suppressed immune systems after an organ transplant. These patients are given immunosuppressive drugs to keep their immune system from rejecting the new organ. This increases the chances of developing KS in someone infected with KSHV (14).

AIDS-associated (Epidemic) is the commonest type of KS found in individuals infected with HIV (15). This type of KS is considered an AIDS-defining malignancy. It is an opportunistic disease responsible for severe morbidity and mortality in people living with AIDS (16). It is more aggressive than the other types of KS and produces multiple lesions, often on the face and trunk and also leads to the development of internal tumours in the oral cavity and lungs (17,18).

There has been a significant reduction in the incidences of KS, and in some cases, established KS undergoes remission with the introduction of Highly Active Antiretroviral Therapy (HAART) in the treatment of HIV infection (19,20). The lower incidences and regression observed with HAART following initiation of treatment are attributed

to immune reconstitution achieved by inhibition of HIV-1 replication (21). HAART also leads to intracellular cytokine production, which triggers the production of angiogenic factors, thus reducing the reactivation of HHV8 (22). Zambia has a high incidence of both epidemic and African forms of KS, and despite the introduction of HAART, cases of KS are still being reported in HIV-infected individuals (23). Thus, the present study investigated the trends in KS incidences in Zambia from 2008 to 2017, long after the introduction of HAART in the country.

MATERIALS AND METHODS

Study Site

The study was conducted in Zambia, a landlocked country in sub-Saharan Africa. It has eight neighbouring countries: Tanzania, Zimbabwe, Malawi, Botswana, Angola, the Democratic Republic of Congo (DRC), Namibia and Mozambique. Zambia has a geographical area of 753.612 km^2 and lies between latitudes 8° and 18° South and longitudes 22°and 34° East (24).

DATA SOURCE

Data was obtained from the Zambia National Cancer Registry (ZNCR). The ZNCR is a registry in Zambia that keeps population-based cancer data. It is located at the national referral hospital called University Teaching Hospital (UTH). Data is received from all health facilities countrywide through a standardised register that is used in all health facilities. Most of the cancers are detected in various health facilities and then sent to UTH for specialised treatment. The ZNCR receives the filled-in registers with all patient details and other necessary information.

STUDY DESIGN

This was a retrospective cross-sectional study. Information was retrieved from the ZNCR from 2008 to 2017. Files were selected randomly, and case files were selected by picking the tenth file.

Data Extraction

Three hundred and twenty cases of HIV-infected individuals on HAART that developed KS were included in the study, and excluded were cases of KS due to other causes. The sample size was calculated using the formula: , where N is the sample size, Z is the standard deviation set at 1.96, d is the degree of precision required to set at 0.05, and P is the prevalence of KS in HIV/AIDS patients. The prevalence of KS was found to be 22.2 per cent and 7.5 per cent in males and females, respectively (25). Using a prevalence of 29.7 per cent, the sample size calculated was 320. Key variables collected at baseline included age, gender, HIV status, ART status, and year of diagnosis.

Data Analysis

The data obtained was exported to the Statistical Package for Social Sciences (SPSS) version 21 for statistical analysis. Baseline demographic data and characteristics were analysed using descriptive statistics. The distribution of KS and the variables such as age and sex were analysed and presented in the form of frequencies, percentages and tables.

Ethical Considerations

Ethical approval was granted by the University of Zambia School of Medicine Research Ethics Committee (Certificate Number: IRB00001131 of IORG0000774), and permission to

review files was obtained from the ZNCR. This research extracted secondary data for Kaposi's Sarcoma patients from the national database, and as such, informed consents were not applicable.

RESULTS

Proportion of KS Cases in the Ten Provinces of Zambia

Records of 320 KS-positive patients were obtained from the ZNCR and analysed for the years 2008-2017. KS cases increased exponentially from 5.6 per cent (20/320) in 2008 to 21.25 per cent (68/320) in 2014. However, there was a decline in the number of cases from 2015 to 2017 from 13.13 per cent (42/320) to 9.38 per cent (30/320) respectively (Figure 1). Most KS patients were from Lusaka province, and the number of males was higher than that of females, 43.75 per cent (140/320) and 25.31 per cent (81/320), respectively. This was followed by Central Province, which had a proportion of males of 3.75 per cent (12/320) and females of 2.50% (8/320). Western Province had the least number of patients, with a proportion of 0.63 per cent (2/320) and no females (Table 1). Out of the 320 total cases reported, 19.06 per cent (61/320) developed KS while on HAART, while 80.94 per cent (259/320) developed KS before the commencement of HAART.

The proportion of Kaposi's Sarcoma Cases based on Age and Sex

The proportion of Kaposi's sarcoma cases was high in the age group 21-40 years, and males, 35.94 per cent (115/320), were more affected than females, 25.63 per cent (82/320). This was followed by

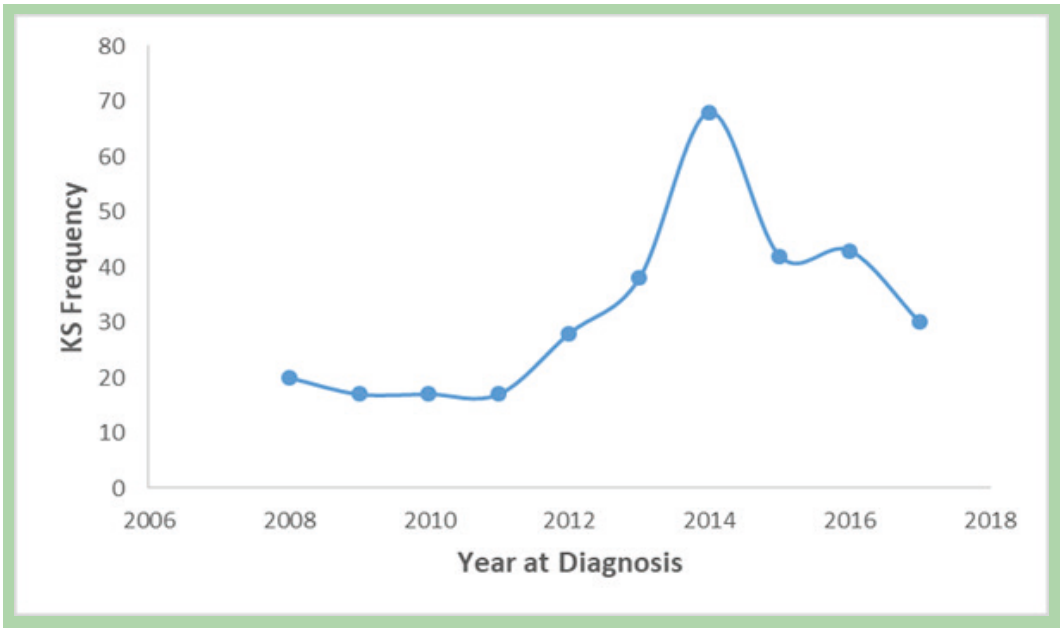

Figure 1: Cumulative KS cases in Zambia between 2008-2017.KS cases increased exponentially between the years 2008 and 2014 before decreasing from 2015 to 2017.

Table 1: Distribution of KS by Province between 2008 and 2017

Age (Years)	Male Frequency (n=320)	Proportion (%)	Female Frequency (n=320)	Proportion (%)
≥ 20	6	1.88	10	3.13
21-40	115	35.94	82	25.63
41-60	58	18.13	28	8.75
61-80	13	4.06	6	1.88
≥ 80	2	0.63	0	0.00

n= number of participants, KS = Kaposi's Sarcoma

the age group 41-60 years, in which more males, 18.13 per cent (58/320), were equally more affected than females, 8.75 per cent (28/320). The age group ≥ 80 had the least KS cases, with males being the only ones affected by KS (Table 2). Of the total KS cases obtained, 39.38 per cent (126/320) were females, and 60.63 per cent (194/320) were males. More cases of KS were recorded in males than in females for each of the years from 2008 to 2016; in 2017, more cases were recorded in females (Figure 2).

Figure 2: Distribution of KS cases according to gender and year at diagnosis. For each year from 2008 to 2016, cases of KS were more prevalent in males than in females. In 2017, KS was more prevalent in females than in males.

Table 2: Distribution of Kaposi's Sarcoma by Age and Sex

Province	Male Frequency (n=320)	Proportion (%)	Female Frequency (n=320)	Proportion (%)
Central	12	3.75	8	2.50
Copperbelt	6	1.88	10	3.13
Eastern	10	3.12	7	2.19
Luapula	1	0.31	2	0.63
Lusaka	140	43.75	81	25.31
North Western	3	0.94	3	0.94
Northern	7	2.19	6	1.88
Southern	12	3.75	6	1.88
Muchinga	4	1.25	0	0.00
Western	2	0.63	0	0.00

n= number of participants, KS = Kaposi's Sarcoma

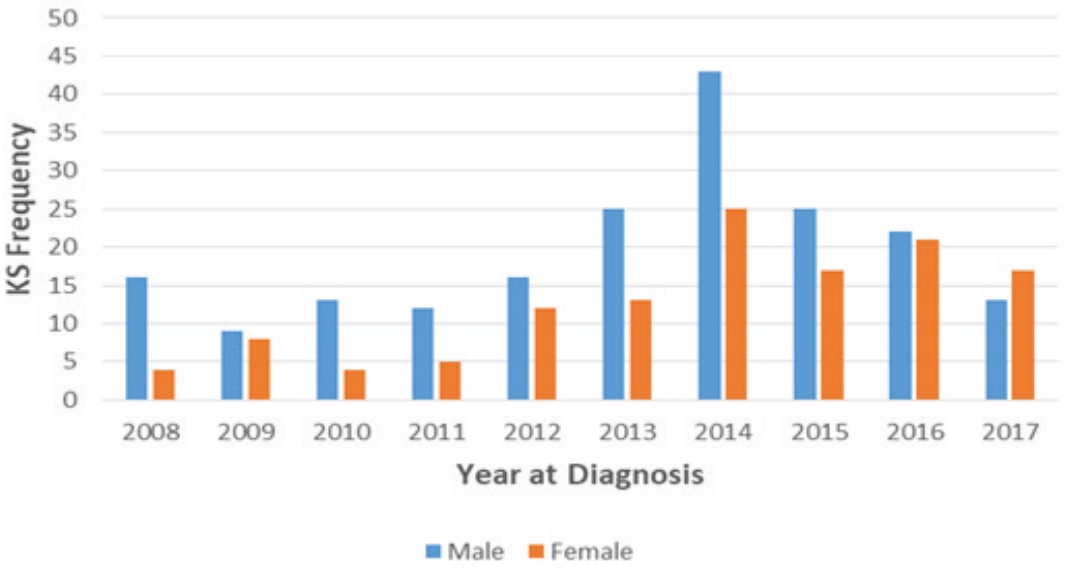

Figure 2: Distribution of KS cases according to gender and year at diagnosis. For each year from 2008 to 2016, cases of KS were more prevalent in males than in females. In 2017, KS was more prevalent in females than in males.

DISCUSSION

Zambia is considered part of the KS belt, and Kaposi's Sarcoma has continued to be of great public health concern despite the rolling out of HAART (26). The present study sought to investigate the local epidemiology of KS cases in the era of HAART from 2008 to 2017 from the ZNCR.

The current study indicates an increase in KS cases from 2008 to 2014, followed by a decrease in the subsequent years. The KS trends in the present study are similar to those observed in a previous study conducted in Zambia (24). However, while this study reported on KS in the era of HAART, the previous study reported on the prevalence and annual incidence of KS and HIV. The increase in the number of cases in these years could be attributed to the continued increase in HIV cases in Zambia, because the interaction between HIV and KSHV facilitates the replication of KSHV, leading to an increased risk of developing KS (5). However, the decrease in the number of KS cases in the subsequent years could be due to underdiagnosis because the early lesions of KS resemble other vascular lesions such as haemangiomas and haematomas. Moreover, patients present late to the hospital when the disease has already advanced (27).

The other plausible reason for the decrease in KS cases in the subsequent years could be due to the increased use of HAART in HIV/AIDS treatment (25). Similar studies in the sub-region have also reported a decline in KS cases following the commencement of HAART (28). This is in line with the trend in developed countries in which the use of HAART has significantly reduced

the incidence of AIDS-related KS, and patients on HAART present with KS, which is less aggressive (29). The effects of HAART on the development of KS are multifactorial but include suppression of HIV viral replication, restoration of immunity and reduction of mortality, thereby reducing the risk of KS (21). Besides the effects of HAART on HIV, preclinical studies have shown that many HAART drugs have antitumour effects (30,31). The introduction of HAART has reduced KS cases but not entirely eradicated them (23,31). This corroborates the findings in the current study, which showed that 19.1 per cent of HIV/AIDS patients developed KS while on HAART.

The highest number of cases were recorded in Lusaka Province, followed by Central Province, while the least number of cases were recorded in Western Province. This contrasts with previous studies in Zambia, which reported that Eastern province had the highest number of cases, followed by Lusaka Province (24). The high number of KS cases recorded in Lusaka Province, in the current study, is attributed to the availability of a well-established Dermatology and Venereology Division located at the national referral hospital, where suspected KS cases are referred for diagnosis and treatment (23).

The results demonstrate that the age group 21-40 years had the highest number of KS cases, consistent with previous studies conducted in Zambia and Nigeria, in which KS cases were high in the middle-aged groups (26,32,33). The detection of KS in this age group could be due to involvement in high-risk behaviour such as unprotected sexual activities or having multiple sexual partners leading to contraction of HIV and hence increasing the risk of KS disease.

Previous studies have shown that KS cases are more common in males than females (20,30,32,33). Similarly, our results indicate a male predominance of KS cases. The reduced KS cases in women could be attributed to gender-related factors, including hormonal, environmental and genetic factors. The hormones, human gonadotropin and oestrogen, are protective factors in KS development based on inhibition of the growth of KS cell lines, and they also have a direct effect on the anti-tumour immune response (26,34,35).

CONCLUSION

Results have shown an overall decline in KS cases in Zambia from 2014 to 2017. However, cases of KS are still being recorded despite the rollout of HAART countrywide. The hardest-hit age group is 21-40 years, where more males than females are affected by KS. Therefore, efforts to reduce HIV infection through behavioural and lifestyle change and improvement of HAART services and wide coverage should be encouraged to mitigate cases of KS. Active KS awareness, screening, and HIV testing nationwide are recommended.

ACKNOWLEDGEMENT

The researchers sincerely thank the Department of Medical Education and Development at the University of Zambia for facilitating the project's conceptualisation. Our deepest gratitude goes to the Cancer Diseases Hospital and the Zambia National Cancer Registry for the support rendered during data collection.

Funding Statement

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of Interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Lihachev A, Lihacova I, Plorina E V., Lange M, Derjabo A, Spigulis J. Differentiation of seborrheic keratosis from basal cell carcinoma, nevi and melanoma by RGB autofluorescence imaging. Biomed Opt Express. 2018;9(4).
2. Karabajakian A, Ray-Coquard I, Blay JY. Molecular Mechanisms of Kaposi Sarcoma Development. Cancers (Basel) [Internet]. 2022;2022:1869. Available from: https://doi.org/10.3390/cancers
3. Gonçalves PH, Uldrick TS, Yarchoan R. HIV-associated Kaposi sarcoma and related diseases. Vol. 31, AIDS. 2017.
4. Giffin L, Damania B. KSHV: Pathways to tumorigenesis and persistent infection. In: Advances in Virus Research. 2014.
5. Liu Z, Fang Q, Zuo J, Minhas V, Wood C, Zhang T. The worldwide incidence of Kaposi's Sarcoma in the HIV/AIDS era. HIV Med. 2018;19(5).
6. Facciolà A, Rullo EV, Ceccarelli M, D'aleo F, Di Rosa M, Pinzone MR, et al. Kaposi's Sarcoma in HIV-infected patients in the era of new antiretrovirals. Eur Rev Med Pharmacol Sci. 2017;21(24).
7. Fardet L, Stoebner PE, Bachelez H, Descamps V, Kerob D, Meunier L, et al. Treatment with taxanes of refractory or life-threatening Kaposi sarcoma not associated with human immunodeficiency virus infection. Cancer. 2006;106(8).
8. Mariggiò G, Koch S, Schulz TF. Kaposi sarcoma herpesvirus pathogenesis. Vol. 372, Philosophical Transactions of the Royal Society B: Biological Sciences. 2017.
9. Vincenzi B, D'Onofrio L, Frezza AM, Grasso RF, Fausti V, Santini D, et al. Classic Kaposi Sarcoma: To treat or not to treat? BMC Res Notes. 2015;8(1).
10. Lanternier F, Lebbé C, Schartz N, Farhi D, Ve Marcelin AG, Kérob D, et al. Kaposi's Sarcoma in HIV-negative men having sex with men.
11. Friedman-Kien AE, Saltzman BR. Clinical manifestations of classical, endemic African, and epidemic AIDS-associated Kaposi's Sarcoma . J Am Acad Dermatol. 1990; 22 (6).
12. Ziegler JL. Endemic Kaposi's Sarcoma in Africa and local volcanic soils. The Lancet. 1993;342(8883).
13. Cesarman E, Chang Y, Moore PS, Said JW, Knowles DM. Kaposi's Sarcoma–Associated Herpesvirus-Like DNA Sequences in AIDS-Related Body-Cavity–Based Lymphomas. New England Journal of Medicine. 1995;332(18).
14. Lebbé C, Legendre C, Francès C. Kaposi sarcoma in transplantation. Transplant Rev. 2008;22(4).
15. La Ferla L, Pinzone MR, Nunnari G, Martellotta F, Lleshi A, Tirelli U, et al. Kaposi' s Sarcoma in HIV-positive patients: The state of art in the HAART-era. Eur Rev Med Pharmacol Sci. 2013;17(17).

16. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5).
17. Levine AM, Tulpule A. Clinical aspects and management of AIDS-related Kaposi's Sarcoma [Internet]. Available from: www.ejconline.com
18. Sparano JA. Clinical aspects and management of AIDS-related Kaposi's Sarcoma. Eur J Cancer. 2001: 37(10).
19. Bohlius J, Valeri F, Maskew M, Prozesky H, Garone D, Sengayi M, et al. Kaposi's Sarcoma in HIV-infected patients in South Africa: Multicohort study in the antiretroviral therapy era. Int J Cancer. 2014 Dec 1;135(11):2644–52.
20. Motlhale M, Sitas F, Bradshaw D, Chen WC, Singini MG, de Villiers CB, et al. Epidemiology of Kaposi's Sarcoma in sub-Saharan Africa. Vol. 78, Cancer Epidemiology. Elsevier Ltd; 2022.
21. Stebbing J, Portsmouth S, Gazzard B. How does HAART lead to the resolution of Kaposi's Sarcoma? Journal of Antimicrobial Chemotherapy. 2003;51(5).
22. Gantt S, Cattamanchi A, Krantz E, Magaret A, Selke S, Kuntz SR, et al. Reduced human herpesvirus-8 oropharyngeal shedding associated with protease inhibitor-based antiretroviral therapy. Journal of Clinical Virology. 2014;60(2).
23. Ngalamika O, Minhas V, Wood C. Kaposi's Sarcoma at the University Teaching Hospital, Lusaka, Zambia in the antiretroviral therapy era. Vol. 136, International Journal of Cancer. 2015.
24. Kalubula M, Shen H, Makasa M. Epidemiology of kaposi's sarcoma in Zambia, 2007-2014. Malawi Medical Journal. 2020;32(2).
25. Zyaambo C, Nzala SH, Babaniyi O, Songolo P, Funkhouser E, Siziya S. Distribution of cancers in Zambia: evidence from the Zambia National Cancer Registry (1990-2009). J Public Health Epidemiol. 2013;5(2).
26. Tembo R, Kaile T, Kafita D, Chisanga C, Kalonda A, Zulu E, et al. Detection of human herpes virus 8 in Kaposi's sarcoma tissues at the University Teaching Hospital, Lusaka, Zambia. Pan African Medical Journal. 2017;27.
27. Maskew M, Fox MP, van Cutsem G, Chu K, MacPhail P, Boulle A, et al. Treatment Response and Mortality among Patients Starting Antiretroviral Therapy with and without Kaposi Sarcoma: A Cohort Study. PLoS One. 2013;8(6).
28. Chaabna K, Bray F, Wabinga HR, Chokunonga E, Borok M, Vanhems P, et al. Kaposi sarcoma trends in Uganda and Zimbabwe: A sustained decline in incidence? Int J Cancer. 2013;133(5).
29. Chalya PL, Mbunda F, Rambau PF, Jaka H, Masalu N, Mirambo M, et al. Kaposi's Sarcoma: A 10-year experience with 248 patients at a single tertiary care hospital in Tanzania, Cancer. BMC Res Notes. 2015;8(1).
30. Kagu MB, Nggada HA, Garandawa HI, Askira BH, Durosinmi MA. AIDS-associated Kaposi's Sarcoma in Northeastern Nigeria. Singapore Med J. 2006;47(12).

31. Shmakova A, Germini D, Vassetzky Y. HIV-1, HAART and cancer: A complex relationship. Vol. 146, International Journal of Cancer. 2020.
32. Mandong BM, Chirdan LB, Anyebe AO, Mannaseh AN. HISTOPATHOLOGICAL STUDY OF KAPOSI'S SARCOMA IN JOS: A 16-YEAR REVIEW. Ann Afr Med. 2004: 3(4).
33. Forae GD, Obaseki DE. Trends and histopathological patterns of Kaposi Sarcoma at the university of Benin teaching hospital, Benin city, Nigeria. Oman Med J. 2018;33(4).
34. Phipps W, Ssewankambo F, Nguyen H, Saracino M, Wald A, Corey L, et al. Gender differences in clinical presentation and outcomes of epidemic kaposi sarcoma in Uganda. PLoS One. 2010;5(11).
35. Chaabna K, Newton R, Vanhems P, Laouar M, Forman D, Boudiaf Z, et al. Cancer incidence and all-cause mortality in HIV-positive patients in Northeastern Algeria before and during the era of highly active antiretroviral therapy. J Cancer Res Ther. 2016;12(2).